Metallomics

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Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells

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"Serum ferritin" presents a paradox, as the iron storage protein ferritin is not synthesised in serum yet is to be found there. Serum ferritin is also a well known inflammatory marker, but it is unclear whether serum ferritin reflects or causes inflammation, or whether it is involved in an inflammatory cycle. We argue here that serum ferritin arises from damaged cells, and is thus a marker of cellular damage. The protein in serum ferritin is considered benign, but it has lost (*i.e.* dumped) most of its normal complement of iron which when unliganded is highly toxic. The facts that serum ferritin levels can correlate with both disease and with body iron stores are thus expected on simple chemical kinetic grounds. Serum ferritin levels also correlate with other phenotypic readouts such as erythrocyte morphology. Overall, this systems approach serves to explain a number of apparent paradoxes of serum ferritin, including (i) why it correlates with biomarkers of cell damage, (ii) why it correlates with biomarkers of hydroxyl radical formation (and oxidative stress) and (iii) therefore why it correlates with the presence and/or severity of numerous diseases. This leads to suggestions for how one might exploit the corollaries of the recognition that serum ferritin levels mainly represent a consequence of cell stress and damage.

Introduction

In mammals (in contrast, for instance, to some functions in insects[1–4]), ferritin is supposed to be a cellular means of storing iron,[5] not of transporting it, yet serum ferritin levels are widely measured as indicators of iron status. However, the soluble transferrin receptor (sTfR) : log ferritin ratio (sTfR Index) probably provides a better estimate of body iron over a wide range of normal and depleted iron stores.[6–9] This is because serum ferritin levels can be raised significantly in response to inflammation and/or a variety of diseases (see later). "Serum ferritin" thus presents something of a paradox. Taking a systems approach, we develop and summarise the view that "serum ferritin" actually originates from damaged cells (and thus reflects cellular damage), that it contains some iron but has lost or liberated most of its normal content, and that since the protein part of ferritin is assumed to be benign, that it is this (initially) free iron that correlates with and is causative of disease. The rest of this analytical and synthetic review summarises the wide-ranging evidence for this. We necessarily start by reviewing iron metabolism from a systems point of view (Fig. 1).

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A systems biology overview of human iron metabolism

A starting point for systems biology is the creation of the network (mathematically a 'graph') of interacting partners (*e.g.* ref. 10–14). To this end, a number of recent genomic-level or systems biology reviews have summarised the chief features of human iron metabolism (*e.g.* ref. 15–19). (Systems genetics analyses are also available.[20–23]) For the present purposes, aimed at seeking the 'function' of human serum ferritin (SF), we shall take a particularly high level view, and assume that the body has a very restricted number of compartments. Fig. 2, updated from ref. 15 shows essentially just three: intestinal tissue, peripheral tissue and blood/serum, and (see also ref. 24, 25 and *cf.* ref. 26) these will be quite sufficient.

Thus, as is well known, ferric salts and ions are poorly water soluble (hence the need for siderophores – better known in microbiology[27–30]), and much of the complex (redox) chemistry of iron in the body is designed to deal with this. In addition to its existence in divalent and trivalent states, iron is also capable

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of being liganded in up to 6 places (4 equatorial, 2 polar), and this liganding is necessary to stop its otherwise exceptional reactivity, specifically the production of the very damaging hydroxyl radical that reacts in nanoseconds with the nearest biological substances[15,17] *via* the Fenton reaction[31–35] of H_2O_2 and Fe(II). This may be coupled to the re-reduction of Fe(III) to Fe(II) by superoxide in the Haber–Weiss reaction,[31–35] such that unliganded (or poorly liganded) iron moieties are catalytic and thus especially dangerous. Thus, while iron is vital for living processes, there is an exceptionally important need to sequester iron in a suitably liganded form, and cellular ferritin is a major means of doing this.[36]

Leaving aside haem, and also nutrient-derived ferritins,[37,38] iron is absorbed in the intestine as ferrous ions and transported in the serum bound (in the ferric form) to transferrin, where it can enter peripheral tissues *via* suitable receptors, being re-reduced in the process. Ferrous iron is incorporated into ferritin, simultaneously being oxidised at a di-iron centre[39] to ferric iron. Thus, importantly, ferritin is made in cells (including intestinal cells), and not in serum. We also note the evidence for the presence of ferritin within erythrocytes,[40–54] the largest volume fraction of serum.[55] In nucleated cells, ferritin resides mainly in the cytoplasm, but there are nuclear[56–61] and mitochondrial[62–64] forms (not considered here, as our focus is serum ferritin). An overview of cellular iron metabolism is given in Fig. 3.

Although there are bacterial (and other) ferritins that have only 12 subunits,[65] human ferritins consist of 24 subunits of a light (L) and heavy (H) chain arranged by self-assembly in a tetracosameric, octahedral cage with 4-3-2 symmetry (*e.g.* ref. 5, 66–70). In humans, the molecular masses of the two chains are 19 (173 amino acids) and 21 kDa (183 amino acids), respectively,[61] and the subunits are structurally interchangeable,[71] even between mammalian species.[72] The heavy subunit is primarily responsible for the ferroxidase activity of the ferritin complex,[39] whereas the light subunit (L also standing for Lacks catalysis[73]) facilitates the storage of iron into the ferritin core.[61] Many X-ray structures are known.[74] Broadly, each subunit consists of a 4-helix bundle, and their self-assembly (whether iron is present or not) is energetically extremely favourable – the melting or denaturation temperature of the 24mer cage is some 40°C greater than that of an individual subunit.[75]

Iron loading mechanism of ferritin

The main features of the typical 24-subunit ferritin architecture (shown as an all-H-chain variant) are given in Fig. 4. Human ferritin is some 12 nm diameter overall, with a 2 nm thick protein shell and a hollow internal 8 nm diameter cavity capable of holding up to 4500 iron atoms. Ferrous ions can diffuse into (and out of) the core *via* the eight, hydrophilic ~4 Å × 15–20 Å channels located at the 3-fold symmetry axis,[70,73,76–82] where they are oxidised by dioxygen (or H_2O_2 if present) at a di-iron catalytic site to form $Fe(III)_2$–O products that then form the $Fe_2O_3 \cdot H_2O$ mineral core.[78,83,84] Other materials such as phosphate may also serve as counterions.[82,85] Ferritin $Fe^{3+}O$ nucleation channels open onto the internal surfaces of ferritin protein cages at the four-fold symmetry axes of the ferritin protein cage.[82] The six channels located at the 4-fold axis of the protein are hydrophobic; their function does not seem to be known with any certainty, but they may permit entry of dioxygen and/or H_2O_2.[77]

It is not quite so clear how (after storage as Fe(III) in the ferritin core) Fe(II) exits the channels[81,86] to become available to cells, nor how the physiological (*in vivo*) reductant reaches the potential site of reduction inside the small channels. It is not clear even what the physiological reductant is,[87] though NADH and FMN have been reported to serve,[82,88] as have superoxide[89] and other materials.[81]

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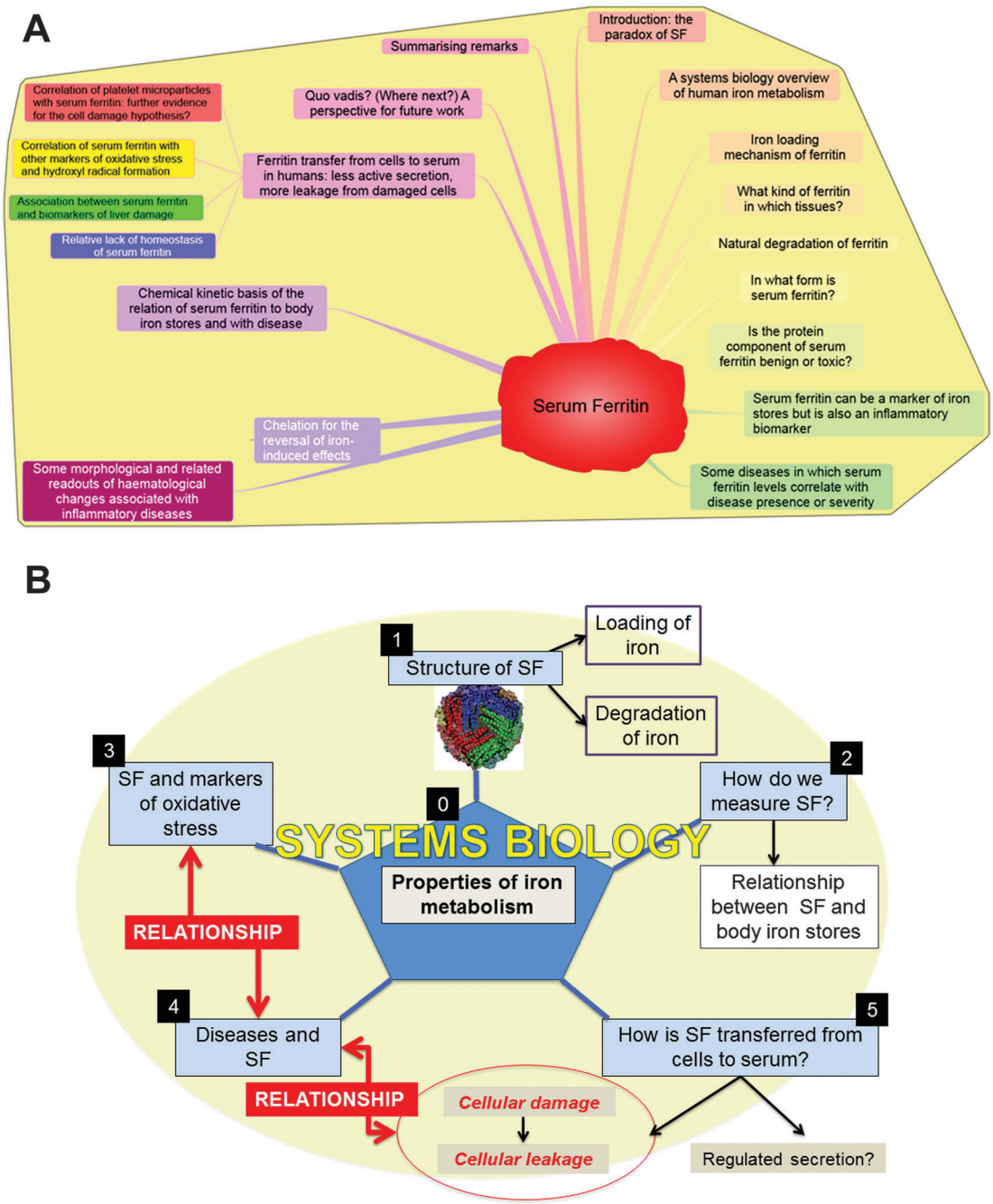

Fig. 1 An overview of this manuscript. (A) A Mind map representation; to read this start at "1 o'clock" and go clockwise. (B) A representation as an infographic, covering (0) the systems biology of iron metabolism, (1) the nature and structure of serum ferritin (SF), (2) the relationship between SF and body iron stores and its measurement, the relationship between SF and (3) markers of oxidative stress and (4) disease, and finally (5) the evidence that ferritin is transferred from cells to serum mainly *via* cell damage and leakage rather than by regulated secretion.

How much iron in cellular/tissue ferritin?

The number of iron atoms/ferritin cage is said to average 1000–1500 normally,[73] governed more by iron availability than anything else, with a maximum of 4500 iron atoms normally being quoted (*e.g.*, ref. 90–92, and attained for iron overload conditions or when loaded artificially *in vitro*). Direct observation also leads to a mode value of ~1500 in a liver biopsy from a patient with hereditary haemochromatosis.[93]

What kind of ferritin in which tissues?

As mentioned, from a structural point of view in terms of forming the 24mer nanocage, ferritin H and L forms are interchangeable.[71] Similarly, as expected, ferritin is expressed in most tissues. Thus, human protein atlas expression data for the light chain

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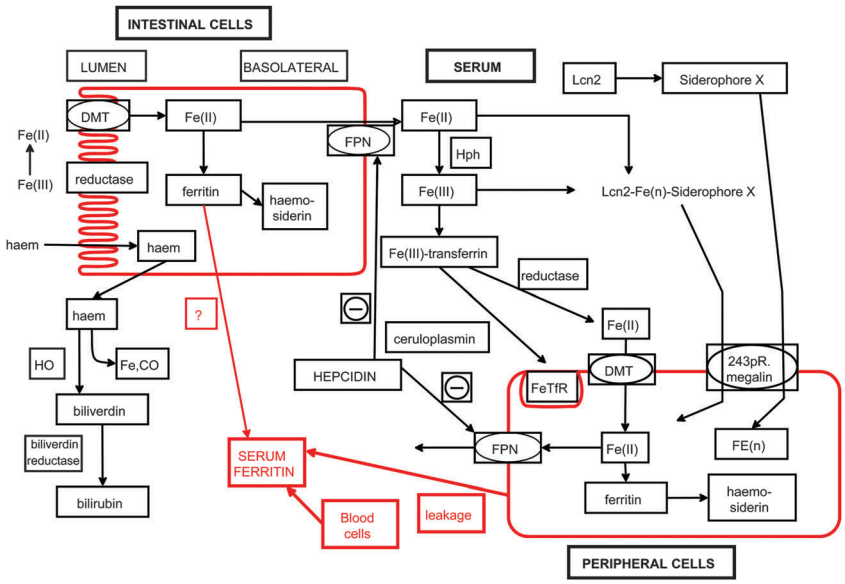

Fig. 2 A high-level, three-compartment overview of iron metabolism (based on[15]) and the means by which we consider that ferritin appears in serum by leakage from peripheral (and possibly intestinal) cells. BR biliverdin reductase, DMT1 divalent metal transporter1, HO haem oxygenase, Hph hephaestin, TfR transferrin receptor, Lcn2 lipocalin2, also known as Neutrophil gelatinase-associated lipocalin. Diagrams rendered by Dr Steve O'Hagan.

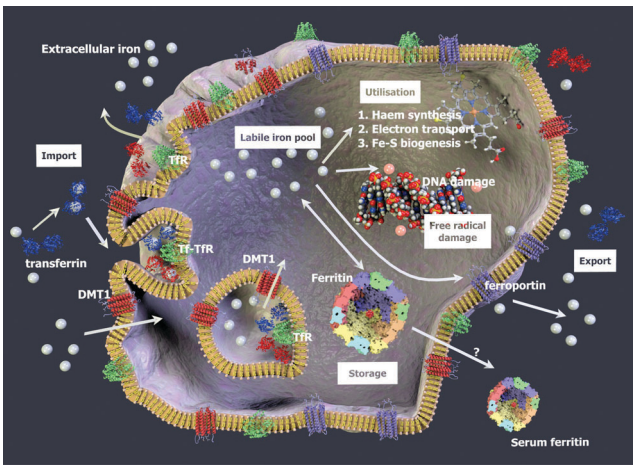

Fig. 3 Some relevant aspects of cellular iron metabolism, including ferritin and its possible loss to serum. The figure is not to scale, and is based in part on.[67] Membrane protein concentrations shown are lower (for clarity) than those in real cell membranes.[458] Diagram rendered by Dr Steve O'Hagan.

http://www.proteinatlas.org/ENSG00000087086/normal show it mainly in CNS, bone marrow, spleen, liver, kidney, lung and adipocytes. Expression of the heavy chain is broadly similar http://www.proteinatlas.org/ENSG00000167996/normal save that it is also highly expressed in breast, uterus, testis, prostate and thyroid tissue. In terms of the actual stoichiometries of L:H in ferritin molecules in different tissues (which also affects the ordering or crystallinity of the mineral core[73,87]) there is rather less information, and variations in this may be causative of disease.[94,95] Clearly, for a 24-subunit molecule with two kinds of subunits, one can build 25 canonical 'isoferritins'.[74] Liver and spleen ferritin is mainly the L subunit while heart and brain ferritin is mainly the H subunit. Serum ferritin is mainly in the L form,[5,96] consistent with the view that it typically originates in the liver.[97] The same (*i.e.* mainly the L form) is presumably true for erythrocyte ferritin, in that this is what the usual ELISA tests for serum ferritin are designed to detect.

Natural degradation of ferritin

The exact circumstances under which ferritin is normally degraded *in vivo* (if it is intact) are not entirely clear, but what is clear is that there is a fundamental conceptual problem, in that if the only part degraded is the protein the result is the damaging liberation of unliganded iron. Certainly, as expected for normal cellular degradation, the proteasome is involved,[38,98] but there is also a major lysosomal degradation pathway.[38,99–103] We note too that overexpression can lead to the formation of ferritin inclusion bodies.[104]

As well as proteolytic degradation, there are other means of ferritin removal. Thus, haemosiderin is an insoluble material formed from damaged ferritin (ferritin with exposed and potentially chemically reactive mineral sites), commonly appearing under conditions of iron overload and often reflecting a poorer disease prognosis (*e.g.* ref. 71, 105–112). (Note that another insoluble cellular degradation cluster – lipofuscin (*e.g.* ref. 113–116) – is different, as it does not contain haemosiderin.) However, the insoluble substance neuromelanin (*e.g.* ref. 115, 117–119) may contain ferritin or ferritin-like material.[120–122] The question of what happens to haemosiderin seems rather poorly understood, but in contrast to ferritin it is not normally seen (nor at least measured) in serum;[123,124] since it is composed of large, insoluble aggregates it is possibly not surprising that it does not leak from cells. Overall, however, it seems that we have comparatively little information on the

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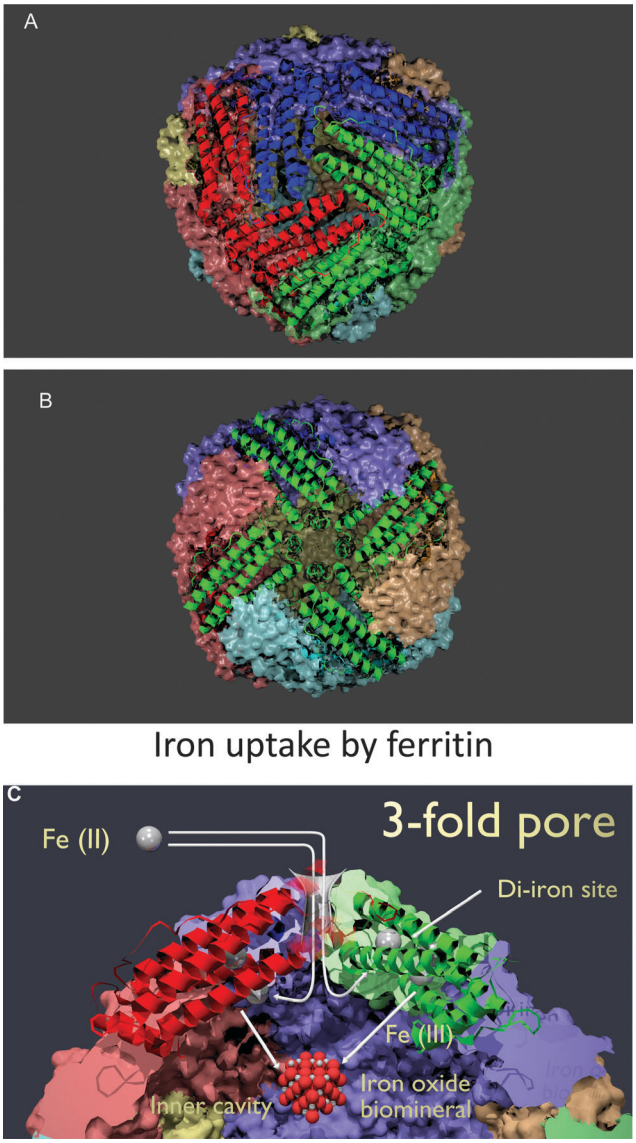

Fig. 4 The architecture of a human ferritin, rendered from PDB structure 1FHA (all-H-chain variant). (A) A view down one of the hydrophilic channels representing the 3-fold axis of symmetry through which iron enters the ferroxidase site en route to the core. (B) A view down the hydrophobic channels representing the 4-fold axis of symmetry (whose function is unknown). (C) Entry of Fe^{2+} into ferritin *via* a hydrophilic channel, and conversion at a di-iron site to Fe^{3+}, based loosely on a diagram in[73] – note that for clarity the iron atoms are not drawn to scale. Diagrams rendered by Dr Steve O'Hagan.

important question of what happens to its iron content when the protein part of the ferritin molecule either leaves the intracellular environment or is degraded.

In what form is serum ferritin measured?

As mentioned previously, ferritin has an H and L form that are structurally interchangeable. Serum (L-)ferritin is usually measured with antibodies; only rarely is its iron content measured as well. Mass spectrometric methods, that can measure both protein and internal materials, may thus be expected to become the methods of choice.[125–128] When such measurements are done, serum ferritin is usually found to contain some iron, but nothing like its full complement.[91,92,97,129,130] This implies that it has lost it, whether during or after effluxing from the cells in which it originates.[87]

Is the protein component of serum ferritin benign or toxic?

This question arises because if the iron has escaped and now (say) the inside of the ferritin is exposed in the serum it might have effects that the intact protein does not (given that the intact protein is extremely stable to thermal unfolding[75]). There is some fragmentary evidence that serum ferritin itself may have apoptotic and other actions on cells.[68,131,132] However, at present it is rather difficult to answer the question of how benign the protein-only form of ferritin (*i.e.* apoferritin) actually is, since serum ferritin does always tend to contain at least some iron, which can be released and is then not at all benign. When the iron is varied systematically, it is iron-loaded ferritin that is the more toxic,[133] with apoferritin in fact being protective.[133–137] An important piece of evidence comes from the fact that homozygous ferritin knockout mice are embryo-lethal[138] but that heterozygous $Fth^{+/-}$ mice are fairly normal save that they have greatly increased levels of serum ferritin but unchanged serum iron.[139] This shows us, importantly, (i) that iron and ferritin can be regulated independently, and (ii) that excess ferritin protein is not of itself toxic *in vivo* (see also ref. 140). Hereditary hyperferritinemia-cataract syndrome is another disease in which serum ferritin is high but there is no evidence of systemic iron overload.[141–146] However, as well as (sometimes) being a marker of liver iron stores, serum ferritin is also an inflammatory marker, and there is often a considerable correlation between disease status and the serum ferritin protein level as measured using antibodies (which do not distinguish ferritins with varying iron content).

Serum ferritin can be a marker of iron stores but is also an inflammatory biomarker

What matters from the point of view of mammalian biology is both the total amount of iron and its speciation. While iron is necessary in every metabolising tissue, a substantial amount of iron is held in the liver, so 'liver iron stores' are often taken as the gold standard. Traditionally, these were measured in a biopsy, although this is not something that can be done with any frequency. Fortunately non-invasive measurement and imaging methods, *e.g.* neutron-stimulated emission controlled tomography,[147] SQUID-biosusceptometry[129,148] and (in particular) MRI (*e.g.* ref. 149–158), also widely used for brain imaging (*e.g.* ref. 159–161), are coming through. In some cases, where there is no inflammation and/or if a specific iron-related disease state is known, liver iron content can correlate with serum ferritin (*e.g.* ref. 162 and 163), but more often the correlation is poor (*e.g.* ref. 129, 157, 164–171). This is more or less inevitable when serum ferritin levels can be affected by two

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largely independent causes, *viz.* iron status and inflammatory status. Thus, as mentioned above, serum ferritin alone is falling out of favour as a marker of iron status, with serum ('soluble') transferrin receptor (sTfR) being seen as much more useful, since sTfR may be used to distinguish the anaemia of chronic disease from iron-deficiency anaemia.[172] In particular, the "sTfR Index" (the sTfR/log ferritin ratio when both are measured in μg L^{-1}) is now considered to provide an estimate of body iron over a wide range of normal and depleted iron stores,[6–9] and again is thus better for discriminating iron deficiency anaemia from the anaemia of chronic disease[9,173–175] (*cf.* ref. 176).

In consequence, and especially in countries where inflammatory diseases are highly prevalent, it would seem that serum ferritin may in general be a better marker of inflammation than of iron status.

Some diseases in which serum ferritin levels correlate with the presence or severity of disease

One of us has previously listed a great many (inflammatory) diseases in which iron dysregulation clearly plays a major role (*e.g.* ref. 15 and 17), but did not there distinguish serum ferritin explicitly. It is therefore helpful to set down some of the studies in which serum ferritin is known to associate with disease and/or disease severity, and this is done in Table 1.

There can be very little doubt that high serum ferritin levels accompany a great many diseases, and the corollary of this is that iron-induced hydroxyl radical formation leading to oxidative damage is likely to be a contributory factor in all of them. In addition, there are other useful phenotypic readouts that change with serum ferritin, and the next section describes one.

Table 1 A selection of diseases in which their presence or severity is known to be related to serum ferritin levels. The table purposely excludes classic 'iron overload' diseases such as haemochromatosis, thalassaemia and myelodysplastic syndrome. It also excludes syndromes such as Alzheimer's disease[177–179] and Parkinson's disease,[18,180] where a great many papers show dysregulation of iron metabolism in brain tissue but where there is very little work in serum. In the case of rheumatoid arthritis some of the studies involved synovial fluid; like serum, this is an extracellular fluid

Disease or syndrome	Selected references
Acute respiratory distress syndrome	181–184
Amyotrophic lateral sclerosis	185–189
Atherosclerosis	96, 190–200
Cancer	201–214
Cirrhosis of the liver	215–217
Coronary artery disease	218–221
Diabetes mellitus, type 2	221–249
Hypertension	250–254
Metabolic syndrome	235, 236, 252, 255–272
Multiple sclerosis	273–276
Myocardial infarction	277–285
Non-alcoholic fatty liver disease	260, 262, 264, 270, 286–301
Preeclampsia	302–306
Rheumatoid arthritis	307–314
Sepsis/SIRS	315–318
Stroke	319–330
Systemic lupus erythematosus	274, 331–342

Some morphological and related readouts of haematological changes associated with inflammatory diseases

While not the entire focus of this review, we highlight two other accompaniments to the unliganded iron caused by its loss from ferritin, namely morphological changes to both fibrin and erythrocytes. Thus, we have recently been developing the idea that many of the consequences of unliganded iron can be observed directly, by changes in properties such as erythrocyte (RBC) morphology and deformability and the nature and morphology of fibrin fibres generated in the presence of thrombin (as is observed in a number of diseases[343–346]). When thrombin is added to healthy whole blood, the RBCs will keep their typical discoid shape while fibrin fibres will form over and around the RBCs (such a typical healthy RBC (from an individual with a serum ferritin of 19 ng·mL^{-1}), surrounded by fibrin is shown in Fig. 5A). However, in inflammatory conditions, where iron overload is present, the RBCs lose their typical discoid shape, while the fibrin network forms a dense matted layer.

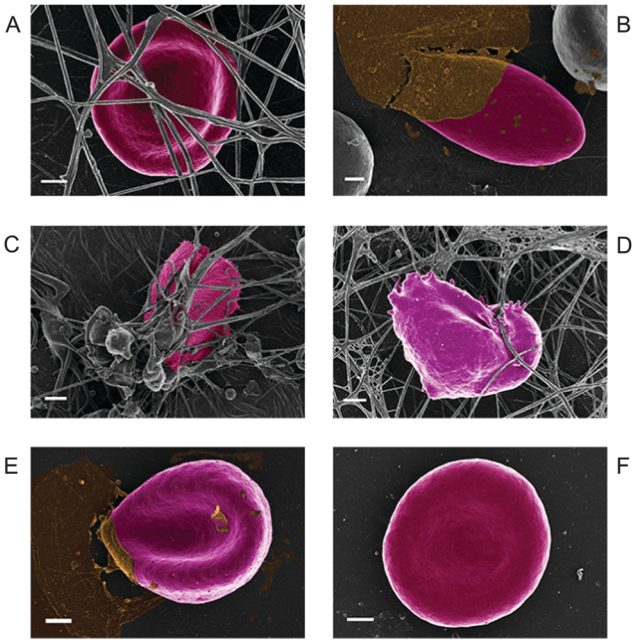

Fig. 5 A to D: whole blood with added thrombin, taken from females. (A) Erythrocyte surrounded by fibrin network, from a healthy individual (serum ferritin (SF) = 19 ng mL^{-1}); (B) erythrocyte from a hereditary hemochromatosis individual (C282Y/C282Y) showing elongated shape with (in brown) matted fibrin (serum ferritin (SF) = 508 ng mL^{-1}); (C) erythrocyte of an individual with a pro-thrombin mutation (G20210A – heterozygous) as well as anti-phospholipid syndrome, showing fibrin forming a covering on the elongated erythrocyte (serum ferritin (SF) = 177 ng mL^{-1}); (D) erythrocyte from a high serum ferritin Alzheimer's disease individual, showing architectural changes of the cell (serum ferritin (SF) = 256 ng mL^{-1}). E and F: whole blood smears (without added thrombin) (E) erythrocyte of hereditary hemochromatosis individual (serum ferritin (SF) = 508 ng mL^{-1}); (F) erythrocyte from hereditary hemochromatosis individual after addition of the iron chelator desferal (167 μM). Scale bar = 1 μm. Ethical clearance was obtained by E Pretorius for SEM analysis.

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This was previously noted in RBCs of hereditary haemochromatosis, pro-thrombin mutation and antiphospholipid syndrome with increased serum ferritin levels and in high serum ferritin levels in Alzheimer's disease.[347–351] Fig. 5B–D show examples of RBCs and fibrin in these conditions. The corollary is clear, namely that these kinds of changes should be observable in cases where we see high serum ferritin, and some examples have already been published.

In the presence of iron, the already compromised RBCs are entrapped in the pathological fibrin masses. Iron plays an important role in the change of a netlike fibrin layer to a matted mass. We previously showed that healthy fibrin can be changed to resemble this matted appearance, when physiological levels of iron are added to plasma.[352] Such matted fibrin morphology was also previously noted in type II diabetes, thrombotic ischemic stroke and systemic lupus erythematosus. Here the compromised RBCs twist around the fibres and this may cause a tight and rigid clot that might be particularly resistant to fibrinolysis.[353–355]

As well as undergoing a shape change, the RBC membranes, in the presence of iron overload, also lose their elastic ability (deformability). This was noted in Alzheimer's Disease individuals with iron overload, where their RBCs have a decreased membrane elasticity.[347] A changed RBC membrane roughness was also noted in diabetes.[356]

Further, RBC shape and membrane changes have been noted in smokers and in individuals with Chronic Obstructive Pulmonary Disorder (COPD).[357,358] Both conditions are known to cause a general inflammatory state in the user as well as increased serum ferritin levels,[359] and this may aid in the developing of the changed RBC deformability.

RBCs are extremely adaptable cells, particularly due to their rheological properties that force them to deform and reform under shear forces when they travel through narrow capillaries, while in the presence of high (poorly liganded) iron levels, they lose this deformability. By contrast, diseased RBCs can regain their discoid shape when selected chelators are added.[350] Here we show how an RBC from a HH individual can return to the typical discoid shape after the addition of physiological levels of the iron chelator Desferal (Fig. 5E and F). This may have profound clinical implications under conditions where iron overload is present.

Thus, this unliganded iron affects (negatively) at least three things that can each contribute to vascular woes: erythrocyte morphology, erythrocyte deformability and fibrin structure/morphology.

Chelation for the reversal of iron-induced effects

The recognition that these changes can be reversed by known iron chelators leads to the recognition of a further prediction: that disease severity may be decreased through the use of iron chelators that may be pharmacological or nutritional. For the former, three iron chelators have been approved for clinical use (*e.g.* ref. 15, 360–364), *viz.* desferal/deferoxamine/desferrioxamine,[365] L1/deferiprone[366–368] and deferasirox.[369–372] From the nutritional point of view, there is considerable evidence that many of the benefits of polyphenolic antioxidants (such as are found in coloured, and especially purple, fruits) derive from their ability to chelate unliganded iron (see *e.g.* ref. 17, 373–380).

Chemical kinetic basis of the relation of serum ferritin to liver iron stores and with disease

Many dozens of references indicate that in normal humans (without overt inflammation) serum ferritin levels are more or less closely related to body iron stores (*e.g.* in the liver) as judged by magnetic resonance imaging, biopsy or repeated phlebotomies. A selection of such references includes.[163,169,381–385]

Since there is normally a decent correlation between body iron stores and serum ferritin, a series of simple (even first order) reactions in which cells release ferritin can account for this (Fig. 6). The question arises as to the nature of this 'release'.

Ferritin transfer from cells to serum in humans: less active secretion, more simply leakage from damaged cells

Partly because a fraction of serum ferritin is glycosylated, as judged more or less solely by its ability to bind to concanavalin A (not a very specific assay), it is occasionally stated that ferritin is 'secreted' (*e.g.* ref. 382, 386 and 387), implying a controlled

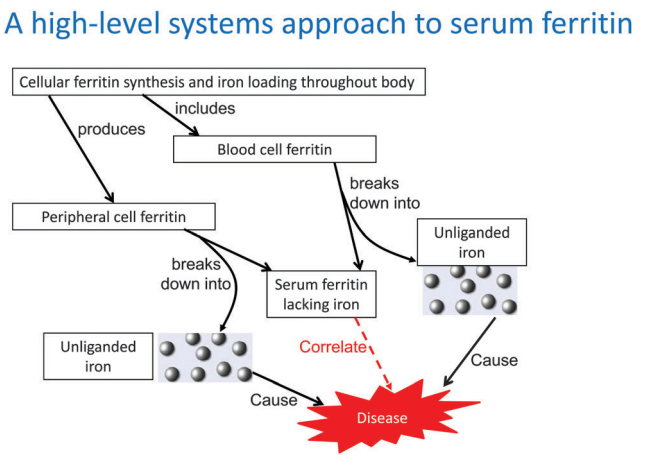

Fig. 6 A high-level systems approach to serum ferritin. The diagram serves to illustrate why there tend to be correlations between the amount of ferritin in cells, the rate of its excretion by cell damage (involving liberation of unliganded iron) and the levels of serum ferritin. The serum ferritin correlates with disease but the cause is iron, with which it too can correlate. As with any systems biology network, multiple differences in different elements of the network can lead to the same overall effects, explaining the lack of a perfect correlation with any individual process. Thus a first order rate of efflux of ferritin is the product of (and thus contains contributions from) both the internal ferritin concentration and the rate constant for efflux, which may vary independently. For these purposes we do not discriminate the many individual iron species.

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process, but without – so far as we are aware – any actual evidence for secretion rather than leakage being the mechanism *in vivo*. Indeed when ferritin is genuinely secreted, as it is for instance in insects,[3,4,388] it has suitable leader (secretion signal) sequences, and mammalian ferritins do not.

This said, in cell cultures, there is some (scant) evidence for a comparatively small amount of regulated secretion,[389] and one paper states that secretion can be decreased by brefeldin, an inhibitor of Golgi processes.[390] This secreted form is said to be mainly the more acidic H form[131] and is glycosylated. We note that both SCARA5 and the transferrin receptor can act as receptors for serum ferritin,[68,391,392] as can TIM-2 in mice,[393] that can in some circumstances be taken up into cells.[394] There is also evidence for active secretion (of a non-glycosylated form) in mice.[395] Overall, however, there is not as yet any real evidence for regulated or active secretion in humans *in vivo*, such that the origin of serum ferritin must indeed largely, if not entirely, be seen as cellular damage. A number of analyses in the literature are consistent with this, and the following four sections pertain.

Relative lack of homeostasis of serum ferritin

The 'normal range' of a biochemical concentration is a body fluid is usually taken as the middle 95 percentiles. Somewhat like the Gini indices of economics,[396] it is then possible to assess the ratio of particular percentiles, which gives an indication of the spread of these among populations. We shall call this ratio (of the 2.5th and 97.5th percentile) the 95 percentile ratio or 95PR. A small spread implies a tighter degree of regulation or control. The large normal range of serum ferritin (18–350 ng mL^{-1}) relative to other biochemical variables (http://www.globalrph.com/labs_def.htm#Ferritin_), with a 95PR of nearly 20, implies that it is not the subject of homeostasis, *i.e.* that its appearance is not regulated. One might also comment on the very low normal concentrations of serum ferritin (up to say 350 ng mL^{-1} in men, up to say 150 ng mL^{-1} in women) relative to say transferrin (1.88–3.41 mg mL^{-1}) (http://www.globalrph.com/labs_t.htm) or fibrinogen (2–4 mg mL^{-1}).

Association between serum ferritin and biomarkers of liver damage

As stated by Theil:[70] "serum ferritin likely originates from cell leakage". The figure in[67] implies a similar role. Similarly, Hubel[305] points out correlations between serum aspartate aminotransferase (a marker of hepatocellular damage) and SF,[397] which again implies that serum ferritin originates from cellular damage. Many other authors (*e.g.* ref. 87, 91, 129, 288, 382 and 398) take a similar view. Serum alanine aminotransferase is another well known marker of liver damage that correlates with serum ferritin,[93,215,257,287–289,399–407] consistent with the view that serum ferritin is indeed a marker of damaged cells. In this regard, it is worth noting that the rate of cell turnover, and especially liver cell turnover/regeneration, can be very high (*e.g.* ref. 408–411).

Correlation of serum ferritin with other markers of oxidative stress and hydroxyl radical formation

Since intracellular ferritin is a means of storing iron safely,[412] and indeed its synthesis is increased in response to oxidative stress,[413–416] one should not necessarily expect serum ferritin to be related to biomarkers reflecting hydroxyl radical formation *via* the Fenton reaction, that is catalysed by unliganded iron. However, in a similar vein to the liver damage above, serum ferritin levels do correlate with serum markers of hydroxyl radical formation such as 8-hydroxydeoxyguanosine,[17,417–424] 27-hydroxycholesterol,[425] 4-hydroxynonenal,[131,290] isoprostanes,[426,427] and malondialdehyde.[406,428–436] Given that only unliganded iron can do this, the easiest interpretation of such data is that the serum ferritin has lost its iron and that it is this unliganded iron that catalyses hydroxyl radical formation and thus the production of these markers. An extensive food processing literature also documents this loss of iron from ferritin in muscle foods (*e.g.* ref. 437–439), where the consequent lipid oxidation is a major issue in causing rancid tastes, and where metal chelators decrease it.[440,441]

Correlation of platelet microparticles with serum ferritin – further evidence for the cell damage hypothesis

As mentioned, a considerable number of papers note the presence of ferritin in erythrocytes, the largest cellular compartment in blood.[40,43–50,53,54] In RBCs, one of the more notable cell death mechanisms is eryptosis, a suicidal death of erythrocytes; this is characterized by erythrocyte shrinkage, blebbing, and phospholipid scrambling of the cell membrane. There is limited evidence that eryptosis occurs in iron overload conditions like β-thalassemia.[442] It is noteworthy that erythrocyte-derived microparticles are also often observable in the blood of patients with diseases associated with high serum ferritin levels (Table 1).[443–453] These microparticles are circulating fragments derived from blebbing and shedding of cell membranes through several mechanisms that include activation, apoptosis (in nucleated cells) and cell damage.[444,454] These microparticles are well-known in cardiovascular, neoplastic, and inflammatory diseases and this again implies a correlation between cellular damage and serum ferritin. Cell damage also releases both phospholipids and DNA, and (in a similar vein) ferritin levels are also raised in diseases in which antibodies to such molecules are also present (*e.g.* ref. 455–457).

Summarising remarks

Although serum ferritin is widely seen as an inflammatory biomarker, our understanding of its role as an intracellular iron storage protein gives no explanation of why it should even exist in serum. The view summarised here is that serum ferritin leaks from damaged cells, losing most of its iron on the way, and leaving that iron in an unliganded form that can impact negatively on health. This unliganded iron can of course stimulate further cell damage.[17] This overall view serves straightforwardly to explain the following, known observations.

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(1) Serum ferritin exists, despite the fact that ferritin is not synthesised in the serum.

(2) Serum ferritin lacks most of the iron it contained when intracellular.

(3) The intracellular ferritin must have 'dumped' its unliganded iron somewhere, where it can participate in Haber–Weiss and Fenton reactions, creating hydroxyl radicals and consequent further cellular damage.

(4) The serum ferritin protein is itself considered benign.[139]

(5) Yet the level of serum ferritin correlates with numerous inflammatory and degenerative diseases.

Quo vadis (where next)? A perspective for future work

We consider the summary presented here rather persuasive, as it has considerable explanatory power in terms of accounting for the nature and consequences of serum ferritin, and providing corollaries of the fact that it has largely 'lost' its iron that are borne out by evidence. It also leads us to note some of the experiments that need to be done. First, we need to understand much better the state of both cellular and serum ferritin in terms both of its subunit composition and the nature and extent of its iron content. We also need to understand better the different cellular and tissue distributions of the variously loaded forms, and we certainly need to determine the toxicity displayed, or protection afforded, by the different forms of well characterised ferritins under different circumstances. Far from implying that serum ferritin is a poor biomarker, it leads us rather to suggest that we need to follow it (and its sequelae) more carefully and longitudinally during the development or otherwise of various diseases, and to test how well its changes reflect therapeutic benefits to disease progression. Only then will we determine its true utility, whether alone or in combination with other biomarkers.

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References

1 A. Mehta, A. Deshpande and F. Missirlis, Genetic screening for novel *Drosophila* mutants with discrepancies in iron metabolism, *Biochem. Soc. Trans.*, 2008, **36**, 1313–1316.

2 F. Missirlis, S. Kosmidis, T. Brody, M. Mavrakis, S. Holmberg, W. F. Odenwald, E. M. Skoulakis and T. A. Rouault, Homeostatic mechanisms for iron storage revealed by genetic manipulations and live imaging of *Drosophila* ferritin, *Genetics*, 2007, **177**, 89–100.

3 D. Q. D. Pham and J. J. Winzerling, Insect ferritins: Typical or atypical?, *Biochim. Biophys. Acta*, 2010, **1800**, 824–833.

4 X. Tang and B. Zhou, Ferritin is the key to dietary iron absorption and tissue iron detoxification in *Drosophila melanogaster*, *FASEB J.*, 2013, **27**, 288–298.

5 P. Arosio, R. Ingrassia and P. Cavadini, Ferritins: A family of molecules for iron storage, antioxidation and more, *Biochim. Biophys. Acta*, 2009, **1790**, 589–599.

6 B. S. Skikne, C. H. Flowers and J. D. Cook, Serum transferrin receptor: a quantitative measure of tissue iron deficiency, *Blood*, 1990, **75**, 1870–1876.

7 Y. Beguin, Soluble transferrin receptor for the evaluation of erythropoiesis and iron status, *Clin. Chim. Acta*, 2003, **329**, 9–22.

8 B. S. Skikne, Serum transferrin receptor, *Am. J. Hematol.*, 2008, **83**, 872–874.

9 B. S. Skikne, K. Punnonen, P. H. Caldron, M. T. Bennett, M. Rehu, G. H. Gasior, J. S. Chamberlin, L. A. Sullivan, K. R. Bray and P. C. Southwick, Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: A prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index, *Am. J. Hematol.*, 2011, **86**, 923–927.

10 E. Klipp, R. Herwig, A. Kowald, C. Wierling and H. Lehrach, *Systems biology in practice: concepts, implementation and clinical application*, Wiley/VCH, Berlin, 2005.

11 D. B. Kell and J. D. Knowles, The role of modeling in systems biology, in *System modeling in cellular biology: from concepts to nuts and bolts*, ed. Z. Szallasi, J. Stelling and V. Periwal, MIT Press, Cambridge, 2006, pp. 3–18.

12 D. B. Kell, Metabolomics, modelling and machine learning in systems biology: towards an understanding of the languages of cells. The 2005 Theodor Bücher lecture, *FEBS J.*, 2006, **273**, 873–894.

13 B. Ø. Palsson, *Systems biology: properties of reconstructed networks*, Cambridge University Press, Cambridge, 2006.

14 U. Alon, *An introduction to systems biology: design principles of biological circuits*, Chapman and Hall/CRC, London, 2006.

15 D. B. Kell, Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases, *BMC Med. Genomics*, 2009, **2**, 2.

16 V. Hower, P. Mendes, F. M. Torti, R. Laubenbacher, S. Akman, V. Shulaev and S. V. Torti, A general map of iron metabolism and tissue-specific subnetworks, *Mol. Biosyst.*, 2009, **5**, 422–443.

17 D. B. Kell, Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples, *Arch. Toxicol.*, 2010, **577**, 825–889.

18 C. Funke, S. A. Schneider, D. Berg and D. B. Kell, Genetics and iron in the systems biology of Parkinson's disease and some related disorders, *Neurochem. Int.*, 2013, **62**, 637–652.

19 S. Mitchell and P. Mendes, A Computational Model of Liver Iron Metabolism, http://arxiv.org/pdf/1308.5826v1.pdf, 2013.

20 L. C. Jellen, J. L. Beard and B. C. Jones, Systems genetics analysis of iron regulation in the brain, *Biochimie*, 2009, **91**, 1255–1259.

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21 B. C. Jones, J. L. Beard, J. N. Gibson, E. L. Unger, R. P. Allen, K. A. McCarthy and C. J. Earley, Systems genetic analysis of peripheral iron parameters in the mouse, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 2007, **293**, R116–R124.
22 D. Hwang, I. Y. Lee, H. Yoo, N. Gehlenborg, J. H. Cho, B. Petritis, D. Baxter, R. Pitstick, R. Young, D. Spicer, N. D. Price, J. G. Hohmann, S. J. Dearmond, G. A. Carlson and L. E. Hood, A systems approach to prion disease, *Mol. Syst. Biol.*, 2009, **5**, 252.
23 L. Yin, E. L. Unger, L. C. Jellen, C. J. Earley, R. P. Allen, A. Tomaszewicz, J. C. Fleet and B. C. Jones, Systems genetic analysis of multivariate response to iron deficiency in mice, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 2012, **302**, R1282–R1296.
24 C. Berzuini, P. C. Franzone, M. Stefanelli and C. Viganotti, Iron kinetics: modelling and parameter estimation in normal and anemic states, *Comput. Biomed. Res.*, 1978, **11**, 209–227.
25 P. C. Franzone, A. Paganuzzi and M. Stefanelli, A mathematical model of iron metabolism, *J. Math. Biol.*, 1982, **15**, 173–201.
26 T. J. S. Lopes, T. Luganskaja, M. Vujić Spasić, M. W. Hentze, M. U. Muckenthaler, K. Schümann and J. G. Reich, Systems analysis of iron metabolism: the network of iron pools and fluxes, *BMC Syst. Biol.*, 2010, **4**, 112.
27 G. Winkelmann, Ecology of siderophores with special reference to the fungi, *Biometals*, 2007, **20**, 379–392.
28 M. Sandy and A. Butler, Microbial iron acquisition: marine and terrestrial siderophores, *Chem. Rev.*, 2009, **109**, 4580–4595.
29 R. C. Hider and X. Kong, Chemistry and biology of siderophores, *Nat. Prod. Rep.*, 2010, **27**, 637–657.
30 M. Miethke, Molecular strategies of microbial iron assimilation: from high-affinity complexes to cofactor assembly systems, *Metallomics*, 2013, **5**, 15–28.
31 S. Akatsuka, Y. Yamashita, H. Ohara, Y. T. Liu, M. Izumiya, K. Abe, M. Ochiai, L. Jiang, H. Nagai, Y. Okazaki, H. Murakami, Y. Sekido, E. Arai, Y. Kanai, O. Hino, T. Takahashi, H. Nakagama and S. Toyokuni, Fenton reaction induced cancer in wild type rats recapitulates genomic alterations observed in human cancer, *PLoS One*, 2012, **7**, e43403.
32 S. Goldstein, D. Meyerstein and G. Czapski, The Fenton reagents, *Free Radical Biol. Med.*, 1993, **15**, 435–445.
33 S. Toyokuni, Iron and carcinogenesis: from Fenton reaction to target genes, *Redox Rep.*, 2002, **7**, 189–197.
34 P. Wardman and L. P. Candeias, Fenton chemistry: An introduction, *Radiat. Res.*, 1996, **145**, 523–531.
35 C. C. Winterbourn, Toxicity of iron and hydrogen peroxide: the Fenton reaction, *Toxicol. Lett.*, 1995, **82–83**, 969–974.
36 X. Liu and E. C. Theil, Ferritins: dynamic management of biological iron and oxygen chemistry, *Acc. Chem. Res.*, 2005, **38**, 167–175.
37 E. C. Theil, H. Chen, C. Miranda, H. Janser, B. Elsenhans, M. T. Nunez, F. Pizarro and K. Schumann, Absorption of iron from ferritin is independent of heme iron and ferrous salts in women and rat intestinal segments, *J. Nutr.*, 2012, **142**, 478–483.
38 M. C. Linder, Mobilization of stored iron in mammals: a review, *Nutrients*, 2013, **5**, 4022–4050.
39 K. H. Ebrahimi, E. Bill, P. L. Hagedoorn and W. R. Hagen, The catalytic center of ferritin regulates iron storage *via* Fe(II)-Fe(III) displacement, *Nat. Chem. Biol.*, 2012, **8**, 941–948.
40 F. S. Porter, Erythrocyte ferritin, *Pediatr. Res.*, 1973, **7**, 954–957.
41 E. R. Bauminger, S. G. Cohen, S. Ofer and E. A. Rachmilewitz, Quantitative studies of ferritinlike iron in erythrocytes of thalassemia, sickle-cell anemia, and hemoglobin Hammersmith with Mössbauer spectroscopy, *Proc. Natl. Acad. Sci. U. S. A.*, 1979, **76**, 939–943.
42 A. Jacobs, S. W. Peters, E. R. Bauminger, J. Eikelboom, S. Ofer and E. A. Rachmilewitz, Ferritin concentration in normal and abnormal erythrocytes measured by immunoradiometric assay with antibodies to heart and spleen ferritin and Mössbauer spectroscopy, *Br. J. Haematol.*, 1981, **49**, 201–207.
43 M. B. Van der Weyden, H. Fong, L. Hallam and M. J. Breidahl, A rapid and simple assay for human erythrocyte ferritin, *Clin. Chim. Acta*, 1983, **127**, 397–401.
44 M. B. Van Der Weyden, H. Fong, H. H. Salem, R. G. Batey and F. J. Dudley, Erythrocyte ferritin content in idiopathic haemochromatosis and alcoholic liver disease with iron overload, *BMJ*, 1983, **286**, 752–754.
45 L. Muylle, F. L. Van de Vyver and P. P. Blockx, Erythrocyte ferritin content in idiopathic haemochromatosis and alcoholic liver disease with iron overload, *BMJ*, 1983, **286**, 2064–2065.
46 A. Piperno, M. T. Taddei, M. Sampietro, S. Fargion, P. Arosio and G. Fiorelli, Erythrocyte ferritin in thalassemia syndromes, *Acta Haematol.*, 1984, **71**, 251–256.
47 H. H. Bodemann, A. Rieger, K. J. Bross, H. Schroter-Urban and G. W. Lohr, Erythrocyte and plasma ferritin in normal subjects, blood donors and iron deficiency anemia patients, *Blut*, 1984, **48**, 131–137.
48 A. Piperno, M. Sampietro, M. T. Taddei and G. Fiorelli, Factors affecting erythrocyte ferritin content in thalassaemia intermedia, *Br. J. Haematol.*, 1984, **56**, 173–174.
49 S. W. Peters, S. J. May and A. Jacobs, Erythrocyte ferritin concentration in patients with myelodysplastic syndromes, *J. Clin. Pathol.*, 1985, **38**, 113–114.
50 M. K. Cruickshank, J. Ninness, A. Curtis, R. M. Barr, P. R. Flanagan, C. N. Ghent and L. S. Valberg, Usefulness of erythrocyte ferritin analysis in hereditary hemochromatosis, *CMAJ*, 1987, **136**, 1259–1264.
51 M. I. Oshtrakh and V. A. Semionkin, Mössbauer study of red blood cells from patients with erythremia, *FEBS Lett.*, 1989, **257**, 41–44.
52 E. R. Bauminger, E. Fibach, A. M. Konijn, S. Ofer and E. A. Rachmilewitz, Mössbauer studies of iron uptake, ferritin and hemoglobin synthesis and denaturation in erythroid cell cultures, *Hyperfine Interact.*, 1991, **66**, 11–23.
53 V. Christopoulou, A. Varsou, A. Travlou and G. Drivas, Erythrocyte ferritin in patients with chronic renal failure and heterozygous beta-thalassemia, *Nephron*, 2002, **91**, 463–467.

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54 C. Novembrino, A. Porcella, D. Conte, A. F. de Vecchi, G. Buccianti, S. Lonati, L. Duca, A. Ciani and F. Bamonti-Catena, Erythrocyte ferritin concentration: analytical performance of the immunoenzymatic IMx-Ferritin (Abbott) assay, *Clin. Chem. Lab. Med.*, 2005, **43**, 449–453.
55 H. Beving, L. E. G. Eriksson, C. L. Davey and D. B. Kell, Dielectric properties of human blood and erythrocytes at radio frequencies (0.2-10 MHz): dependence on medium composition, *Eur. Biophys. J.*, 1994, **23**, 207–215.
56 C. Cai, A. Ching, C. Lagace and T. Linsenmayer, Nuclear ferritin-mediated protection of corneal epithelial cells from oxidative damage to DNA, *Dev. Dyn.*, 2008, **237**, 2676–2683.
57 N. Surguladze, K. M. Thompson, J. L. Beard, J. R. Connor and M. G. Fried, Interactions and reactions of ferritin with DNA, *J. Biol. Chem.*, 2004, **279**, 14694–14702.
58 N. Surguladze, S. Patton, A. Cozzi, M. G. Fried and J. R. Connor, Characterization of nuclear ferritin and mechanism of translocation, *Biochem. J.*, 2005, **388**, 731–740.
59 M. V. Nurminskaya, C. J. Talbot, D. I. Nurminsky, K. E. Beazley and T. F. Linsenmayer, Nuclear ferritin: a ferritoid-ferritin complex in corneal epithelial cells, *Invest. Ophthalmol. Visual Sci.*, 2009, **50**, 3655–3661.
60 H. L. Storr, B. Kind, D. A. Parfitt, J. P. Chapple, M. Lorenz, K. Koehler, A. Huebner and A. J. Clark, Deficiency of ferritin heavy-chain nuclear import in triple A syndrome implies nuclear oxidative damage as the primary disease mechanism, *Mol. Endocrinol.*, 2009, **23**, 2086–2094.
61 A. A. Alkhateeb and J. R. Connor, Nuclear ferritin: A new role for ferritin in cell biology, *Biochim. Biophys. Acta*, 2010, **1800**, 793–797.
62 P. Arosio and S. Levi, Cytosolic and mitochondrial ferritins in the regulation of cellular iron homeostasis and oxidative damage, *Biochim. Biophys. Acta*, 2010, **1800**, 783–792.
63 A. Campanella, E. Rovelli, P. Santambrogio, A. Cozzi, F. Taroni and S. Levi, Mitochondrial ferritin limits oxidative damage regulating mitochondrial iron availability: hypothesis for a protective role in Friedreich ataxia, *Hum. Mol. Genet.*, 2009, **18**, 1–11.
64 W. S. Wu, Y. S. Zhao, Z. H. Shi, S. Y. Chang, G. J. Nie, X. L. Duan, S. M. Zhao, Q. Wu, Z. L. Yang, B. L. Zhao and Y. Z. Chang, Mitochondrial ferritin attenuates beta-amyloid-induced neurotoxicity: reduction in oxidative damage through the Erk/P38 mitogen-activated protein kinase pathways, *Antioxid. Redox Signaling*, 2013, **18**, 158–169.
65 S. C. Andrews, The Ferritin-like superfamily: Evolution of the biological iron storeman from a rubrerythrin-like ancestor, *Biochim. Biophys. Acta*, 2010, **1800**, 691–705.
66 K. Orino and K. Watanabe, Molecular, physiological and clinical aspects of the iron storage protein ferritin, *Vet. J.*, 2008, **178**, 191–201.
67 M. A. Knovich, J. A. Storey, L. G. Coffman, S. V. Torti and F. M. Torti, Ferritin for the clinician, *Blood Rev.*, 2009, **23**, 95–104.
68 W. Wang, M. A. Knovich, L. G. Coffman, F. M. Torti and S. V. Torti, Serum ferritin: Past, present and future, *Biochim. Biophys. Acta*, 2010, **1800**, 760–769.
69 R. K. Watt, The many faces of the octahedral ferritin protein, *Biometals*, 2011, **24**, 489–500.
70 E. C. Theil, Ferritin: The Protein Nanocage and Iron Biomineral in Health and in Disease, *Inorg. Chem.*, 2013, **52**, 12223–12233.
71 P. M. Harrison and P. Arosio, Ferritins: Molecular properties, iron storage function and cellular regulation, *Biochim. Biophys. Acta*, 1996, **1275**, 161–203.
72 P. Rucker, F. M. Torti and S. V. Torti, Role of H and L subunits in mouse ferritin, *J. Biol. Chem.*, 1996, **271**, 33352–33357.
73 E. C. Theil, Ferritin protein nanocages use ion channels, catalytic sites, and nucleation channels to manage iron/oxygen chemistry, *Curr. Opin. Chem. Biol.*, 2011, **15**, 304–311.
74 R. R. Crichton and J. P. Declercq, X-ray structures of ferritins and related proteins, *Biochim. Biophys. Acta*, 2010, **1800**, 706–718.
75 D. J. E. Huard, K. M. Kane and F. A. Tezcan, Re-engineering protein interfaces yields copper-inducible ferritin cage assembly, *Nat. Chem. Biol.*, 2013, **9**, 169–176.
76 F. Bou-Abdallah, G. Zhao, G. Biasiotto, M. Poli, P. Arosio and N. D. Chasteen, Facilitated diffusion of iron(II) and dioxygen substrates into human H-chain ferritin. A fluorescence and absorbance study employing the ferroxidase center substitution Y34W, *J. Am. Chem. Soc.*, 2008, **130**, 17801–17811.
77 F. Bou-Abdallah, The iron redox and hydrolysis chemistry of the ferritins, *Biochim. Biophys. Acta*, 2010, **1800**, 719–731.
78 T. Tosha, H. L. Ng, O. Bhattasali, T. Alber and E. C. Theil, Moving Metal Ions through Ferritin-Protein Nanocages from Three-Fold Pores to Catalytic Sites, *J. Am. Chem. Soc.*, 2010, **132**, 14562–14569.
79 P. Turano, D. Lalli, I. C. Felli, E. C. Theil and I. Bertini, NMR reveals pathway for ferric mineral precursors to the central cavity of ferritin, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 545–550.
80 I. Bertini, D. Lalli, S. Mangani, C. Pozzi, C. Rosa, E. C. Theil and P. Turano, Structural Insights into the Ferroxidase Site of Ferritins from Higher Eukaryotes, *J. Am. Chem. Soc.*, 2012, **134**, 6169–6176.
81 F. Carmona, Ò. Palacios, N. Gálvez, R. Cuesta, S. Atrian, M. Capdevila and J. M. Domínguez-Vera, Ferritin iron uptake and release in the presence of metals and metalloproteins: Chemical implications in the brain, *Coord. Chem. Rev.*, 2013, **257**, 2752–2764.
82 E. C. Theil, R. K. Behera and T. Tosha, Ferritins for Chemistry and for Life, *Coord. Chem. Rev.*, 2013, **257**, 579–586.
83 T. Tosha, R. K. Behera and E. C. Theil, Ferritin ion channel disorder inhibits Fe(II)/O2 reactivity at distant sites, *Inorg. Chem.*, 2012, **51**, 11406–11411.
84 R. K. Watt, A unified model for ferritin iron loading by the catalytic center: implications for controlling "free iron" during oxidative stress, *ChemBioChem*, 2013, **14**, 415–419.
85 R. K. Watt, R. J. Hilton and D. M. Graff, Oxido-reduction is not the only mechanism allowing ions to traverse the ferritin protein shell, *Biochim. Biophys. Acta*, 2010, **1800**, 745–759.

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86 M. R. Hasan, T. Tosha and E. C. Theil, Ferritin Contains Less Iron (Fe-59) in Cells When the Protein Pores Are Unfolded by Mutation, *J. Biol. Chem.*, 2008, **283**, 31394–31400.
87 J. M. Domínguez-Vera, B. Fernández and N. Gálvez, Native and synthetic ferritins for nanobiomedical applications: recent advances and new perspectives, *Future Med. Chem.*, 2010, **2**, 609–618.
88 G. Melman, F. Bou-Abdallah, E. Vane, P. Maura, P. Arosio and A. Melman, Iron release from ferritin by flavin nucleotides, *Biochim. Biophys. Acta*, 2013, **1830**, 4669–4674.
89 F. Bou-Abdallah, J. McNally, X. X. Liu and A. Melman, Oxygen catalyzed mobilization of iron from ferritin by iron(III) chelate ligands, *Chem. Commun.*, 2011, **47**, 731–733.
90 F. M. Torti and S. V. Torti, Regulation of ferritin genes and protein, *Blood*, 2002, **99**, 3505–3516.
91 H. Yamanishi, S. Iyama, Y. Yamaguchi, Y. Kanakura and Y. Iwatani, Relation between iron content of serum ferritin and clinical status factors extracted by factor analysis in patients with hyperferritinemia, *Clin. Biochem.*, 2002, **35**, 523–529.
92 T. Konz, E. Añón Alvarez, M. Montes-Bayon and A. Sanz-Medel, Antibody labeling and elemental mass spectrometry (inductively coupled plasma-mass spectrometry) using isotope dilution for highly sensitive ferritin determination and iron-ferritin ratio measurements, *Anal. Chem.*, 2013, **85**, 8334–8340.
93 Y. H. Pan, K. Sader, J. J. Powell, A. Bleloch, M. Gass, J. Trinick, A. Warley, A. Li, R. Brydson and A. Brown, 3D morphology of the human hepatic ferritin mineral core: new evidence for a subunit structure revealed by single particle analysis of HAADF-STEM images, *J. Struct. Biol.*, 2009, **166**, 22–31.
94 J. Dobson, Magnetic iron compounds in neurological disorders, *Ann. N. Y. Acad. Sci.*, 2004, **1012**, 183–192.
95 J. Gałązka-Friedman, Iron as a risk factor in neurological diseases, *Hyperfine Interact.*, 2008, **182**, 31–44.
96 D. G. Meyers, The iron hypothesis – does iron cause atherosclerosis?, *Clin. Cardiol.*, 1996, **19**, 925–929.
97 P. Arosio, M. Yokota and J. W. Drysdale, Characterization of Serum Ferritin in Iron Overload – Possible Identity to Natural Apoferritin, *Br. J. Haematol.*, 1977, **36**, 199–207.
98 M. Rudeck, T. Volk, N. Sitte and T. Grune, Ferritin oxidation *in vitro*: implication of iron release and degradation by the 20S proteasome, *IUBMB Life*, 2000, **49**, 451–456.
99 T. Z. Kidane, E. Sauble and M. C. Linder, Release of iron from ferritin requires lysosomal activity, *Am. J. Physiol.*, 2006, **291**, C445–C455.
100 Y. Zhang, M. Mikhael, D. Xu, Y. Li, S. Soe-Lin, B. Ning, W. Li, G. Nie, Y. Zhao and P. Ponka, Lysosomal proteolysis is the primary degradation pathway for cytosolic ferritin and cytosolic ferritin degradation is necessary for iron exit, *Antioxid. Redox Signaling*, 2010, **13**, 999–1009.
101 T. Asano, M. Komatsu, Y. Yamaguchi-Iwai, F. Ishikawa, N. Mizushima and K. Iwai, Distinct mechanisms of ferritin delivery to lysosomes in iron-depleted and iron-replete cells, *Mol. Cell. Biol.*, 2011, **31**, 2040–2052.
102 T. C. Iancu, Ultrastructural aspects of iron storage, transport and metabolism, *J. Neural Transm.*, 2011, **118**, 329–335.
103 A. Terman and T. Kurz, Lysosomal Iron, Iron Chelation, and Cell Death, *Antioxid. Redox Signaling*, 2013, **18**, 888–898.
104 R. Vidal, L. Miravalle, X. Gao, A. G. Barbeito, M. A. Baraibar, S. K. Hekmatyar, M. Widel, N. Bansal, M. B. Delisle and B. Ghetti, Expression of a mutant form of the ferritin light chain gene induces neurodegeneration and iron overload in transgenic mice, *J. Neurosci.*, 2008, **28**, 60–67.
105 E. Miyazaki, J. Kato, M. Kobune, K. Okumura, K. Sasaki, N. Shintani, P. Arosio and Y. Niitsu, Denatured H-ferritin subunit is a major constituent of haemosiderin in the liver of patients with iron overload, *Gut*, 2002, **50**, 413–419.
106 P. Zamboni, M. Izzo, L. Fogato, S. Carandina and V. Lanzara, Urine hemosiderin: a novel marker to assess the severity of chronic venous disease, *J. Vasc. Surg.*, 2003, **37**, 132–136.
107 C. Quintana, S. Bellefqih, J. Y. Laval, J. L. Guerquin-Kern, T. D. Wu, J. Avila, I. Ferrer, R. Arranz and C. Patino, Study of the localization of iron, ferritin, and hemosiderin in Alzheimer's disease hippocampus by analytical microscopy at the subcellular level, *J. Struct. Biol.*, 2006, **153**, 42–54.
108 C. Quintana, About the presence of hemosiderin in the hippocampus of Alzheimer patients, *J. Alzheimer's Dis.*, 2007, **12**, 157–160.
109 P. Zamboni, S. Lanzara, F. Mascoli, A. Caggiati and A. Liboni, Inflammation in venous disease, *Int. Angiol.*, 2008, **27**, 361–369.
110 F. Maldonado, J. G. Parambil, E. S. Yi, P. A. Decker and J. H. Ryu, Haemosiderin-laden macrophages in the bronchoalveolar lavage fluid of patients with diffuse alveolar damage, *Eur. Respir. J.*, 2009, **33**, 1361–1366.
111 H. L. Persson and L. K. Vainikka, Lysosomal iron in pulmonary alveolar proteinosis: a case report, *Eur. Respir. J.*, 2009, **33**, 673–679.
112 N. Sakalihasan and J. B. Michel, Functional imaging of atherosclerosis to advance vascular biology, *Eur. J. Vasc. Endovasc. Surg.*, 2009, **37**, 728–734.
113 A. Terman and U. T. Brunk, Lipofuscin, *Int. J. Biochem. Cell Biol.*, 2004, **36**, 1400–1404.
114 T. Jung, N. Bader and T. Grune, Lipofuscin: formation, distribution, and metabolic consequences, *Ann. N. Y. Acad. Sci.*, 2007, **1119**, 97–111.
115 K. L. Double, V. N. Dedov, H. Fedorow, E. Kettle, G. M. Halliday, B. Garner and U. T. Brunk, The comparative biology of neuromelanin and lipofuscin in the human brain, *Cell. Mol. Life Sci.*, 2008, **65**, 1669–1682.
116 A. Höhn, T. Jung, S. Grimm and T. Grune, Lipofuscin-bound iron is a major intracellular source of oxidants: role in senescent cells, *Free Radical Biol. Med.*, 2010, **48**, 1100–1108.
117 M. Gerlach, A. X. Trautwein, L. Zecca, M. B. H. Youdim and P. Riederer, Mössbauer Spectroscopic Studies of Purified Human Neuromelanin Isolated from the Substantia-Nigra, *J. Neurochem.*, 1995, **65**, 923–926.
118 K. L. Double, M. Gerlach, V. Schunemann, A. X. Trautwein, L. Zecca, M. Gallorini, M. B. Youdim, P. Riederer and

Open Access Article. Published on 24 January 2014. Downloaded on 9/2/2025 9:26:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

D. Ben-Shachar, Iron-binding characteristics of neuromelanin of the human substantia nigra, *Biochem. Pharmacol.*, 2003, **66**, 489–494.

119 M. Gerlach, K. L. Double, D. Ben-Shachar, L. Zecca, M. B. Youdim and P. Riederer, Neuromelanin and its interaction with iron as a potential risk factor for dopaminergic neurodegeneration underlying Parkinson's disease, *Neurotoxic Res.*, 2003, **5**, 35–44.

120 L. Zecca, M. Gallorini, V. Schunemann, A. X. Trautwein, M. Gerlach, P. Riederer, P. Vezzoni and D. Tampellini, Iron, neuromelanin and ferritin content in the substantia nigra of normal subjects at different ages: consequences for iron storage and neurodegenerative processes, *J. Neurochem.*, 2001, **76**, 1766–1773.

121 S. Bohic, K. Murphy, W. Paulus, P. Cloetens, M. Salome, J. Susini and K. Double, Intracellular Chemical Imaging of the Developmental Phases of Human Neuromelanin Using Synchrotron X-ray Microspectroscopy, *Anal. Chem.*, 2008, **80**, 9557–9566.

122 F. Tribl, E. Asan, T. Arzberger, T. Tatschner, E. Langenfeld, H. E. Meyer, G. Bringmann, P. Riederer, M. Gerlach and K. Marcus, Identification of L-ferritin in neuromelanin granules of the human substantia nigra: a targeted proteomics approach, *Mol. Cell. Proteomics*, 2009, **8**, 1832–1838.

123 H. Saito, A. Tomita, H. Ohashi, H. Maeda, H. Hayashi and T. Naoe, Determination of ferritin and hemosiderin iron in patients with normal iron stores and iron overload by serum ferritin kinetics, *Nagoya J. Med. Sci.*, 2012, **74**, 39–49.

124 H. Saito, H. Hayashi, A. Tomita, H. Ohashi, H. Maeda and T. Naoe, Increasing and Decreasing Phases of Ferritin and Hemosiderin Iron Determined by Serum Ferritin Kinetics, *Nagoya J. Med. Sci.*, 2013, **75**, 213–223.

125 G. Ricolleau, C. Charbonnel, L. Lode, D. Loussouarn, M. P. Joalland, R. Bogumil, S. Jourdain, S. Minvielle, M. Campone, R. Déporte-Fety, L. Campion and P. Jézéquel, Surface-enhanced laser desorption/ionization time of flight mass spectrometry protein profiling identifies ubiquitin and ferritin light chain as prognostic biomarkers in node-negative breast cancer tumors, *Proteomics*, 2006, **6**, 1963–1975.

126 M. E. del Castillo Busto, M. Montes-Bayón and A. Sanz-Medel, The potential of mass spectrometry to study iron-containing proteins used in clinical diagnosis, *Anal. Chim. Acta*, 2009, **634**, 1–14.

127 M. Hoppler, C. Zeder and T. Walczyk, Quantification of Ferritin-Bound Iron in Plant Samples by Isotope Tagging and Species-Specific Isotope Dilution Mass Spectrometry, *Anal. Chem.*, 2009, **81**, 7368–7372.

128 H. Q. Huang, X. H. Hu, X. P. Fang, T. M. Cao and B. Kong, Characteristics of H and L Subunits with Mass Spectrometry, Electrophoresis and Transmission Electron Microscopy in Liver Ferritin of *Dasyatis Akajei*, *Chin. J. Anal. Chem.*, 2009, **37**, 631–636.

129 P. Nielsen, U. Günther, M. Dürken, R. Fischer and J. Düllmann, Serum ferritin iron in iron overload and liver damage: Correlation to body iron stores and diagnostic relevance, *J. Lab. Clin. Med.*, 2000, **135**, 413–418.

130 K. Watanabe, Y. Yamashita, K. Ohgawara, M. Sekiguchi, N. Satake, K. Orino and S. Yamamoto, Iron content of rat serum ferritin, *J. Vet. Med. Sci.*, 2001, **63**, 587–589.

131 N. Bresgen, H. Jaksch, H. Lacher, I. Ohlenschlager, K. Uchida and P. M. Eckl, Iron-mediated oxidative stress plays an essential role in ferritin-induced cell death, *Free Radical Biol. Med.*, 2010, **48**, 1347–1357.

132 A. A. Alkhateeb, B. Han and J. R. Connor, Ferritin stimulates breast cancer cells through an iron-independent mechanism and is localized within tumor-associated macrophages, *Breast Cancer Res. Treat.*, 2013, **137**, 733–744.

133 T. Kurz, B. Gustafsson and U. T. Brunk, Cell sensitivity to oxidative stress is influenced by ferritin autophagy, *Free Radical Biol. Med.*, 2011, **50**, 1647–1658.

134 B. Garner, K. Roberg and U. T. Brunk, Endogenous ferritin protects cells with iron-laden lysosomes against oxidative stress, *Free Radical Res.*, 1998, **29**, 103–114.

135 B. Garner, W. Li, K. Roberg and U. T. Brunk, On the cytoprotective role of ferritin in macrophages and its ability to enhance lysosomal stability, *Free Radical Res.*, 1997, **27**, 487–500.

136 H. L. Persson, K. J. Nilsson and U. T. Brunk, Novel cellular defenses against iron and oxidation: ferritin and autophagocytosis preserve lysosomal stability in airway epithelium, *Redox Rep.*, 2001, **6**, 57–63.

137 T. Kurz, J. W. Eaton and U. T. Brunk, The role of lysosomes in iron metabolism and recycling, *Int. J. Biochem. Cell Biol.*, 2011, **43**, 1686–1697.

138 C. Ferreira, D. Bucchini, M. E. Martin, S. Levi, P. Arosio, B. Grandchamp and C. Beaumont, Early embryonic lethality of H ferritin gene deletion in mice, *J. Biol. Chem.*, 2000, **275**, 3021–3024.

139 C. Ferreira, P. Santambrogio, M. E. Martin, V. Andrieu, G. Feldmann, D. Henin and C. Beaumont, H ferritin knockout mice: a model of hyperferritinemia in the absence of iron overload, *Blood*, 2001, **98**, 525–532.

140 J. t. Wilkinson, X. Di, K. Schönig, J. L. Buss, N. D. Kock, J. M. Cline, T. L. Saunders, H. Bujard, S. V. Torti and F. M. Torti, Tissue-specific expression of ferritin H regulates cellular iron homoeostasis *in vivo*, *Biochem. J.*, 2006, **395**, 501–507.

141 G. Hetet, I. Devaux, N. Soufir, B. Grandchamp and C. Beaumont, Molecular analyses of patients with hyperferritinemia and normal serum iron values reveal both L ferritin IRE and 3 new ferroportin (SLC11A3) mutations, *Blood*, 2003, **102**, 1904–1910.

142 K. P. Burdon, S. Sharma, C. S. Chen, D. P. Dimasi, D. A. Mackey and J. E. Craig, A novel deletion in the FTL gene causes hereditary hyperferritinemia cataract syndrome (HHCS) by alteration of the transcription start site, *Hum. Mutat.*, 2007, **28**, 742.

143 C. Kannengiesser, A. M. Jouanolle, G. Hetet, A. Mosser, F. Muzeau, D. Henry, E. Bardou-Jacquet, M. Mornet, P. Brissot, Y. Deugnier, B. Grandchamp and C. Beaumont, A new missense mutation in the L ferritin coding sequence associated with elevated levels of glycosylated ferritin in

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serum and absence of iron overload, *Haematologica*, 2009, **94**, 335–339.

144 J. Álvarez-Coca-Gonzalez, M. I. Moreno-Carralero, J. Martinez-Pérez, M. Méndez, M. García-Ros and M. J. Morán-Jiménez, The hereditary hyperferritinemia-cataract syndrome: a family study, *Eur. J. Pediatr.*, 2010, **169**, 1553–1555.

145 C. Beaumont, Miscellaneous Iron-Related Disorders, in *Iron Physiology and Pathophysiology in Humans*, ed. G. J. Anderson and G. D. McLaren, 2012, pp. 417–439.

146 S. Luscieti, G. Tolle, J. Aranda, C. B. Campos, F. Risse, É. Morán, M. U. Muckenthaler and M. Sánchez, Novel mutations in the ferritin-L iron-responsive element that only mildly impair IRP binding cause hereditary hyperferritinaemia cataract syndrome, *Orphanet. J. Rare Dis.*, 2013, **8**, 30.

147 G. A. Agasthya, B. C. Harrawood, J. P. Shah and A. J. Kapadia, Sensitivity analysis for liver iron measurement through neutron stimulated emission computed tomography: a Monte Carlo study in GEANT4, *Phys. Med. Biol.*, 2012, **57**, 113–126.

148 P. Nielsen, R. Engelhardt, J. Dullmann and R. Fischer, Non-invasive liver iron quantification by SQUID-biosusceptometry and serum ferritin iron as new diagnostic parameters in hereditary hemochromatosis, *Blood Cells, Mol., Dis.*, 2002, **29**, 451–458.

149 A. Castiella, J. M. Alústiza, J. I. Emparanza, E. M. Zapata, B. Costero and M. I. Díez, Liver iron concentration quantification by MRI: are recommended protocols accurate enough for clinical practice?, *Eur. Radiol.*, 2010, **21**, 137–141.

150 M. I. Argyropoulou and L. Astrakas, MRI evaluation of tissue iron burden in patients with beta-thalassaemia major, *Pediatr. Radiol.*, 2007, **37**, 1191–1200; quiz 1308-1199.

151 O. Dereure, N. Jumez, D. Bessis, B. Gallix and B. Guillot, Measurement of liver iron content by magnetic resonance imaging in 20 patients with overt porphyria cutanea tarda before phlebotomy therapy: a prospective study, *Acta Derm.-Venereol.*, 2008, **88**, 341–345.

152 K. M. Musallam, M. D. Cappellini, J. C. Wood, I. Motta, G. Graziadei, H. Tamim and A. T. Taher, Elevated liver iron concentration is a marker of increased morbidity in patients with beta thalassemia intermedia, *Haematologica*, 2011, **96**, 1605–1612.

153 K. M. Musallam, M. D. Cappellini and A. T. Taher, Evaluation of the 5mg/g liver iron concentration threshold and its association with morbidity in patients with beta-thalassemia intermedia, *Blood Cells, Mol., Dis.*, 2013, **51**, 35–38.

154 V. Positano, B. Salani, A. Pepe, M. F. Santarelli, D. De Marchi, A. Ramazzotti, B. Favilli, E. Cracolici, M. Midiri, P. Cianciulli, M. Lombardi and L. Landini, Improved T2* assessment in liver iron overload by magnetic resonance imaging, *Magn. Reson. Imaging*, 2009, **27**, 188–197.

155 C. Rose, P. Vandevenne, E. Bourgeois, N. Cambier and O. Ernst, Liver iron content assessment by routine and simple magnetic resonance imaging procedure in highly transfused patients, *Eur. J. Haematol.*, 2006, **77**, 145–149.

156 K. Tziomalos and V. Perifanis, Liver iron content determination by magnetic resonance imaging, *World J. Gastroenterol.*, 2010, **16**, 1587–1597.

157 S. Tony, S. Daar, M. Elshinawy, S. Al-Zadjaly, M. Al-Khabori and Y. Wali, T2* MRI in regularly transfused children with thalassemia intermedia: serum ferritin does not reflect liver iron stores, *Pediatr. Hematol. Oncol.*, 2012, **29**, 579–584.

158 K. Ziv, G. Meir, A. Harmelin, E. Shimoni, E. Klein and M. Neeman, Ferritin as a reporter gene for MRI: chronic liver over expression of H-ferritin during dietary iron supplementation and aging, *NMR Biomed.*, 2010, **23**, 523–531.

159 E. M. Haacke, N. Y. Cheng, M. J. House, Q. Liu, J. Neelavalli, R. J. Ogg, A. Khan, M. Ayaz, W. Kirsch and A. Obenaus, Imaging iron stores in the brain using magnetic resonance imaging, *Magn. Reson. Imaging*, 2005, **23**, 1–25.

160 W. Kirsch, G. McAuley, B. Holshouser, F. Petersen, M. Ayaz, H. V. Vinters, C. Dickson, E. M. Haacke, W. Britt Iii, J. Larsen, I. Kim, C. Mueller, M. Schrag and D. Kido, Serial susceptibility weighted MRI measures brain iron and microbleeds in dementia, *J. Alzheimer's Dis.*, 2009, **17**, 599–609.

161 W. Zheng, H. Nichol, S. Liu, Y. C. Cheng and E. M. Haacke, Measuring iron in the brain using quantitative susceptibility mapping and X-ray fluorescence imaging, *NeuroImage*, 2013, **78C**, 68–74.

162 M. J. Kim, D. G. Mitchell, K. Ito, H. W. Hann, Y. N. Park and P. N. Kim, Hepatic iron deposition on MR imaging in patients with chronic liver disease: correlation with serial serum ferritin concentration, *Abdom. Imaging*, 2001, **26**, 149–156.

163 A. W. Olthof, P. E. Sijens, H. G. Kreeftenberg, P. Kappert, R. Irwan, E. J. van der Jagt and M. Oudkerk, Correlation between serum ferritin levels and liver iron concentration determined by MR imaging: impact of hematologic disease and inflammation, *Magn. Reson. Imaging*, 2007, **25**, 228–231.

164 O. G. Papakonstantinou, T. G. Maris, V. Kostaridou, A. D. Gouliamos, G. K. Koutoulas, A. E. Kalovidouris, G. B. Papavassiliou, G. Kordas, C. Kattamis and L. J. Vlahos, *et al.*, Assessment of liver iron overload by T2-quantitative magnetic resonance imaging: correlation of T2-QMRI measurements with serum ferritin concentration and histologic grading of siderosis, *Magn. Reson. Imaging*, 1995, **13**, 967–977.

165 P. D. Jensen, F. T. Jensen, T. Christensen and J. Ellegaard, Evaluation of transfusional iron overload before and during iron chelation by magnetic resonance imaging of the liver and determination of serum ferritin in adult non-thalassaemic patients, *Br. J. Haematol.*, 1995, **89**, 880–889.

166 P. D. Jensen, F. T. Jensen, T. Christensen, H. Eiskjaer, U. Baandrup and J. L. Nielsen, Evaluation of myocardial iron by magnetic resonance imaging during iron chelation therapy with deferrioxamine: indication of close relation between myocardial iron content and chelatable iron pool, *Blood*, 2003, **101**, 4632–4639.

167 P. D. Jensen, F. T. Jensen, T. Christensen, J. L. Nielsen and J. Ellegaard, Relationship between hepatocellular injury and transfusional iron overload prior to and during iron

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chelation with desferrioxamine: a study in adult patients with acquired anemias, *Blood*, 2003, **101**, 91–96.

168 Z. Pakbaz, R. Fischer, E. Fung, P. Nielsen, P. Harmatz and E. Vichinsky, Serum ferritin underestimates liver iron concentration in transfusion independent thalassemia patients as compared to regularly transfused thalassemia and sickle cell patients, *Pediatr. Blood Cancer*, 2007, **49**, 329–332.

169 A. Taher, F. El Rassi, H. Isma'eel, S. Koussa, A. Inati and M. D. Cappellini, Correlation of liver iron concentration determined by R2 magnetic resonance imaging with serum ferritin in patients with thalassemia intermedia, *Haematologica*, 2008, **93**, 1584–1586.

170 A. Kolnagou, K. Natsiopoulos, M. Kleanthous, A. Ioannou and G. J. Kontoghiorghes, Liver iron and serum ferritin levels are misleading for estimating cardiac, pancreatic, splenic and total body iron load in thalassemia patients: factors influencing the heterogenic distribution of excess storage iron in organs as identified by MRI T2*, *Toxicol. Mech. Methods*, 2013, **23**, 48–56.

171 D. A. Tsitsikas, R. Nzouakou, V. Ameen, B. Sirigireddy and R. J. Amos, Comparison of Serial Serum Ferritin Measurements and Liver Iron Concentration Assessed by MRI in Adult Transfused Patients with Sickle Cell Disease, *Eur. J. Haematol.*, 2014, **92**, 164–167.

172 B. J. Ferguson, B. S. Skikne, K. M. Simpson, R. D. Baynes and J. D. Cook, Serum Transferrin Receptor Distinguishes the Anemia of Chronic Disease from Iron-Deficiency Anemia, *J. Lab. Clin. Med.*, 1992, **119**, 385–390.

173 K. Punnonen, K. Irjala and A. Rajamäki, Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency, *Blood*, 1997, **89**, 1052–1057.

174 J. D. Cook, Diagnosis and management of iron-deficiency anaemia, *Best Pract. Res., Clin. Haematol.*, 2005, **18**, 319–332.

175 E. Hanif, M. Ayyub, M. Anwar, W. Ali and M. Bashir, Evaluation of serum transferrin receptor concentration in diagnosing and differentiating iron deficiency anaemia from anaemia of chronic disorders, *J. Pak. Med. Assoc.*, 2005, **55**, 13–16.

176 E. Joosten, R. Van Loon, J. Billen, N. Blanckaert, R. Fabri and W. Pelemans, Serum transferrin receptor in the evaluation of the iron status in elderly hospitalized patients with anemia, *Am. J. Hematol.*, 2002, **69**, 1–6.

177 A. Skoumalová and J. Hort, Blood markers of oxidative stress in Alzheimer's disease, *J. Cell. Mol. Med.*, 2012, **16**, 2291–2300.

178 K. Henriksen, S. E. O'Bryant, H. Hampel, J. Q. Trojanowski, T. J. Montine, A. Jeromin, K. Blennow, A. Lönneborg, T. Wyss-Coray, H. Soares, C. Bazenet, M. Sjögren, W. Hu, S. Lovestone, M. A. Karsdal and M. W. Weiner, The future of blood-based biomarkers for Alzheimer's disease, *Alzheimer's Dementia*, 2014, **10**, 115–131.

179 M. Schrag, C. Mueller, M. Zabel, A. Crofton, W. M. Kirsch, O. Ghribi, R. Squitti and G. Perry, Oxidative stress in blood in Alzheimer's disease and mild cognitive impairment: a meta-analysis, *Neurobiol. Dis.*, 2013, **59**, 100–110.

180 K. Ikeda, Y. Nakamura, T. Kiyozuka, J. Aoyagi, T. Hirayama, R. Nagata, H. Ito, K. Iwamoto, K. Murata, Y. Yoshii, K. Kawabe and Y. Iwasaki, Serological profiles of urate, paraoxonase-1, ferritin and lipid in Parkinson's disease: changes linked to disease progression, *Neurodegener. Dis.*, 2011, **8**, 252–258.

181 K. G. Connelly, M. Moss, P. E. Parsons, E. E. Moore, F. A. Moore, P. C. Giclas, P. A. Seligman and J. E. Repine, Serum ferritin as a predictor of the acute respiratory distress syndrome, *Am. J. Respir. Crit. Care Med.*, 1997, **155**, 21–25.

182 R. A. Sharkey, S. C. Donnelly, K. G. Connelly, C. E. Robertson, C. Haslett and J. E. Repine, Initial serum ferritin levels in patients with multiple trauma and the subsequent development of acute respiratory distress syndrome, *Am. J. Respir. Crit. Care Med.*, 1999, **159**, 1506–1509.

183 A. L. Lagan, G. J. Quinlan, S. Mumby, D. D. Melley, P. Goldstraw, G. J. Bellingan, M. R. Hill, D. Briggs, P. Pantelidis, R. M. du Bois, K. I. Welsh and T. W. Evans, Variation in iron homeostasis genes between patients with ARDS and healthy control subjects, *Chest*, 2008, **133**, 1302–1311.

184 Y. Y. Park, Ischemia/reperfusion Lung Injury Increases Serum Ferritin and Heme Oxygenase-1 in Rats, *Korean J. Physiol. Pharmacol.*, 2009, **13**, 181–187.

185 E. F. Goodall, M. S. Haque and K. E. Morrison, Increased serum ferritin levels in amyotrophic lateral sclerosis (ALS) patients, *J. Neurol.*, 2008, **255**, 1652–1656.

186 M. Qureshi, R. H. Brown Jr., J. T. Rogers and M. E. Cudkowicz, Serum ferritin and metal levels as risk factors for amyotrophic lateral sclerosis, *Open Neurol. J.*, 2008, **2**, 51–54.

187 K. Ikeda, T. Hirayama, T. Takazawa, K. Kawabe and Y. Iwasaki, Relationships between Disease Progression and Serum Levels of Lipid, Urate, Creatinine and Ferritin in Japanese Patients with Amyotrophic Lateral Sclerosis: A Cross-Sectional Study, *Intern. Med.*, 2012, **51**, 1501–1508.

188 Y. Nadjar, P. Gordon, P. Corcia, G. Bensimon, L. Pieroni, V. Meininger and F. Salachas, Elevated serum ferritin is associated with reduced survival in amyotrophic lateral sclerosis, *PLoS One*, 2012, **7**, e45034.

189 X. W. Su, Z. Simmons, R. M. Mitchell, L. Kong, H. E. Stephens and J. R. Connor, Biomarker-Based Predictive Models for Prognosis in Amyotrophic Lateral Sclerosis, *JAMA Neurol.*, 2013, **70**, 1505–1511.

190 S. Kiechl, J. Willeit, G. Egger, W. Poewe and F. Oberhollenzer, Body iron stores and the risk of carotid atherosclerosis: prospective results from the Bruneck study, *Circulation*, 1997, **96**, 3300–3307.

191 S. A. You, S. R. Archacki, G. Angheloiu, C. S. Moravec, S. Rao, M. Kinter, E. J. Topol and Q. Wang, Proteomic approach to coronary atherosclerosis shows ferritin light chain as a significant marker: evidence consistent with iron hypothesis in atherosclerosis, *Physiol. Genomics*, 2003, **13**, 25–30.

192 B. Wolff, H. Volzke, J. Ludemann, D. Robinson, D. Vogelgesang, A. Staudt, C. Kessler, J. B. Dahm, U. John and S. B. Felix,

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Association between high serum ferritin levels and carotid atherosclerosis in the study of health in Pomerania (SHIP), *Stroke*, 2004, **35**, 453–457.

193 K. A. Reis, G. Guz, H. Ozdemir, Y. Erten, V. Atalay, Z. Bicik, Z. N. Ozkurt, M. Bali and S. Sindel, Intravenous iron therapy as a possible risk factor for atherosclerosis in end-stage renal disease, *Int. Heart J.*, 2005, **46**, 255–264.

194 S. A. You and Q. Wang, Ferritin in atherosclerosis, *Clin. Chim. Acta*, 2005, **357**, 1–16.

195 J. J. M. Marx, A. E. R. Kartikasari and N. A. Georgiou, Can iron chelators influence the progression of atherosclerosis?, *Hemoglobin*, 2008, **32**, 123–134.

196 J. L. Sullivan, Iron in arterial plaque: A modifiable risk factor for atherosclerosis, *Biochim. Biophys. Acta*, 2009, **1790**, 718–723.

197 N. Ahluwalia, A. Genoux, J. Ferrieres, B. Perret, M. Carayol, L. Drouet and J. B. Ruidavets, Iron status is associated with carotid atherosclerotic plaques in middle-aged adults, *J. Nutr.*, 2010, **140**, 812–816.

198 R. G. DePalma, V. W. Hayes, B. K. Chow, G. Shamayeva, P. E. May and L. R. Zacharski, Ferritin levels, inflammatory biomarkers, and mortality in peripheral arterial disease: A substudy of the Iron (Fe) and Atherosclerosis Study (FeAST) Trial, *J. Vasc. Surg.*, 2010, **51**, 1498–1503.

199 P. Syrovatka, P. Kraml, K. Hulikova, L. Fialova, M. Vejrazka, J. Crkovska, J. Potockova and M. Andel, Iron stores are associated with asymptomatic atherosclerosis in healthy men of primary prevention, *Eur. J. Clin. Invest.*, 2011, **41**, 846–853.

200 L. R. Zacharski, R. G. Depalma, G. Shamayeva and B. K. Chow, The Statin-Iron Nexus: Anti-Inflammatory Intervention for Arterial Disease Prevention, *Am. J. Public Health*, 2013, **103**, e105–e112.

201 J. T. Hazard and J. W. Drysdale, Ferritinaemia in cancer, *Nature*, 1977, **265**, 755–756.

202 B. M. Jones, M. Worwood and A. Jacobs, Serum ferritin in patients with cancer: determination with antibodies to HeLa cell and spleen ferritin, *Clin. Chim. Acta*, 1980, **106**, 203–214.

203 A. Jacobs, Serum ferritin and malignant tumours, *Med. Oncol. Tumor Pharmacother.*, 1984, **1**, 149–156.

204 J. H. Silber, A. E. Evans and M. Fridman, Models to Predict Outcome from Childhood Neuroblastoma – the Role of Serum Ferritin and Tumor Histology, *Cancer Res.*, 1991, **51**, 1426–1433.

205 R. L. Nelson, F. G. Davis, E. Sutter, L. H. Sobin, J. W. Kikendall and P. Bowen, Body iron stores and risk of colonic neoplasia, *J. Natl. Cancer Inst.*, 1994, **86**, 455–460.

206 Z. Kırkalı, M. Güzelsoy, M. U. Mungan, G. Kırkalı and K. Yörükoğlu, Serum ferritin as a clinical marker for renal cell carcinoma: influence of tumor size and volume, *Urol. Int.*, 1999, **62**, 21–25.

207 S. Hercberg, C. Estaquio, S. Czernichow, L. Mennen, N. Noisette, S. Bertrais, J. C. Renversez, S. Briancon, A. Favier and P. Galan, Iron status and risk of cancers in the SU.VI.MAX cohort, *J. Nutr.*, 2005, **135**, 2664–2668.

208 L. R. Zacharski, B. K. Chow, P. S. Howes, G. Shamayeva, J. A. Baron, R. L. Dalman, D. J. Malenka, C. K. Ozaki and P. W. Lavori, Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial, *J. Natl. Cancer Inst.*, 2008, **100**, 996–1002.

209 K. H. Zhang, H. Y. Tian, X. Gao, W. W. Lei, Y. Hu, D. M. Wang, X. C. Pan, M. L. Yu, G. J. Xu, F. K. Zhao and J. G. Song, Ferritin heavy chain-mediated iron homeostasis and subsequent increased reactive oxygen species production are essential for epithelial-mesenchymal transition, *Cancer Res.*, 2009, **69**, 5340–5348.

210 A. A. Alkhateeb, K. Leitzel, S. M. Ali, C. Campbell-Baird, M. Evans, E. M. Fuchs, W. J. Köstler, A. Lipton and J. Connor, Elevation in inflammatory serum biomarkers predicts response to trastuzumab-containing therapy, *PLoS One*, 2012, **7**, e51379.

211 A. A. Alkhateeb and J. R. Connor, The significance of ferritin in cancer: Anti-oxidation, inflammation and tumorigenesis, *Biochim. Biophys. Acta*, 2013, **1836**, 245–254.

212 A. Amid, N. Barrowman, A. Vijenthira, P. Lesser, K. Mandel and R. Ramphal, Risk factors for hyperferritinemia secondary to red blood cell transfusions in pediatric cancer patients, *Pediatr. Blood Cancer*, 2013, **60**, 1671–1675.

213 A. Alkhateeb, L. Zubritsky, B. Kinsman, K. Leitzel, C. Campbell-Baird, S. M. Ali, J. Connor and A. Lipton, Elevation in Multiple Serum Inflammatory Biomarkers Predicts Survival of Pancreatic Cancer Patients with Inoperable Disease, *J. Gastrointest. Cancer*, 2014, DOI: 10.1007/12029-013-9564-9.

214 R. Orlandi, M. De Bortoli, C. M. Ciniselli, E. Vaghi, D. Caccia, V. Garrisi, S. Pizzamiglio, S. Veneroni, C. Bonini, R. Agresti, M. G. Daidone, D. Morelli, C. Camaschella, P. Verderio and I. Bongarzone, Hepcidin and ferritin blood level as noninvasive tools for predicting breast cancer, *Ann. Oncol.*, 2014, DOI: 10.1093/annonc/mdt490.

215 K. Jurczyk, M. Wawrzynowicz-Syczewska, A. Boroń-Kaczmarska and Z. Sych, Serum iron parameters in patients with alcoholic and chronic cirrhosis and hepatitis, *Med. Sci. Monit.*, 2001, **7**, 962–965.

216 D. H. G. Crawford, T. L. Murphy, L. E. Ramm, L. M. Fletcher, A. D. Clouston, G. J. Anderson, V. N. Subramaniam, L. W. Powell and G. A. Ramm, Serum Hyaluronic Acid with Serum Ferritin Accurately Predicts Cirrhosis and Reduces the Need for Liver Biopsy in C282Y Hemochromatosis, *Hepatology*, 2009, **49**, 418–425.

217 T. C. H. Tan, D. H. Crawford, M. E. Franklin, L. A. Jaskowski, G. A. Macdonald, J. R. Jonsson, M. J. Watson, P. J. Taylor and L. M. Fletcher, The serum hepcidin:ferritin ratio is a potential biomarker for cirrhosis, *Liver Int.*, 2012, **32**, 1391–1399.

218 M. E. Olesnevich, M. Fanelli Kuczmarski, M. Mason, C. Fang, A. B. Zonderman and M. K. Evans, Serum ferritin levels associated with increased risk for developing CHD in a low-income urban population, *Public Health Nutr.*, 2012, **15**, 1291–1298.

219 K. C. Sung, S. M. Kang, E. J. Cho, J. B. Park, S. H. Wild and C. D. Byrne, Ferritin is independently associated with the

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presence of coronary artery calcium in 12,033 men, *Arterioscler., Thromb., Vasc. Biol.*, 2012, **32**, 2525–2530.

220 Y. Zhou, T. Liu, C. Tian, P. Kang and C. Jia, Association of serum ferritin with coronary artery disease, *Clin. Biochem.*, 2012, **45**, 1336–1341.

221 B. Ponikowska, T. Suchocki, B. Paleczny, M. Olesinska, S. Powierza, L. Borodulin-Nadzieja, K. Reczuch, S. von Haehling, W. Doehner, S. D. Anker, J. G. Cleland and E. A. Jankowska, Iron Status and Survival in Diabetic Patients With Coronary Artery Disease, *Diabetes Care*, 2013, **36**, 4147–4156.

222 J. T. Salonen, T. P. Tuomainen, K. Nyyssonen, H. M. Lakka and K. Punnonen, Relation between iron stores and non-insulin dependent diabetes in men: case-control study, *BMJ*, 1998, **317**, 727.

223 E. S. Ford and M. E. Cogswell, Diabetes and serum ferritin concentration among U.S. adults, *Diabetes Care*, 1999, **22**, 1978–1983.

224 J. G. Wilson, J. H. Lindquist, S. C. Grambow, E. D. Crook and J. F. Maher, Potential role of increased iron stores in diabetes, *Am. J. Med. Sci.*, 2003, **325**, 332–339.

225 R. Jiang, J. E. Manson, J. B. Meigs, J. Ma, N. Rifai and F. B. Hu, Body iron stores in relation to risk of type 2 diabetes in apparently healthy women, *JAMA*, 2004, **291**, 711–717.

226 M. Mert, M. Korkmaz, M. Temizel and M. Acar, The Level of Ferritin in Diabetic and Nondiabetic Patients with Acute Myocardial Infarction, *Turk. J. Med. Sci.*, 2005, **35**, 25–34.

227 R. T. Acton, J. C. Barton, L. V. Passmore, P. C. Adams, M. R. Speechley, F. W. Dawkins, P. Sholinsky, D. M. Reboussin, G. D. McLaren, E. L. Harris, T. C. Bent, T. M. Vogt and O. Castro, Relationships of serum ferritin, transferrin saturation, and HFE mutations and self-reported diabetes in the Hemochromatosis and Iron Overload Screening (HEIRS) study, *Diabetes Care*, 2006, **29**, 2084–2089.

228 E. M. Alissa, W. H. Ahmed, N. Al-Ama and G. A. Ferns, Relationship between indices of iron status and coronary risk factors including diabetes and the metabolic syndrome in Saudi subjects without overt coronary disease, *J. Trace Elem. Med. Biol.*, 2007, **21**, 242–254.

229 N. G. Forouhi, A. H. Harding, M. Allison, M. S. Sandhu, A. Welch, R. Luben, S. Bingham, K. T. Khaw and N. J. Wareham, Elevated serum ferritin levels predict new-onset type 2 diabetes: results from the EPIC-Norfolk prospective study, *Diabetologia*, 2007, **50**, 949–956.

230 M. L. Jehn, E. Guallar, J. M. Clark, D. Couper, B. B. Duncan, C. M. Ballantyne, R. C. Hoogeveen, Z. L. Harris and J. S. Pankow, A prospective study of plasma ferritin level and incident diabetes: the Atherosclerosis Risk in Communities (ARIC) Study, *Am. J. Epidemiol.*, 2007, **165**, 1047–1054.

231 L. Sun, O. H. Franco, F. B. Hu, L. Cai, Z. Yu, H. Li, X. Ye, Q. Qi, J. Wang, A. Pan, Y. Liu and X. Lin, Ferritin concentrations, metabolic syndrome, and type 2 diabetes in middle-aged and elderly chinese, *J. Clin. Endocrinol. Metab.*, 2008, **93**, 4690–4696.

232 J. A. Kolberg, T. Jørgensen, R. W. Gerwien, S. Hamren, M. P. McKenna, E. Moler, M. W. Rowe, M. S. Urdea, X. M. Xu, T. Hansen, O. Pedersen and K. Borch-Johnsen, Development of a type 2 diabetes risk model from a panel of serum biomarkers from the Inter99 cohort, *Diabetes Care*, 2009, **32**, 1207–1212.

233 S. N. Rajpathak, J. P. Crandall, J. Wylie-Rosett, G. C. Kabat, T. E. Rohan and F. B. Hu, The role of iron in type 2 diabetes in humans, *Biochim. Biophys. Acta*, 2009, **1790**, 671–681.

234 C. H. Kim, H. K. Kim, S. J. Bae, J. Y. Park and K. U. Lee, Association of elevated serum ferritin concentration with insulin resistance and impaired glucose metabolism in Korean men and women, *Metabolism*, 2011, **60**, 414–420.

235 B. K. Lee, Y. Kim and Y. I. Kim, Association of serum ferritin with metabolic syndrome and diabetes mellitus in the South Korean general population according to the Korean National Health and Nutrition Examination Survey 2008, *Metabolism*, 2011, **60**, 1416–1424.

236 J. H. Ryoo, M. G. Kim, D. W. Lee and J. Y. Shin, The relationship between serum ferritin and metabolic syndrome in healthy Korean men, *Diabetes/Metab. Res. Rev.*, 2011, **27**, 597–603.

237 W. Bao, Y. Rong, S. Rong and L. Liu, Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a systematic review and meta-analysis, *BMC Med.*, 2012, **10**, 119.

238 V. Lyssenko, T. Jørgensen, R. W. Gerwien, T. Hansen, M. W. Rowe, M. P. McKenna, J. Kolberg, O. Pedersen, K. Borch-Johnsen and L. Groop, Validation of a multi-marker model for the prediction of incident type 2 diabetes mellitus: combined results of the Inter99 and Botnia studies, *Diabet. Vasc. Dis. Res.*, 2012, **9**, 59–67.

239 J. Montonen, H. Boeing, A. Steffen, R. Lehmann, A. Fritsche, H. G. Joost, M. B. Schulze and T. Pischon, Body iron stores and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study, *Diabetologia*, 2012, **55**, 2613–2621.

240 Z. Zhao, S. Li, G. Liu, F. Yan, X. Ma, Z. Huang and H. Tian, Body iron stores and heme-iron intake in relation to risk of type 2 diabetes: a systematic review and meta-analysis, *PLoS One*, 2012, **7**, e41641.

241 A. O. Aregbesola, S. Voutilainen, J. K. Virtanen, J. Mursu and T. P. Tuomainen, Body Iron Stores and the Risk of Type 2 Diabetes in Middle-Aged Men, *Eur. J. Endocrinol.*, 2013, **169**, 247–253.

242 B. Batchuluun, T. Matsumata, N. Erdenebileg, G. Tsagaantsooj, K. Boldbaatar and A. Khasag, Serum ferritin level is higher in poorly controlled patients with Type 2 diabetes and people without diabetes, aged over 55 years, *Diabetic Med.*, 2013, DOI: 10.1111/dme.12343.

243 X. Guo, D. Zhou, P. An, Q. Wu, H. Wang, A. Wu, M. Mu, D. Zhang, Z. Zhang, L. He, Y. Liu and F. Wang, Associations between serum hepcidin, ferritin and Hb concentrations and type 2 diabetes risks in a Han Chinese population, *Br. J. Nutr.*, 2013, 1–6.

244 C. H. Jung, M. J. Lee, J. Y. Hwang, J. E. Jang, J. Leem, J. Y. Park, J. Lee, H. K. Kim and W. J. Lee, Elevated serum ferritin level is associated with the incident type 2 diabetes

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in healthy korean men: a 4 year longitudinal study, *PLoS One*, 2013, **8**, e75250.

245 D. Kundu, A. Roy, T. Mandal, U. Bandyopadhyay, E. Ghosh and D. Ray, Relation of iron stores to oxidative stress in type 2 diabetes, *Niger. J. Clin. Pract.*, 2013, **16**, 100–103.

246 S. K. Kunutsor, T. A. Apekey, J. Walley and K. Kain, Ferritin levels and risk of type 2 diabetes mellitus: an updated systematic review and meta-analysis of prospective evidence, *Diabetes/Metab. Res. Rev.*, 2013, **29**, 308–318.

247 L. Sun, G. Zong, A. Pan, X. W. Ye, H. X. Li, Z. J. Yu, Y. Zhao, S. R. Zou, D. X. Yu, Q. L. Jin, F. B. Hu and X. Lin, Elevated Plasma Ferritin Is Associated with Increased Incidence of Type 2 Diabetes in Middle-Aged and Elderly Chinese Adults, *J. Nutr.*, 2013, **143**, 1459–1465.

248 D. L. White and A. Collinson, Red meat, dietary heme iron, and risk of type 2 diabetes: the involvement of advanced lipoxidation endproducts, *Adv. Nutr.*, 2013, **4**, 403–411.

249 N. Wlazlo, M. M. J. van Greevenbroek, I. Ferreira, E. H. J. M. Jansen, E. J. M. Feskens, C. J. H. van der Kallen, C. G. Schalkwijk, B. Bravenboer and C. D. A. Stehouwer, Iron metabolism is associated with adipocyte insulin resistance and plasma adiponectin: the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) study, *Diabetes Care*, 2013, **36**, 309–315.

250 A. Piperno, P. Trombini, M. Gelosa, V. Mauri, V. Pecci, A. Vergani, A. Salvioni, R. Mariani and G. Mancia, Increased serum ferritin is common in men with essential hypertension, *J. Hypertens.*, 2002, **20**, 1513–1518.

251 E. Coban, E. Alkan, S. Altuntas and Y. Akar, Serum ferritin levels correlate with hypertensive retinopathy, *Med. Sci. Monit.*, 2010, **16**, CR92–CR95.

252 K. S. Houschyar, R. Lüdtke, G. J. Dobos, U. Kalus, M. Broecker-Preuss, T. Rampp, B. Brinkhaus and A. Michalsen, Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: results from a randomized clinical trial, *BMC Med.*, 2012, **10**.

253 M. K. Kim, K. H. Baek, K. H. Song, M. I. Kang, J. H. Choi, J. C. Bae, C. Y. Park, W. Y. Lee and K. W. Oh, Increased Serum Ferritin Predicts the Development of Hypertension Among Middle-Aged Men, *Am. J. Hypertens.*, 2012, **25**, 492–497.

254 B. Choi, K. J. Yeum, S. J. Park, K. N. Kim and N. S. Joo, Elevated serum ferritin and mercury concentrations are associated with hypertension; analysis of the fourth and fifth Korea national health and nutrition examination survey (KNHANES IV-2, 3, 2008-2009 and V-1, 2010), *Environ. Toxicol.*, 2013, DOI: 10.1002/tox.21899.

255 M. Jehn, J. M. Clark and E. Guallar, Serum ferritin and risk of the metabolic syndrome in U.S. adults, *Diabetes Care*, 2004, **27**, 2422–2428.

256 C. Bozzini, D. Girelli, O. Olivieri, N. Martinelli, A. Bassi, G. De Matteis, I. Tenuti, V. Lotto, S. Friso, F. Pizzolo and R. Corrocher, Prevalence of body iron excess in the metabolic syndrome, *Diabetes Care*, 2005, **28**, 2061–2063.

257 K. M. Choi, K. W. Lee, H. Y. Kim, J. A. Seo, S. G. Kim, N. H. Kim, D. S. Choi and S. H. Baik, Association among serum ferritin, alanine aminotransferase levels, and metabolic syndrome in Korean postmenopausal women, *Metabolism*, 2005, **54**, 1510–1514.

258 A. S. González, D. B. Guerrero, M. B. Soto, S. P. Diáz, M. Martinez-Olmos and O. Vidal, Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin, *Eur. J. Clin. Nutr.*, 2006, **60**, 802–809.

259 V. Tsimihodimos, I. Gazi, R. Kalaitzidis, M. Elisaf and K. C. Siamopoulos, Increased serum ferritin concentrations and liver enzyme activities in patients with metabolic syndrome, *Metab. Syndr. Relat. Disord.*, 2006, **4**, 196–203.

260 P. Trombini and A. Piperno, Ferritin, metabolic syndrome and NAFLD: elective attractions and dangerous liaisons, *J. Hepatol.*, 2007, **46**, 549–552.

261 I. S. Vari, B. Balkau, A. Kettaneh, P. André, J. Tichet, F. Fumeron, E. Caces, M. Marre, B. Grandchamp and P. Ducimetière, Ferritin and transferrin are associated with metabolic syndrome abnormalities and their change over time in a general population: Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR), *Diabetes Care*, 2007, **30**, 1795–1801.

262 S. Zelber-Sagi, D. Nitzan-Kaluski, Z. Halpern and R. Oren, NAFLD and hyperinsulinemia are major determinants of serum ferritin levels, *J. Hepatol.*, 2007, **46**, 700–707.

263 S. Tsimikas, J. Willeit, M. Knoflach, M. Mayr, G. Egger, M. Notdurfter, J. L. Witztum, C. J. Wiedermann, Q. Xu and S. Kiechl, Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: results from the Bruneck study, *Eur. Heart J.*, 2009, **30**, 107–115.

264 L. Valenti, P. Dongiovanni, B. M. Motta, D. W. Swinkels, P. Bonara, R. Rametta, L. Burdick, C. Frugoni, A. L. Fracanzani and S. Fargion, Serum hepcidin and macrophage iron correlate with MCP-1 release and vascular damage in patients with metabolic syndrome alterations, *Arterioscler., Thromb., Vasc. Biol.*, 2011, **31**, 683–690.

265 P. Hämäläinen, J. Saltevo, H. Kautiainen, P. Mäntyselkä and M. Vanhala, Erythropoietin, ferritin, haptoglobin, hemoglobin and transferrin receptor in metabolic syndrome: a case control study, *Cardiovasc. Diabetol.*, 2012, **11**, 116.

266 S. K. Park, J. H. Ryoo, M. G. Kim and J. Y. Shin, Association of serum ferritin and the development of metabolic syndrome in middle-aged Korean men: a 5-year follow-up study, *Diabetes Care*, 2012, **35**, 2521–2526.

267 H. T. Kang, J. A. Linton and J. Y. Shim, Serum ferritin level is associated with the prevalence of metabolic syndrome in Korean adults: the 2007-2008 Korean National Health and Nutrition Examination Survey, *Clin. Chim. Acta*, 2012, **413**, 636–641.

268 J. H. Yoon, J. A. Linton, S. B. Koh and H. T. Kang, Serum ferritin concentrations predict incidence of metabolic syndrome in rural Korean adults, *Clin. Chem. Lab. Med.*, 2012, **50**, 2057–2059.

269 J. S. Chang, S. M. Lin, T. C. Huang, J. C. Chao, Y. C. Chen, W. H. Pan and C. H. Bai, Serum ferritin and risk of the

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metabolic syndrome: a population-based study, *Asia Pac. J. Clin. Nutr.*, 2013, **22**, 400–407.

270 C. Datz, T. K. Felder, D. Niederseer and E. Aigner, Iron homeostasis in the Metabolic Syndrome, *Eur. J. Clin. Invest.*, 2013, **43**, 215–224.

271 L. Guo, F. Jiang, Y. T. Tang, M. Y. Si and X. Y. Jiao, The Association of Serum Vascular Endothelial Growth Factor and Ferritin in Diabetic Microvascular Disease, *Diabetes Technol. Ther.*, 2013, DOI: 10.1089/dia.2013.0181.

272 J. Li, R. Wang, D. Luo, S. Li and C. Xiao, Association between Serum Ferritin Levels and Risk of the Metabolic Syndrome in Chinese Adults: A Population Study, *PLoS One*, 2013, **8**, e74168.

273 C. Sfagos, A. C. Makis, A. Chaidos, E. C. Hatzimichael, A. Dalamaga, K. Kosma and K. L. Bourantas, Serum ferritin, transferrin and soluble transferrin receptor levels in multiple sclerosis patients, *Mult. Scler.*, 2005, **11**, 272–275.

274 H. Orbach, G. Zandman-Goddard, H. Amital, V. Barak, Z. Szekanecz, G. Szucs, K. Danko, E. Nagy, T. Csepany, J. F. Carvalho, A. Doria and Y. Shoenfeld, Novel biomarkers in autoimmune diseases: prolactin, ferritin, vitamin D, and TPA levels in autoimmune diseases, *Ann. N. Y. Acad. Sci.*, 2007, **1109**, 385–400.

275 G. Zandman-Goddard and Y. Shoenfeld, Hyperferritinemia in autoimmunity, *Isr. Med. Assoc. J.*, 2008, **10**, 83–84.

276 R. Da Costa, M. Szyper-Kravitz, Z. Szekanecz, T. Csépány, K. Dankó, Y. Shapira, G. Zandman-Goddard, H. Orbach, N. Agmon-Levin and Y. Shoenfeld, Ferritin and Prolactin levels in multiple sclerosis, *Isr. Med. Assoc. J.*, 2011, **13**, 91–95.

277 J. T. Salonen, K. Nyyssonen, H. Korpela, J. Tuomilehto, R. Seppanen and R. Salonen, High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men, *Circulation*, 1992, **86**, 803–811.

278 C. Moroz, H. Bessler, M. Katz, I. Zahavi, H. Salman and M. Djaldetti, Elevated serum ferritin level in acute myocardial infarction, *Biomed. Pharmacother.*, 1997, **51**, 126–130.

279 T. P. Tuomainen, K. Punnonen, K. Nyyssonen and J. T. Salonen, Association between body iron stores and the risk of acute myocardial infarction in men, *Circulation*, 1998, **97**, 1461–1466.

280 K. Klipstein-Grobusch, J. F. Koster, D. E. Grobbee, J. Lindemans, H. Boeing, A. Hofman and J. C. M. Witteman, Serum ferritin and risk of myocardial infarction in the elderly: the Rotterdam Study, *Am. J. Clin. Nutr.*, 1999, **69**, 1231–1236.

281 D. Claeys, M. Walting, F. Julmy, W. A. Wuillemin and B. J. Meyer, Haemochromatosis mutations and ferritin in myocardial infarction: a case-control study, *Eur. J. Clin. Invest.*, 2002, **32**, 3–8.

282 W. D. Silvia, S. Biswas, S. Uthappa and P. Shetty, Ferritin, a potent threat for acute myocardial infarction?, *J. Assoc. Physicians India*, 2003, **51**, 947–950.

283 X. M. Yuan and W. Li, The iron hypothesis of atherosclerosis and its clinical impact, *Ann. Med.*, 2003, **35**, 578–591.

284 M. P. Holay, A. A. Choudhary and S. D. Suryawanshi, Serum ferritin-a novel risk factor in acute myocardial infarction, *Indian Heart J.*, 2012, **64**, 173–177.

285 M. P. Iqbal, N. Mehboobali, A. K. Tareen, M. Yakub, S. P. Iqbal, K. Iqbal and G. Haider, Association of body iron status with the risk of premature acute myocardial infarction in a Pakistani population, *PLoS One*, 2013, **8**, e67981.

286 S. Fargion, M. Mattioli, A. L. Fracanzani, M. Sampietro, D. Tavazzi, P. Fociani, E. Taioli, L. Valenti and G. Fiorelli, Hyperferritinemia, iron overload, and multiple metabolic alterations identify patients at risk for nonalcoholic steatohepatitis, *Am. J. Gastroenterol.*, 2001, **96**, 2448–2455.

287 M. Koruk, S. Tayşi, M. C. Savaş, O. Yilmaz, F. Akçay and M. Karakök, Serum levels of acute phase proteins in patients with nonalcoholic steatohepatitis, *Turk. J. Gastroenterol.*, 2003, **14**, 12–17.

288 E. Bugianesi, P. Manzini, S. D'Antico, E. Vanni, F. Longo, N. Leone, P. Massarenti, A. Piga, G. Marchesini and M. Rizzetto, Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver, *Hepatology*, 2004, **39**, 179–187.

289 T. J. Hsiao, J. C. Chen and J. D. Wang, Insulin resistance and ferritin as major determinants of nonalcoholic fatty liver disease in apparently healthy obese patients, *Int. J. Obes. Relat. Metab. Disord.*, 2004, **28**, 167–172.

290 C. Loguercio, T. De Simone, M. V. D'Auria, I. de Sio, A. Federico, C. Tuccillo, A. M. Abbatecola, C. Del Vecchio Blanco and Italian AISF Clinical Group, Non-alcoholic fatty liver disease: a multicentre clinical study by the Italian Association for the Study of the Liver, *Dig. Liver Dis.*, 2004, **36**, 398–405.

291 G. C. Farrell and C. Z. Larter, Nonalcoholic fatty liver disease: from steatosis to cirrhosis, *Hepatology*, 2006, **43**, S99–S112.

292 L. Valenti, A. L. Fracanzani, P. Dongiovanni, E. Bugianesi, G. Marchesini, P. Manzini, E. Vanni and S. Fargion, Iron depletion by phlebotomy improves insulin resistance in patients with nonalcoholic fatty liver disease and hyperferritinemia: evidence from a case-control study, *Am. J. Gastroenterol.*, 2007, **102**, 1251–1258.

293 E. Aigner and C. Datz, Iron perturbations in human nonalcoholic fatty liver disease (NAFLD): Clinical relevance and molecular mechanisms, *Hepatitis Monthly*, 2008, **8**, 213–220.

294 L. Valenti, D. W. Swinkels, L. Burdick, P. Dongiovanni, H. Tjalsma, B. M. Motta, C. Bertelli, E. Fatta, D. Bignamini, R. Rametta, S. Fargion and A. L. Fracanzani, Serum ferritin levels are associated with vascular damage in patients with nonalcoholic fatty liver disease, *Nutr., Metab. Cardiovasc. Dis.*, 2010, **21**, 568–575.

295 M. Yoneda, Y. Nozaki, H. Endo, H. Mawatari, H. Iida, K. Fujita, K. Yoneda, H. Takahashi, H. Kirikoshi, M. Inamori, N. Kobayashi, K. Kubota, S. Saito, S. Maeyama, K. Hotta and A. Nakajima, Serum ferritin is a clinical biomarker in Japanese patients with nonalcoholic steatohepatitis (NASH) independent of HFE gene mutation, *Dig. Dis. Sci.*, 2010, **55**, 808–814.

296 K. V. Kowdley, The role of iron in nonalcoholic fatty liver disease: the story continues, *Gastroenterology*, 2010, **138**, 817–819.

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297 P. Manousou, G. Kalambokis, F. Grillo, J. Watkins, E. Xirouchakis, M. Pleguezuelo, G. Leandro, V. Arvaniti, G. Germani, D. Patch, V. Calvaruso, D. P. Mikhailidis, A. P. Dhillon and A. K. Burroughs, Serum ferritin is a discriminant marker for both fibrosis and inflammation in histologically proven non-alcoholic fatty liver disease patients, *Liver Int.*, 2011, **31**, 730–739.

298 Y. Sumida, M. Yoneda, H. Hyogo, K. Yamaguchi, M. Ono, H. Fujii, Y. Eguchi, Y. Suzuki, S. Imai, K. Kanemasa, K. Fujita, K. Chayama, K. Yasui, T. Saibara, N. Kawada, K. Fujimoto, Y. Kohgo and T. Okanoue, A simple clinical scoring system using ferritin, fasting insulin, and type IV collagen 7S for predicting steatohepatitis in nonalcoholic fatty liver disease, *J. Gastroenterol.*, 2011, **46**, 257–268.

299 K. V. Kowdley, P. Belt, L. A. Wilson, M. M. Yeh, B. A. Neuschwander-Tetri, N. Chalasani, A. J. Sanyal and J. E. Nelson, Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease, *Hepatology*, 2012, **55**, 77–85.

300 C. W. Kim, Y. Chang, E. Sung, H. Shin and S. Ryu, Serum ferritin levels predict incident non-alcoholic fatty liver disease in healthy Korean men, *Metabolism*, 2012, **61**, 1182–1188.

301 K. M. Utzschneider, A. Largajolli, A. Bertoldo, S. Marcovina, J. E. Nelson, M. M. Yeh, K. V. Kowdley and S. E. Kahn, Serum ferritin is associated with non-alcoholic fatty liver disease and decreased Beta-cell function in non-diabetic men and women, *J. Diabetes Complications*, 2013, DOI: 10.1016/j.jdiacomp.2013.11.007.

302 S. S. Entman, L. D. Richardson and A. P. Killam, Elevated serum ferritin in the altered ferrokinetics of toxemia of pregnancy, *Am. J. Obstet. Gynecol.*, 1982, **144**, 418–422.

303 S. S. Entman, L. D. Richardson and A. P. Killam, Altered ferrokinetics in toxemia of pregnancy – a possible indicator of decreased red cell survival, *Clin. Exp. Hypertens., Part B*, 1983, **2**, 171–178.

304 M. P. Rayman, J. Barlis, R. W. Evans, C. W. Redman and L. J. King, Abnormal iron parameters in the pregnancy syndrome preeclampsia, *Am. J. Obstet. Gynecol.*, 2002, **187**, 412–418.

305 C. A. Hubel, L. M. Bodnar, A. Many, G. Harger, R. B. Ness and J. M. Roberts, Nonglycosylated ferritin predominates in the circulation of women with preeclampsia but not intrauterine growth restriction, *Clin. Chem.*, 2004, **50**, 948–951.

306 I. A. Siddiqui, A. Jaleel, H. M. Kadri, W. A. Saeed and W. Tamimi, Iron status parameters in preeclamptic women, *Arch. Gynecol. Obstet.*, 2011, **284**, 587–591.

307 D. R. Blake, P. A. Bacon, E. J. Eastham and K. Brigham, Synovial fluid ferritin in rheumatoid arthritis, *BMJ*, 1980, **281**, 715–716.

308 R. S. Rothwell and P. Davis, Relationship between serum ferritin, anemia, and disease activity in acute and chronic rheumatoid arthritis, *Rheumatol. Int.*, 1981, **1**, 65–67.

309 P. Biemond, A. J. G. Swaak, H. G. Vaneijk and J. F. Koster, Intraarticular ferritin-bound iron in rheumatoid arthritis – a factor that increases oxygen free radical-induced tissue destruction, *Arthritis Rheum.*, 1986, **29**, 1187–1193.

310 C. Palermo, S. Maddali Bongi and G. Bianucci, Relationship between serum ferritin, iron stores and disease activity in rheumatoid arthritis, *Ric. Clin. Lab.*, 1986, **16**, 463–469.

311 P. Biemond, A. J. G. Swaak, H. G. Vaneijk and J. F. Koster, Superoxide Dependent Iron Release from Ferritin in Inflammatory Diseases, *Free Radical Biol. Med.*, 1988, **4**, 185–198.

312 E. Abe and M. Arai, Synovial fluid ferritin in traumatic hemarthrosis, rheumatoid arthritis and osteoarthritis, *Tohoku J. Exp. Med.*, 1992, **168**, 499–505.

313 K. Yildirim, S. Karatay, M. A. Melikoglu, G. Gureser, M. Ugur and K. Senel, Associations between acute phase reactant levels and disease activity score (DAS28) in patients with rheumatoid arthritis, *Ann. Clin. Lab. Sci.*, 2004, **34**, 423–426.

314 F. Lv, L. J. Song and X. F. Li, Combined measurement of multiple acute phase reactants to predict relapse of rheumatoid arthritis, *Int. J. Rheum. Dis.*, 2013, DOI: 10.1111/1756185X.12186.

315 R. L. Goldenberg, B. M. Mercer, M. Miodovnik, G. R. Thurnau, P. J. Meis, A. Moawad, R. H. Paul, S. F. Bottoms, A. Das, J. M. Roberts, D. McNellis and T. Tamura, Plasma ferritin, premature rupture of membranes, and pregnancy outcome, *Am. J. Obstet. Gynecol.*, 1998, **179**, 1599–1604.

316 P. C. R. Garcia, F. Longhi, R. G. Branco, J. P. Piva, D. Lacks and R. C. Tasker, Ferritin levels in children with severe sepsis and septic shock, *Acta Paediatr.*, 2007, **96**, 1829–1831.

317 T. D. Bennett, K. N. Hayward, R. W. Farris, S. Ringold, C. A. Wallace and T. V. Brogan, Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients, *Pediatr. Crit. Care Med.*, 2011, **12**, e233–e236.

318 M. Suárez-Santamaría, F. Santolaria, A. Pérez-Ramírez, M. R. Aléman-Valls, A. Martínez-Riera, E. González-Reimers, M. J. de la Vega and A. Milena, Prognostic value of inflammatory markers (notably cytokines and procalcitonin), nutritional assessment, and organ function in patients with sepsis, *Eur. Cytokine Network*, 2010, **21**, 19–26.

319 A. Dávalos, J. M. Fernandezreal, W. Ricart, S. Soler, A. Molins, E. Planas and D. Genis, Iron-related damage in acute ischemic stroke, *Stroke*, 1994, **25**, 1543–1546.

320 A. K. Erdemoglu and S. Ozbakir, Serum ferritin levels and early prognosis of stroke, *Eur. J. Neurol.*, 2002, **9**, 633–637.

321 G. M. Bishop and S. R. Robinson, Quantitative analysis of cell death and ferritin expression in response to cortical iron: implications for hypoxia-ischemia and stroke, *Brain Res.*, 2001, **907**, 175–187.

322 A. Armengou and A. Davalos, A review of the state of research into the role of iron in stroke, *J. Nutr., Health Aging*, 2002, **6**, 207–208.

323 E. Millerot, A. S. Prigent-Tessier, N. M. Bertrand, P. J. Faure, C. M. Mossiat, M. E. Giroud, A. G. Beley and C. Marie, Serum ferritin in stroke: a marker of increased body iron stores or stroke severity?, *J. Cereb. Blood Flow Metab.*, 2005, **25**, 1386–1393.

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324 D. L. van der A, D. E. Grobbee, M. Roest, J. J. M. Marx, H. A. Voorbij and Y. T. van der Schouw, Serum ferritin is a risk factor for stroke in postmenopausal women, *Stroke*, 2005, **36**, 1637–1641.

325 M. Millan, T. Sobrino, M. Castellanos, F. Nombela, J. F. Arenillas, E. Riva, I. Cristobo, M. M. Garcia, J. Vivancos, J. Serena, M. A. Moro, J. Castillo and A. Dávalos, Increased body iron stores are associated with poor outcome after thrombolytic treatment in acute stroke, *Stroke*, 2007, **38**, 90–95.

326 M. Mehdiratta, S. Kumar, D. Hackney, G. Schlaug and M. Selim, Association between serum ferritin level and perihematoma edema volume in patients with spontaneous intracerebral hemorrhage, *Stroke*, 2008, **39**, 1165–1170.

327 M. Millán, T. Sobrino, J. F. Arenillas, M. Rodriguez-Yáñez, M. Garcia, F. Nombela, M. Castellanos, N. Pérez de la Ossa, P. Cuadras, J. Serena, J. Castillo and A. Dávalos, Biological signatures of brain damage associated with high serum ferritin levels in patients with acute ischemic stroke and thrombolytic treatment, *Dis. Markers*, 2008, **25**, 181–188.

328 N. P. Pérez de la Ossa, T. Sobrino, Y. Silva, M. Blanco, M. Millán, M. Gomis, J. Agulla, P. Araya, S. Reverté, J. Serena and A. Dávalos, Iron-related brain damage in patients with intracerebral hemorrhage, *Stroke*, 2010, **41**, 810–813.

329 K. H. Choi, M. S. Park, J. T. Kim, T. S. Nam, S. M. Choi, B. C. Kim, M. K. Kim and K. H. Cho, The serum ferritin level is an important predictor of hemorrhagic transformation in acute ischaemic stroke, *Eur. J. Neurol.*, 2012, **19**, 570–577.

330 I. García-Yébenes, M. Sobrado, A. Moraga, J. G. Zarruk, V. G. Romera, J. M. Pradillo, N. Perez de la Ossa, M. A. Moro, A. Dávalos and I. Lizasoain, Iron overload, measured as serum ferritin, increases brain damage induced by focal ischemia and early reperfusion, *Neurochem. Int.*, 2012, **61**, 1364–1369.

331 K. Nishiya and K. Hashimoto, Elevation of serum ferritin levels as a marker for active systemic lupus erythematosus, *Clin. Exp. Rheumatol.*, 1997, **15**, 39–44.

332 M. K. Lim, C. K. Lee, Y. S. Ju, Y. S. Cho, M. S. Lee, B. Yoo and H. B. Moon, Serum ferritin as a serologic marker of activity in systemic lupus erythematosus, *Rheumatol. Int.*, 2001, **20**, 89–93.

333 L. G. Xu, M. Wu, J. C. Hu, Z. H. Zhai and H. B. Shu, Identification of downstream genes up-regulated by the tumor necrosis factor family member TALL-1, *J. Leukocyte Biol.*, 2002, **72**, 410–416.

334 E. Beyan, C. Beyan, A. Demirezer, E. Ertugrul and A. Uzuner, The relationship between serum ferritin levels and disease activity in systemic lupus erythematosus, *Scand. J. Rheumatol.*, 2003, **32**, 225–228.

335 G. Zandman-Goddard, H. Orbach, H. Amital, Z. Szekanecz, G. Szucs, K. Danko, E. Nagy, T. Csepany and Y. Shoenfeld, Elevated levels of ferritin in systemic lupus erythematosus and other autoimmune diseases, *Ann. Rheum. Dis.*, 2007, **66**, 488.

336 A. Parodi, S. Davi, A. B. Pringe, A. Pistorio, N. Ruperto, S. Magni-Manzoni, P. Miettunen, B. Bader-Meunier, G. Espada, G. Sterba, S. Ozen, D. Wright, C. S. Magalhaes, R. Khubchandani, H. Michels, P. Woo, A. Iglesias, D. Guseinova, C. Bracaglia, K. Hayward, C. Wouters, A. Grom, M. Vivarelli, A. Fischer, L. Breda, A. Martini, A. Ravelli and P. R. E. Soc, Macrophage Activation Syndrome in Juvenile Systemic Lupus Erythematosus A Multinational Multicenter Study of Thirty-Eight Patients, *Arthritis Rheum.*, 2009, **60**, 3388–3399.

337 K. Vanarsa, Y. Ye, J. Han, C. Xie, C. Mohan and T. Wu, Inflammation associated anemia and ferritin as disease markers in SLE, *Arthritis Res. Ther.*, 2012, **14**, R182.

338 M. Abbasi, M. Sahebari, A. Amini and M. Saghafi, Hyperferritinemia: A possible marker for diagnosis of systemic lupus erythematosus?, *Life Sci. J.*, 2013, **10**, 335–337.

339 S. Y. Lee, S. W. Lee and W. T. Chung, Severe inflammation may be caused by hyperferritinemia of pseudo-pseudo Meigs' syndrome in lupus patients: two cases reports and a literature review, *Clin. Rheumatol.*, 2013, **32**, 1823–1826.

340 M. A. B. Lozovoy, A. N. C. Simão, S. R. Oliveira, T. M. V. Iryioda, C. Panis, R. Cecchini and I. Dichi, Relationship between iron metabolism, oxidative stress, and insulin resistance in patients with systemic lupus erythematosus, *Scand. J. Rheumatol.*, 2013, **42**, 303–310.

341 S. Vilaiyuk, N. Sirachainan, S. Wanitkun, K. Pirojsakul and J. Vaewpanich, Recurrent macrophage activation syndrome as the primary manifestation in systemic lupus erythematosus and the benefit of serial ferritin measurements: a case-based review, *Clin. Rheumatol.*, 2013, **32**, 899–904.

342 G. Zandman-Goddard, H. Orbach, N. Agmon-Levin, M. Boaz, H. Amital, Z. Szekanecz, G. Szucs, J. Rovensky, E. Kiss, N. Corocher, A. Doria, L. Stojanovich, F. Ingegnoli, P. L. Meroni, B. Rozman, J. Gomez-Arbesu, M. Blank and Y. Shoenfeld, Hyperferritinemia is associated with serologic antiphospholipid syndrome in SLE patients, *Clin. Rev. Allergy Immunol.*, 2013, **44**, 23–30.

343 A. Undas, P. Podolec, K. Zawilska, M. Pieculewicz, I. Jedliński, E. Stępień, E. Konarska-Kuszewska, P. Weglarz, M. Duszynska, E. Hanschke, T. Przewlocki and W. Tracz, Altered fibrin clot structure/function in patients with cryptogenic ischemic stroke, *Stroke*, 2009, **40**, 1499–1501.

344 I. Palka, J. Nessler, B. Nessler, W. Piwowarska, W. Tracz and A. Undas, Altered fibrin clot properties in patients with chronic heart failure and sinus rhythm: a novel prothrombotic mechanism, *Heart*, 2010, **96**, 1114–1118.

345 A. Undas and R. A. S. Ariëns, Fibrin clot structure and function: a role in the pathophysiology of arterial and venous thromboembolic diseases, *Arterioscler., Thromb., Vasc. Biol.*, 2011, **31**, e88–e99.

346 A. Undas, M. Cieśla-Dulb, T. Drżkiewiczb and J. Sadowski, Altered fibrin clot properties are associated with residual vein obstruction: effects of lipoprotein(a) and apolipoprotein(a) isoform, *Thromb. Res.*, 2012, **130**, e184–e187.

347 J. Bester, A. V. Buys, B. Lipinski, D. B. Kell and E. Pretorius, High ferritin levels have major effects on the morphology

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of erythrocytes in Alzheimer's disease, *Front. Aging Neurosci.*, 2013, **5**, 00088.

348 E. Pretorius and B. Lipinski, Thromboembolic ischemic stroke changes red blood cell morphology, *Cardiovasc. Pathol.*, 2013, **22**, 241–242.

349 E. Pretorius and B. Lipinski, Iron alters red blood cell morphology, *Blood*, 2013, **121**, 9.

350 E. Pretorius, J. Bester, N. Vermeulen, B. Lipinski, G. S. Gericke and D. B. Kell, Profound morphological changes in the erythrocytes and fibrin networks of patients with hemochromatosis or with hyperferritinemia, and their normalization by iron chelators and other agents, *PLoS One*, 2014, **9**, e85271.

351 E. Pretorius, N. Vermeulen and J. Bester, Atypical erythrocytes and platelets in a patient with a pro-thrombin mutation, *Platelets*, 2013, DOI: 10.3109/09537104.2013.830709.

352 E. Pretorius, N. Vermeulen, J. Bester, B. Lipinski and D. B. Kell, A novel method for assessing the role of iron and its functional chelation in fibrin fibril formation: the use of scanning electron microscopy, *Toxicol. Mech. Methods*, 2013, **23**, 352–359.

353 B. Lipinski, E. Pretorius, H. M. Oberholzer and W. J. van der Spuy, Interaction of fibrin with red blood cells: the role of iron, *Ultrastruct. Pathol.*, 2012, **36**, 79–84.

354 B. Lipinski and E. Pretorius, Novel pathway of iron-induced blood coagulation: implications for diabetes mellitus and its complications, *Pol. Arch. Med. Wewn.*, 2012, **122**, 115–122.

355 E. Pretorius, J. du Plooy, P. Soma and A. Y. Gasparyan, An ultrastructural analysis of platelets, erythrocytes, white blood cells, and fibrin network in systemic lupus erythematosus, *Rheumatol. Int.*, 2013, DOI: 10.1007/s00296-013-2817-x.

356 A. V. Buys, M. J. Van Rooy, P. Soma, D. Van Papendorp, B. Lipinski and E. Pretorius, Changes in red blood cell membrane structure in type 2 diabetes: a scanning electron and atomic force microscopy study, *Cardiovasc. Diabetol.*, 2013, **12**, 25.

357 S. Gangopadhyay, V. K. Vijayan and S. K. Bansal, Lipids of erythrocyte membranes of COPD patients: a quantitative and qualitative study, *COPD*, 2012, **9**, 322–331.

358 E. Pretorius, J. N. du Plooy, P. Soma, I. Keyser and A. V. Buys, Smoking and fluidity of erythrocyte membranes: A high resolution scanning electron and atomic force microscopy investigation, *Nitric Oxide*, 2013, **35C**, 42–46.

359 C. J. Smith and T. H. Fischer, Particulate and vapor phase constituents of cigarette mainstream smoke and risk of myocardial infarction, *Atherosclerosis*, 2001, **158**, 257–267.

360 G. J. Kontoghiorghes, Future chelation monotherapy and combination therapy strategies in thalassemia and other conditions. Comparison of deferiprone, deferoxamine, ICL670, GT56-252, L1NAll and starch deferoxamine polymers, *Hemoglobin*, 2006, **30**, 329–347.

361 H. Nick, Iron chelation, quo vadis?, *Curr. Opin. Chem. Biol.*, 2007, **11**, 419–423.

362 A. Maggio, A. Filosa, A. Vitrano, G. Aloj, A. Kattamis, A. Ceci, S. Fucharoen, P. Cianciulli, R. W. Grady, L. Prossomariti, J. B. Porter, A. Iacono, M. D. Cappellini, F. Bonifazi, F. Cassara, P. Harmatz, J. Wood and C. Gluud, Iron chelation therapy in thalassemia major: a systematic review with meta-analyses of 1520 patients included on randomized clinical trials, *Blood Cells, Mol., Dis.*, 2011, **47**, 166–175.

363 E. A. Rachmilewitz and P. J. Giardina, How I treat thalassemia, *Blood*, 2011, **118**, 3479–3488.

364 Y. Ma, T. Zhou, X. Kong and R. C. Hider, Chelating agents for the treatment of systemic iron overload, *Curr. Med. Chem.*, 2012, **19**, 2816–2827.

365 T. P. Chang and C. Rangan, Iron poisoning: a literature-based review of epidemiology, diagnosis, and management, *Pediatr. Emerg. Care*, 2011, **27**, 978–985.

366 A. J. Matthews, G. M. Vercellotti, H. J. Menchaca, P. H. Bloch, V. N. Michalek, P. H. Marker, J. Murar and H. Buchwald, Iron and atherosclerosis: inhibition by the iron chelator deferiprone (L1), *J. Surg. Res.*, 1997, **73**, 35–40.

367 K. M. Mitchell, A. L. Dotson, K. M. Cool, A. Chakrabarty, S. H. Benedict and S. M. LeVine, Deferiprone, an orally deliverable iron chelator, ameliorates experimental autoimmune encephalomyelitis, *Mult. Scler.*, 2007, **13**, 1118–1126.

368 R. Galanello, Deferiprone in the treatment of transfusion-dependent thalassemia: a review and perspective, *Ther. Clin. Risk Manage.*, 2007, **3**, 795–805.

369 W. T. Lindsey and B. R. Olin, Deferasirox for transfusion-related iron overload: a clinical review, *Clin. Ther.*, 2007, **29**, 2154–2166.

370 M. D. Cappellini and A. Taher, Long-term experience with deferasirox (ICL670), a once-daily oral iron chelator, in the treatment of transfusional iron overload, *Expert Opin. Pharmacother.*, 2008, **9**, 2391–2402.

371 C. McLeod, N. Fleeman, J. Kirkham, A. Bagust, A. Boland, P. Chu, R. Dickson, Y. Dundar, J. Greenhalgh, B. Modell, A. Olujohungbe, P. Telfer and T. Walley, Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation, *Health Technol. Assess.*, 2009, **13**, iii–iv, ix–xi, 1–121.

372 M. D. Cappellini, J. Porter, A. El-Beshlawy, C. K. Li, J. F. Seymour, M. Elalfy, N. Gattermann, S. Giraudier, J. W. Lee, L. L. Chan, K. H. Lin, C. Rose, A. Taher, S. L. Thein, V. Viprakasit, D. Habr, G. Domokos, B. Roubert and A. Kattamis, Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias, *Haematologica*, 2010, **95**, 557–566.

373 J. A. Joseph, N. A. Denisova, D. Bielinski, D. R. Fisher and B. Shukitt-Hale, Oxidative stress protection and vulnerability in aging: putative nutritional implications for intervention, *Mech. Ageing Dev.*, 2000, **116**, 141–153.

374 K. E. Heim, A. R. Tagliaferro and D. J. Bobilya, Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships, *J. Nutr. Biochem.*, 2002, **13**, 572–584.

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375 S. R. McAnulty, L. S. McAnulty, D. C. Nieman, C. L. Dumke, J. D. Morrow, A. C. Utter, D. A. Henson, W. R. Proulx and G. L. George, Consumption of blueberry polyphenols reduces exercise-induced oxidative stress compared to vitamin C, *Nutr. Res.*, 2004, **24**, 209–221.
376 P. Velayutham, A. Babu and D. M. Liu, Green tea catechins and cardiovascular health: an update, *Curr. Med. Chem.*, 2008, **15**, 1840–1850.
377 M. Akhlaghi and B. Bandy, Mechanisms of flavonoid protection against myocardial ischemia-reperfusion injury, *J. Mol. Cell. Cardiol.*, 2009, **46**, 309–317.
378 N. R. Perron and J. L. Brumaghim, A review of the antioxidant mechanisms of polyphenol compounds related to iron binding, *Cell Biochem. Biophys.*, 2009, **53**, 75–100.
379 N. R. Perron, H. C. Wang, S. N. Deguire, M. Jenkins, M. Lawson and J. L. Brumaghim, Kinetics of iron oxidation upon polyphenol binding, *Dalton Trans.*, 2010, **39**, 9982–9987.
380 N. R. Perron, C. R. Garcia, J. R. Pinzon, M. N. Chaur and J. L. Brumaghim, Antioxidant and prooxidant effects of polyphenol compounds on copper-mediated DNA damage, *J. Inorg. Biochem.*, 2011, **105**, 745–753.
381 R. A. Jacob, H. H. Sandstead, L. M. Klevay and L. K. Johnson, Utility of serum ferritin as a measure of iron deficiency in normal males undergoing repetitive phlebotomy, *Blood*, 1980, **56**, 786–791.
382 C. A. Finch, V. Bellotti, S. Stray, D. A. Lipschitz, J. D. Cook, M. J. Pippard and H. A. Huebers, Plasma ferritin determination as a diagnostic tool, *West. J. Med.*, 1986, **145**, 657–663.
383 J. D. Cook, C. H. Flowers and B. S. Skikne, The quantitative assessment of body iron, *Blood*, 2003, **101**, 3359–3364.
384 A. Kolnagou, D. Yazman, C. Economides, E. Eracleous and G. J. Kontoghiorghes, Uses and limitations of serum ferritin, magnetic resonance imaging T2 and T2* in the diagnosis of iron overload and in the ferrikinetics of normalization of the iron stores in thalassemia using the International Committee on Chelation deferiprone/deferoxamine combination protocol, *Hemoglobin*, 2009, **33**, 312–322.
385 B. D. Maliken, W. F. Avrin, J. E. Nelson, J. Mooney, S. Kumar and K. V. Kowdley, Room-temperature susceptometry predicts biopsy-determined hepatic iron in patients with elevated serum ferritin, *Ann. Hepatol.*, 2012, **11**, 77–84.
386 M. Worwood, S. J. Cragg, M. Wagstaff and A. Jacobs, Binding of human serum ferritin to concanavalin A, *Clin. Sci.*, 1979, **56**, 83–87.
387 N. C. Andrews, Forging a field: the golden age of iron biology, *Blood*, 2008, **112**, 219–230.
388 A. E. Hamburger, A. P. West, Z. A. Hamburger, P. Hamburger and P. J. Bjorkman, Crystal structure of a secreted insect ferritin reveals a symmetrical arrangement of heavy and light chains, *J. Mol. Biol.*, 2005, **349**, 558–569.
389 S. Ghosh, S. Hevi and S. L. Chuck, Regulated secretion of glycosylated human ferritin from hepatocytes, *Blood*, 2004, **103**, 2369–2376.
390 T. N. Tran, S. K. Eubanks, K. J. Schaffer, C. Y. J. Zhou and M. C. Linder, Secretion of ferritin by rat hepatoma cells and its regulation by inflammatory cytokines and iron, *Blood*, 1997, **90**, 4979–4986.
391 J. Y. Li, N. Paragas, R. M. Ned, A. Qiu, M. Viltard, T. Leete, I. R. Drexler, X. Chen, S. Sanna-Cherchi, F. Mohammed, D. Williams, C. S. Lin, K. M. Schmidt-Ott, N. C. Andrews and J. Barasch, Scara5 is a ferritin receptor mediating non-transferrin iron delivery, *Dev. Cell*, 2009, **16**, 35–46.
392 L. Li, C. J. Fang, J. C. Ryan, E. C. Niemi, J. A. Lebrón, P. J. Björkman, H. Arase, F. M. Torti, S. V. Torti, M. C. Nakamura and W. E. Seaman, Binding and uptake of H-ferritin are mediated by human transferrin receptor-1, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 3505–3510.
393 J. Han, W. E. Seaman, X. M. Di, W. Wang, M. Willingham, F. M. Torti and S. V. Torti, Iron Uptake Mediated by Binding of H-Ferritin to the TIM-2 Receptor in Mouse Cells, *PLoS One*, 2011, **6**.
394 J. C. Sibille, H. Kondo and P. Aisen, Interactions between Isolated Hepatocytes and Kupffer Cells in Iron Metabolism – a Possible Role for Ferritin as an Iron Carrier Protein, *Hepatology*, 1988, **8**, 296–301.
395 L. A. Cohen, L. Gutierrez, A. Weiss, Y. Leichtmann-Bardoogo, D. L. Zhang, D. R. Crooks, R. Sougrat, A. Morgenstern, B. Galy, M. W. Hentze, F. J. Lazaro, T. A. Rouault and E. G. Meyron-Holtz, Serum ferritin is derived primarily from macrophages through a nonclassical secretory pathway, *Blood*, 2010, **116**, 1574–1584.
396 R. Wilkinson and K. Pickett, *The spirit level: why equality is better for everyone*, Penguin Books, London, 2009.
397 R. W. G. Chapman, A. Gorman, M. Laulicht, M. A. Hussain, S. Sherlock and A. V. Hoffbrand, Binding of Serum Ferritin to Concanavalin-a in Patients with Iron Overload and with Chronic Liver-Disease, *J. Clin. Pathol.*, 1982, **35**, 481–486.
398 T. V. Adamkiewicz, M. R. Abboud, C. Paley, N. Olivieri, M. Kirby-Allen, E. Vichinsky, J. F. Casella, O. A. Alvarez, J. C. Barredo, M. T. Lee, R. V. Iyer, A. Kutlar, K. M. McKie, V. McKie, N. Odo, B. Gee, J. L. Kwiatkowski, G. M. Woods, T. Coates, W. Wang and R. J. Adams, Serum ferritin level changes in children with sickle cell disease on chronic blood transfusion are nonlinear and are associated with iron load and liver injury, *Blood*, 2009, **114**, 4632–4638.
399 T. Takikawa, H. Hayashi, N. Nishimura, M. Yano, T. Isomura and N. Sakamoto, Correlation between serum levels of alanine aminotransferase and ferritin in male blood donors with antibody to hepatitis C virus, *J. Gastroenterol.*, 1994, **29**, 593–597.
400 C. Caramelo, M. Albalate, T. Bermejillo, S. Navas, A. Ortiz, P. de Sequera, S. Casado and V. Carreño, Relationships between plasma ferritin and aminotransferase profile in haemodialysis patients with hepatitis C virus, *Nephrol., Dial., Transplant.*, 1996, **11**, 1792–1796.
401 B. Dubern, J. P. Girardet and P. Tounian, Insulin resistance and ferritin as major determinants of abnormal serum aminotransferase in severely obese children, *Int. J. Pediatr. Obes.*, 2006, **1**, 77–82.
402 T. Nakagawa, Y. Muramoto, M. Hori, S. Mihara, T. Marubayashi and K. Nakagawa, A preliminary investigation of the association

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between haptoglobin polymorphism, serum ferritin concentration and fatty liver disease, *Clin. Chim. Acta*, 2008, **398**, 34–38.

403 M. Iwasa, N. Hara, K. Iwata, M. Ishidome, R. Sugimoto, H. Tanaka, N. Fujita, Y. Kobayashi and Y. Takei, Restriction of calorie and iron intake results in reduction of visceral fat and serum alanine aminotransferase and ferritin levels in patients with chronic liver disease, *Hepatol. Res.*, 2010, **40**, 1188–1194.

404 E. Ozawa, S. Abiru, S. Nagaoka, K. Yano, A. Komori, K. Migita, H. Yatsuhashi, N. Taura, T. Ichikawa, H. Ishibashi and K. Nakao, Ferritin/alanine aminotransferase ratio as a possible marker for predicting the prognosis of acute liver injury, *J. Gastroenterol. Hepatol.*, 2011, **26**, 1326–1332.

405 P. C. Adams and J. C. Barton, A diagnostic approach to hyperferritinemia with a non-elevated transferrin saturation, *J. Hepatol.*, 2011, **55**, 453–458.

406 S. Uysal, F. Armutcu, T. Aydogan, K. Akin, M. Ikizek and M. R. Yigitoglu, Some inflammatory cytokine levels, iron metabolism and oxidan stress markers in subjects with nonalcoholic steatohepatitis, *Clin. Biochem.*, 2011, **44**, 1375–1379.

407 A. Oguz, A. E. Atay, A. Tas, G. Seven and M. Koruk, Predictive role of acute phase reactants in the response to therapy in patients with chronic hepatitis C virus infection, *Gut Liver*, 2013, **7**, 82–88.

408 J. C. Waterlow, P. J. Garlick and D. J. Millward, *Protein Turnover in Mammalian Tissues and in the Whole Body*, Elsevier/North-Holland, Amsterdam, 1978.

409 H. A. Johnson, R. L. Baldwin, J. France and C. C. Calvert, A model of whole-body protein turnover based on leucine kinetics in rodents, *J. Nutr.*, 1999, **129**, 728–739.

410 J. Pellettieri and A. Sanchez Alvarado, Cell turnover and adult tissue homeostasis: from humans to planarians, *Annu. Rev. Genet.*, 2007, **41**, 83–105.

411 A. J. Claydon and R. J. Beynon, Proteome dynamics: revisiting turnover with a global perspective, *Mol. Cell. Proteomics*, 2012, **11**, 1551–1565.

412 G. Balla, H. S. Jacob, J. Balla, M. Rosenberg, K. Nath, F. Apple, J. W. Eaton and G. M. Vercellotti, Ferritin: a cytoprotective antioxidant strategem of endothelium, *J. Biol. Chem.*, 1992, **267**, 18148–18153.

413 K. Orino, L. Lehman, Y. Tsuji, H. Ayaki, S. V. Torti and F. M. Torti, Ferritin and the response to oxidative stress, *Biochem. J.*, 2001, **357**, 241–247.

414 Y. Tsuji, H. Ayaki, S. P. Whitman, C. S. Morrow, S. V. Torti and F. M. Torti, Coordinate transcriptional and translational regulation of ferritin in response to oxidative stress, *Mol. Cell. Biol.*, 2000, **20**, 5818–5827.

415 K. Hailemariam, K. Iwasaki, B. W. Huang, K. Sakamoto and Y. Tsuji, Transcriptional regulation of ferritin and antioxidant genes by HIPK2 under genotoxic stress, *J. Cell Sci.*, 2010, **123**, 3863–3871.

416 B. W. Huang, P. D. Ray, K. Iwasaki and Y. Tsuji, Transcriptional regulation of the human ferritin gene by coordinated regulation of Nrf2 and protein arginine methyltransferases PRMT1 and PRMT4, *FASEB J.*, 2013, **27**, 3763–3774.

417 M. Nakano, Y. Kawanishi, S. Kamohara, Y. Uchida, M. Shiota, Y. Inatomi, T. Komori, K. Miyazawa, K. Gondo and I. Yamasawa, Oxidative DNA damage (8-hydroxydeoxyguanosine) and body iron status: a study on 2507 healthy people, *Free Radical Biol. Med.*, 2003, **35**, 826–832.

418 Y. Maruyama, M. Nakayama, K. Yoshimura, H. Nakano, H. Yamamoto, K. Yokoyama and B. Lindholm, Effect of repeated intravenous iron administration in haemodialysis patients on serum 8-hydroxy-2′-deoxyguanosine levels, *Nephrol., Dial., Transplant.*, 2007, **22**, 1407–1412.

419 T. P. Tuomainen, S. Loft, K. Nyyssonen, K. Punnonen, J. T. Salonen and H. E. Poulsen, Body iron is a contributor to oxidative damage of DNA, *Free Radical Res.*, 2007, **41**, 324–328.

420 N. Fujita, R. Sugimoto, N. Ma, H. Tanaka, M. Iwasa, Y. Kobayashi, S. Kawanishi, S. Watanabe, M. Kaito and Y. Takei, Comparison of hepatic oxidative DNA damage in patients with chronic hepatitis B and C, *J. Viral Hepat.*, 2008, **15**, 498–507.

421 K. L. Kuo, S. C. Hung, Y. H. Wei and D. C. Tarng, Intravenous iron exacerbates oxidative DNA damage in peripheral blood lymphocytes in chronic hemodialysis patients, *J. Am. Soc. Nephrol.*, 2008, **19**, 1817–1826.

422 K. Broedbaek, H. E. Poulsen, A. Weimann, G. D. Kom, E. Schwedhelm, P. Nielsen and R. H. Boger, Urinary excretion of biomarkers of oxidatively damaged DNA and RNA in hereditary hemochromatosis, *Free Radical Biol. Med.*, 2009, **47**, 1230–1233.

423 A. Hori, T. Mizoue, H. Kasai, K. Kawai, Y. Matsushita, A. Nanri, M. Sato and M. Ohta, Body iron store as a predictor of oxidative DNA damage in healthy men and women, *Cancer Sci.*, 2010, **101**, 517–522.

424 K. Broedbaek, V. Siersma, J. T. Andersen, M. Petersen, S. Afzal, B. Hjelvang, A. Weimann, R. D. Semba, L. Ferrucci and H. E. Poulsen, The association between low-grade inflammation, iron status and nucleic acid oxidation in the elderly, *Free Radical Res.*, 2011, **45**, 409–416.

425 T. P. Tuomainen, U. Diczfalusy, J. Kaikkonen, K. Nyyssonen and J. T. Salonen, Serum ferritin concentration is associated with plasma levels of cholesterol oxidation products in man, *Free Radical Biol. Med.*, 2003, **35**, 922–928.

426 S. Yeoh-Ellerton and M. C. Stacey, Iron and 8-isoprostane levels in acute and chronic wounds, *J. Invest. Dermatol.*, 2003, **121**, 918–925.

427 C. Matayatsuk, C. Y. Lee, R. W. Kalpravidh, P. Sirankapracha, P. Wilairat, S. Fucharoen and B. Halliwell, Elevated F2-isoprostanes in thalassemic patients, *Free Radical Biol. Med.*, 2007, **43**, 1649–1655.

428 A. P. Jewell and R. E. Marcus, Platelet Derived Malonyldialdehyde Production in Patients with Thalassemia Major, *J. Clin. Pathol.*, 1984, **37**, 1043–1045.

429 F. Farinati, R. Cardin, N. Demaria, G. Dellalibera, C. Marafin, E. Lecis, P. Burra, A. Floreani, A. Cecchetto and R. Naccarato, Iron storage, lipid peroxidation and glutathione turnover in chronic anti-HCV positive hepatitis, *J. Hepatol.*, 1995, **22**, 449–456.

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430 J. Mimić-Oka, A. Savić-Radojević, M. Plješa-Ercegovac, M. Opačić, T. Simić, N. Dimković and D. V. Simić, Evaluation of oxidative stress after repeated intravenous iron supplementation, *Renal Failure*, 2005, **27**, 345–351.

431 A. S. De Vriese, D. Borrey, E. Mahieu, I. Claeys, L. Stevens, A. Vanhaeverbeke, M. Roelens and M. R. Langlois, Oral vitamin C administration increases lipid peroxidation in hemodialysis patients, *Nephron Clin. Pract.*, 2008, **108**, c28–c34.

432 S. M. King, C. M. Donangelo, M. D. Knutson, P. B. Walter, B. N. Ames, F. E. Viteri and J. C. King, Daily supplementation with iron increases lipid peroxidation in young women with low iron stores, *Exp. Biol. Med.*, 2008, **233**, 701–707.

433 J. F. R. Mendes, S. F. Arruda, E. M. de Almeida Siqueira, M. K. Ito and E. F. da Silva, Iron status and oxidative stress biomarkers in adults: a preliminary study, *Nutrition*, 2009, **25**, 379–384.

434 A. I. Alsultan, M. A. Seif, T. T. Amin, M. Naboli and A. M. Alsuliman, Relationship between oxidative stress, ferritin and insulin resistance in sickle cell disease, *Eur. Rev. Med. Pharmacol. Sci.*, 2010, **14**, 527–538.

435 T. E. de Jesus dos Santos, G. F. de Sousa, M. C. Barbosa and R. P. Goncalves, The role of iron overload on oxidative stress in sickle cell anemia, *Biomarkers Med.*, 2012, **6**, 813–819.

436 M. S. Elalfy, A. A. Adly, A. A. Attia, F. A. Ibrahim, A. S. Mohammed and A. M. Sayed, Effect of antioxidant therapy on hepatic fibrosis and liver iron concentrations in beta-thalassemia major patients, *Hemoglobin*, 2013, **37**, 257–276.

437 E. A. Decker and B. Welch, Role of ferritin as a lipid oxidation catalyst in muscle food, *J. Agric. Food Chem.*, 1990, **38**, 674–677.

438 J. I. Gray, E. A. Gomaa and D. J. Buckley, Oxidative quality and shelf life of meats, *Meat Sci.*, 1996, **43**, S111–S123.

439 D. U. Ahn and S. M. Kim, Prooxidant effects of ferrous iron, hemoglobin, and ferritin in oil emulsion and cooked-meat homogenates are different from those in raw-meat homogenates, *Poult. Sci.*, 1998, **77**, 348–355.

440 D. U. Ahn, F. H. Wolfe and J. S. Sim, The Effect of Metal Chelators, Hydroxyl Radical Scavengers, and Enzyme-Systems on the Lipid-Peroxidation of Raw Turkey Meat, *Poult. Sci.*, 1993, **72**, 1972–1980.

441 T. Wang, R. Jónsdóttir and G. Ólafsdóttir, Total phenolic compounds, radical scavenging and metal chelation of extracts from Icelandic seaweeds, *Food Chem.*, 2009, **116**, 240–248.

442 F. Lang, E. Lang and M. Foller, Physiology and pathophysiology of eryptosis, *Transfus. Med. Hemother.*, 2012, **39**, 308–314.

443 M. M. Aleman, C. Gardiner, P. Harrison and A. S. Wolberg, Differential contributions of monocyte- and platelet-derived microparticles towards thrombin generation and fibrin formation and stability, *J. Thromb. Haemostasis*, 2011, **9**, 2251–2261.

444 C. T. Nielsen, O. Østergaard, C. Johnsen, S. Jacobsen and N. H. H. Heegaard, Distinct features of circulating microparticles and their relationship to clinical manifestations in Systemic Lupus Erythematosus, *Arthritis Rheum.*, 2011, **63**, 3067–3077.

445 C. T. Nielsen, Circulating microparticles in systemic Lupus Erythematosus, *Dan. Med. J.*, 2012, **59**, B4548.

446 C. T. Nielsen, O. Østergaard, L. Stener, L. V. Iversen, L. Truedsson, B. Gullstrand, S. Jacobsen and N. H. H. Heegaard, Increased IgG on cell-derived plasma microparticles in systemic lupus erythematosus is associated with autoantibodies and complement activation, *Arthritis Rheum.*, 2012, **64**, 1227–1236.

447 L. V. Iversen, O. Østergaard, C. T. Nielsen, S. Jacobsen and N. H. H. Heegaard, A heparin-based method for flow cytometric analysis of microparticles directly from platelet-poor plasma in calcium containing buffer, *J. Immunol. Methods*, 2013, **388**, 49–59.

448 L. Iversen, O. Østergaard, S. Ullman, C. T. Nielsen, P. Halberg, T. Karlsmark, N. H. H. Heegaard and S. Jacobsen, Circulating microparticles and plasma levels of soluble E- and P-selectins in patients with systemic sclerosis, *Scand. J. Rheumatol.*, 2013, **42**, 473–482.

449 O. Østergaard, C. T. Nielsen, L. V. Iversen, J. T. Tanassi, S. Knudsen, S. Jacobsen and N. H. H. Heegaard, Unique protein signature of circulating microparticles in systemic lupus erythematosus, *Arthritis Rheum.*, 2013, **65**, 2680–2690.

450 B. Parker, A. Al-Husain, P. Pemberton, A. P. Yates, P. Ho, R. Gorodkin, L. S. Teh, M. Y. Alexander and I. N. Bruce, Suppression of inflammation reduces endothelial microparticles in active systemic lupus erythematosus, *Ann. Rheum. Dis.*, 2013, DOI: 10.1136/annrheumdis-2012-203028.

451 J. Pereira, G. Alfaro, M. Goycoolea, T. Quiroga, M. Ocqueteau, L. Massardo, C. Pérez, C. Sáez, O. Panes, V. Matus and D. Mezzano, Circulating platelet-derived microparticles in systemic lupus erythematosus. Association with increased thrombin generation and procoagulant state, *Thromb. Haemostasis*, 2006, **95**, 94–99.

452 A. A. G. Tantawy, A. A. M. Adly, E. A. R. Ismail and N. M. Habeeb, Flow cytometric assessment of circulating platelet and erythrocytes microparticles in young thalassemia major patients: relation to pulmonary hypertension and aortic wall stiffness, *Eur. J. Haematol.*, 2013, **90**, 508–518.

453 A. A. G. Tantawy, A. A. M. Adly, E. A. R. Ismail, N. M. Habeeb and A. Farouk, Circulating platelet and erythrocyte microparticles in young children and adolescents with sickle cell disease: Relation to cardiovascular complications, *Platelets*, 2013, **24**, 605–614.

454 I. Porto, G. L. De Maria, L. Di Vito, C. Camaioni, M. Gustapane and L. M. Biasucci, Microparticles in health and disease: small mediators, large role?, *Curr. Vasc. Pharmacol.*, 2011, **9**, 490–500.

455 P. E. Spronk, H. Bootsma and C. G. M. Kallenberg, Anti-DNA antibodies as early predictor for disease

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exacerbations in SLE – Guideline for treatment?, *Clin. Rev. Allergy Immunol.*, 1998, **16**, 211–218.

456 N. Agmon-Levin, C. Rosário, B. S. Katz, G. Zandman-Goddard, P. Meroni, R. Cervera, L. Stojanovich, M. Blank, S. Pierangeli, S. Praprotnik, E. Meis, L. P. Seguro, A. Ruffatti, V. Pengo, A. Tincani, A. Doria and Y. Shoenfeld, Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS), *Lupus*, 2013, **22**, 1327–1335.

457 C. Rosário, G. Zandman-Goddard, E. G. Meyron-Holtz, D. P. D'Cruz and Y. Shoenfeld, The Hyperferritinemic Syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome, *BMC Med.*, 2013, **11**, 185.

458 D. B. Kell and R. Goodacre, Metabolomics and systems pharmacology: why and how to model the human metabolic network for drug discovery, *Drug Discovery Today*, 2014, **19**, 171–182.

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