Nanoscale

ROYAL SOCIETY OF CHEMISTRY

MINIREVIEW

View Article Online
View Journal | View Issue

Cite this: *Nanoscale*, 2023, **15**, 12868

The implication of mesenteric functions and the biological effects of nanomaterials on the mesentery

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A growing number of nanomaterials are being broadly used in food-related fields as well as therapeutics. Oral exposure to these widespread nanomaterials is inevitable, with the intestine being a major target organ. Upon encountering the intestine, these nanoparticles can cross the intestinal barrier, either bypassing cells or *via* endocytosis pathways to enter the adjacent mesentery. The intricate structure of the mesentery and its entanglement with the abdominal digestive organs determine the final fate of nanomaterials in the human body. Importantly, mesentery-governed dynamic processes determine the distribution and subsequent biological effects of nanomaterials that cross the intestine, thus there is a need to understand how nanomaterials interact with the mesentery. This review presents the recent progress in understanding the mesenteric structure and function and highlights the importance of the mesentery in health and disease, with a focus on providing new insights and research directions around the biological effects of nanomaterials on the mesentery. A thorough comprehension of the interactions between nanomaterials and the mesentery will facilitate the design of safer nanomaterial-containing products and the development of more effective nanomedicines to combat intestinal disorders.

Received 29th May 2023,
Accepted 11th July 2023

DOI: 10.1039/d3nr02494f

rsc.li/nanoscale

1. Introduction

Interest in the mesentery was initially increased in 1988 when R. J. Heald conducted "total mesorectal excision" procedures in patients with rectal cancer, resulting in a significant decrease in recurrence rate to below five percent.[1] However, as early as 1909, Jamieson and Dobson highlighted the importance of removing the mesentery and the lymphatic vessels within to treat colon cancer.[2] But it was not until 2016 that the mesentery was definitively classified as a separate human organ, prompting burgeoning research into its physiological functions and its correlation with a variety of diseases.[3] Recent studies have demonstrated that the mesentery is an essential determinant in Crohn's disease, enteritis, and pathologies triggered by local mesenteric lesions, as well as the metastasis of intestinal cancer.[3,4] Furthermore, the mesentery has been revealed to play an important role in the pathogenesis of metabolism-related obesity.[5]

Advancements in nanotechnology have led to the extensive use of nanomaterials in many facets of daily life, including food items, food additives, antimicrobial coatings on food packaging materials, imaging agents, cosmetics, and medicine.[6–8] With the increasing use of such products, significant amounts of nanomaterials inevitably enter the intestine through the oral route, thus affecting the intestine and the nearby mesentery.[9] In recent years, significant effort has been directed toward investigating the biological effects of nanomaterials on normal tissues, such as the liver, spleen, lung, and kidney.[10] Although a few studies have revealed that micro–nano plastics and silver sulfide quantum dots can enter the mesentery and cause immune dysfunction and inflammation,[11,12] the interactions between nanomaterials and the mesentery, especially the pathway of nanomaterial entry into the mesentery, are yet to be explored. In addition, therapeutic systems based on nanomaterials that specifically target the mesentery are still in their infancy due to the lack of knowledge regarding the mechanisms and pathways of drug action on the mesentery.[13]

For both nanosafety and nanomedicine, there is an urgent need to understand nanomaterial–mesentery (nano–mesentery) interactions and their underlying mechanisms, thus

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avoiding the risks and broadening the application of nanomaterials. This review will briefly describe the history of the mesentery as a new organ, explore its structure and function, shed light on the importance of the mesentery in health and diseases, and discuss the biological effects of nanomaterials on the mesentery. This knowledge can be used to gain insight into the mechanisms of mesentery-related diseases and aid in the future development of nanomaterial-based therapeutic strategies.

2. The mesentery as a new human organ

Based on anatomical definitions, an organ fulfills two characteristics: (1) acting as a relatively independent part of the body and (2) performing a vital function.[14] At the outset, the mesentery was perceived as a discrete tissue. However, further anatomical research eventually established the mesentery as an uninterrupted tissue that is necessary for the formation and maintenance of systemic continuity of all abdominal digestive organs. Because the mesentery modulates the growth and development of other abdominal digestive organs,[15] defining the mesentery simply as a mucosal fold connecting the small intestine to the posterior abdominal wall is no longer accurate.[16] In this section, we elaborate on the characteristics of the mesentery as a new organ from the perspectives of development and formation, structural anatomy, function, and immunization.

2.1. A brief history of the mesentery

Leonardo Da Vinci drew the first visual draft of the mesentery, describing it as continuous as a whole and folded in one corner, without a detailed structure. Carl Toldt discovered the mesocolon in 1879, noting that the fascial plane between it and the retroperitoneal membrane was formed by the joining of the visceral peritoneum of the mesocolon and the parietal peritoneum of the retroperitoneum ("Toldt's fascia", Fig. 1).[17] In 1885, Frederick Treves described the presence of the mesentery of the ascending and descending colon on both sides and formed the basis for the classical anatomy and embryology of the mesentery.[18] In 1942, Edward Congdon demonstrated that the left and right mesocolon remained until adulthood and separated from the retroperitoneum.[19] In 2012, electron microscopy was first used to formally confirm the mesentery as a continuous organ.[3] In 2016, J Calvin Coffey proposed the increase in the total number of human organs from 78 to 79 with the addition of the mesentery.[3] Meanwhile, Format Anatomy, the world's most renowned medical textbook, updated its definition of the mesentery. Since then, great effort has been made to understand the mesentery *per se* and mesentery related diseases, such as mesenteric torsion and Crohn's disease.[20] The identification of the mesentery as an organ has sparked a surge of activity in the drug development field, with vasodilator drugs targeting mesenteric arteries being employed for treatment,[21] suggesting that the mesentery can be used as a treatment target in clinical settings. Moreover, the ability of nanomaterials to enter and transit the mesentery *via* the intestine has encouraged interdisciplinary research between nanotechnology and mesentery anatomy.[11]

2.2. The structure and function of the mesentery

The mesentery is a continuous, spiral organ comprising an upper saccular area, a middle-wrinkled area, and a lower folded area. The organ is mainly composed of the small intestinal mesentery, transverse mesocolon, right mesocolon, left

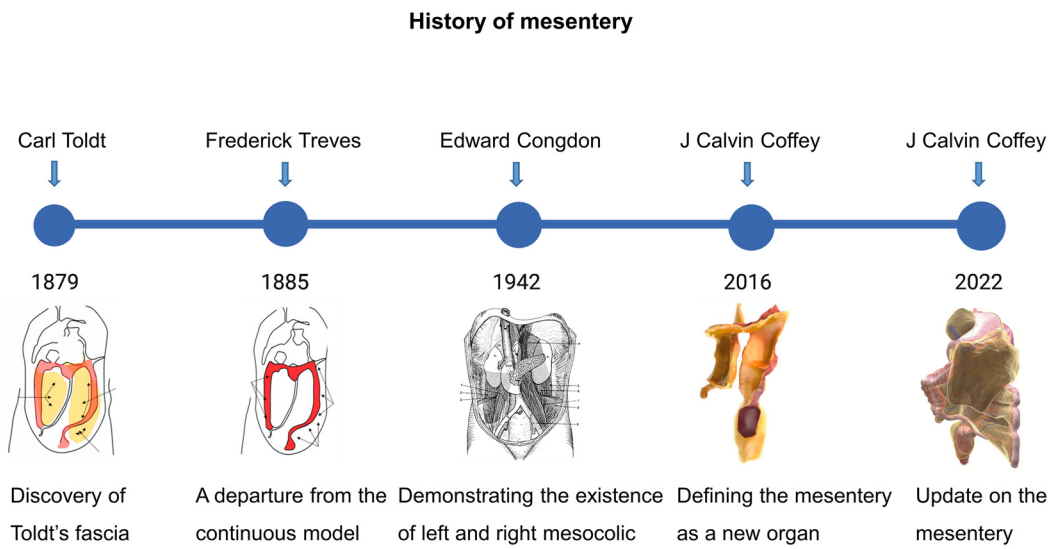

Fig. 1 History of the development of the mesentery. Reproduced with permission.[22] Copyright 2014, Oxford University Press. Reproduced with permission.[19] Copyright 1942, John Wiley and Sons. Reproduced with permission.[3] Copyright 2016, Elsevier. Reproduced with permission.[23] Copyright 2022, Elsevier.

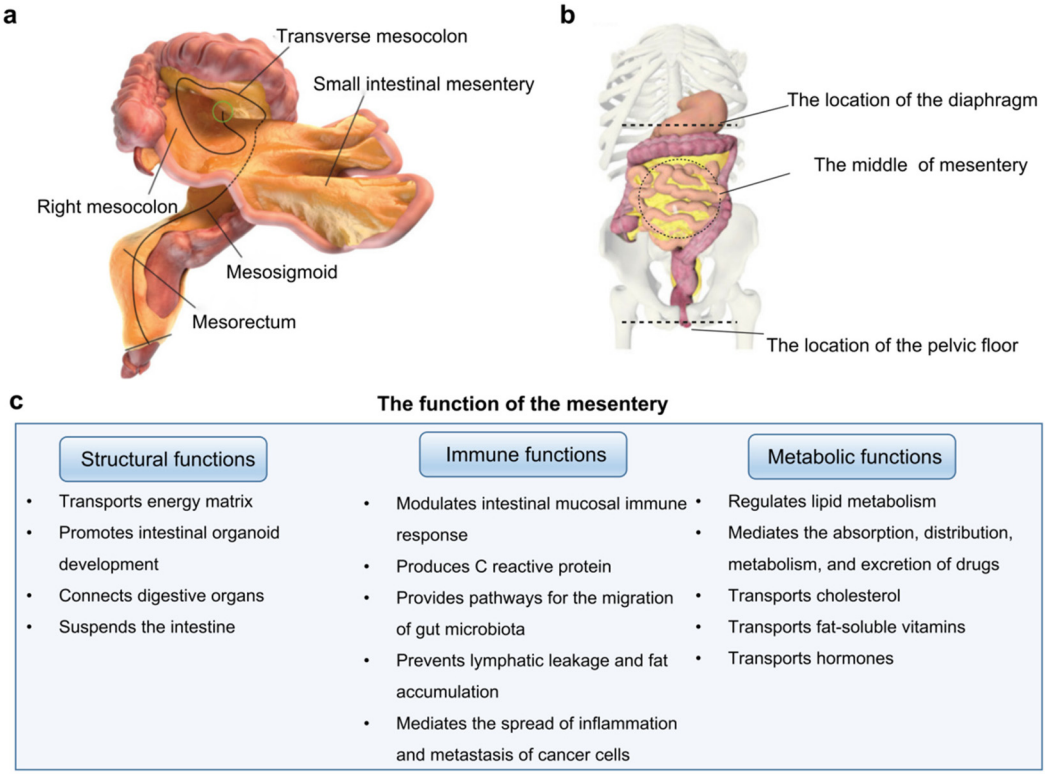

Fig. 2 (a) Structure of the mesentery. Reproduced with permission.[25] (b) Location of the mesentery in the human body. Reproduced with permission.[23] Copyright 2022, Elsevier. Copyright 2016, Elsevier. (c) Functions of the mesentery.

mesocolon, mesosigmoid, and mesorectum (Fig. 2a).[3] The mesentery is structurally independent and has superior arterial and inferior venous drainage. In the middle portion of the organ, the left and right mesentery of the small intestine and the mesosigmoid are close to the posterior abdominal wall and flattened by the peritoneum. Additionally, the mesentery is connected to the diaphragm and the pelvic floor (Fig. 2b),[24,25] thus demonstrating its importance in maintaining the position of all abdominal digestive organs.[26,27]

During the formation and development of the mesentery, not only does its structure change, but its function also evolves. Initially, the primary function of the mesentery is to provide a place for the growth of the abdominal digestive organs. Over time, the mesentery becomes an essential organ connecting, supporting, and suspending the intestine, possibly promoting the development of the intestine through its role in energy transport.[28,29] In addition to its structural functions, the mesentery also possesses immune and metabolic activity (Fig. 2c). Various functional networks in the mesentery play important roles in the human body. The mesentery is mainly composed of connective tissue and stroma, while adipocytes and other cell types, including mesothelial, nervous, vascular, lymphatic, and mesenchymal cells,[3] fill the interstitial space of the mesentery (Fig. 3a).[15,30] This abundance of components has significant physiological and pathological implications in the developmental processes of the mesentery. For instance, the division of lymphatic fibers and blood vessels from the central part of the mesentery strengthens the link between the mesentery and the connected organs.[31] The mesenteric lymph nodes in the mouse mesentery are located near the colon and surrounded by adipose tissue, connecting to the small intestine. This arrangement allows for the independent function of the intestine's immune system (Fig. 3b). The mesentery is initially formed by mesodermal progenitor cells and develops from a trilaminar germ cell disk to the ventral side of the abdomen.[30] This unique position and the organ's connection to the peritoneum make it an important mediator of communication between the digestive system and distal organs. The mesentery also provides incubatory support for the abdominal digestive organs by producing proteins, and functions as a platform for cell migration and neural growth. Furthermore, the mesentery supplies the spleen with arterial blood for differentiation.[23,26,30,32]

2.3. The role of the mesentery in the immune system

The mesentery has been studied in great detail for its role in various biological systems, particularly in the immune system. In mammals, including mice, rats, and cows, the enzymatic repertoire, such as retinal dehydrogenase and *N*-acetyl glucosamine, in the mesenteric lymph nodes participate in the localized synthesis of glycosaminoglycans, thus reinforcing the gut barrier to prevent the invasion of microbes.[13,35–37] Of note, the mesenteric lymph nodes are connected to the bowel wall, and regulate the migration of B cells, T cells, natural killer cells,

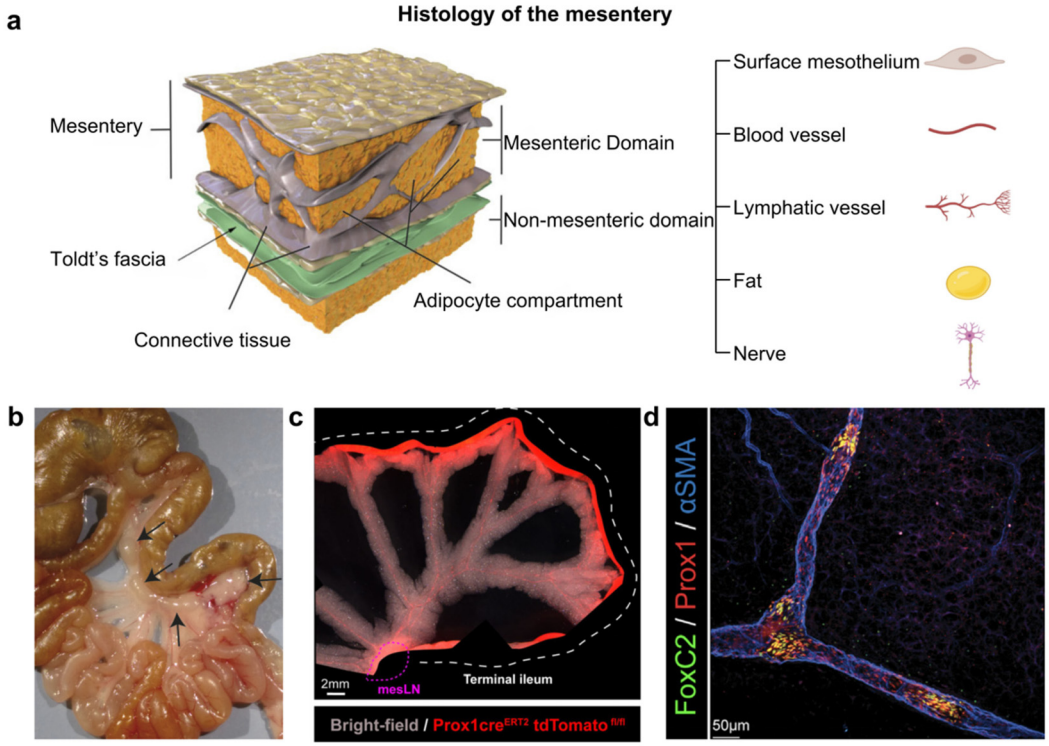

Fig. 3 (a) Histology of the mesentery. Reproduced with permission.[31] Copyright 2023, Elsevier. (b) Structure of the murine mesentery. Black arrows indicate lymph nodes. Reproduced with permission.[33] Copyright 2017, Elsevier. (c) The mesenteric lymph collecting duct structure. The intestinal sections are indicated by dashed lines. Reproduced with permission.[34] Copyright 2021, Elsevier. (d) The mesenteric lymphatic valve. aSMA identifies smooth muscle proteins in lymphatic vessels, Prox1 identifies lymphatic endothelial cells, and FoxC2 identifies valve-associated lymphatic endothelial cells. Reproduced with permission.[34] Copyright 2021, Elsevier.

and dendritic cells to the nearby intestinal mucosa (Fig. 3c).[3,38] In the mesenteric lymphatic vessels, the lymphatic valves allow the unidirectional flow of lymph from the lymph collecting ducts to the central mesenteric lymph nodes, and then into the blood circulation through the thoracic duct (Fig. 3d). A recent report described a specific immune microenvironment in the mesentery in Crohn's disease, ulcerative enteritis, and colorectal cancer, demonstrating an inhibited mesenteric immune response and increased tumor progression,[39] suggesting that the mesentery can modulate immune system reactions. Furthermore, the mesenteric C-reactive protein (an inflammatory marker) is capable of activating the complement cascade and boosting the phagocytosis behavior of macrophages.[40]

3. Mesentery-related diseases

Developments in our understanding of the mesentery's distinct structure and function have led to a greater comprehension of mesentery-related ailments. As the mesentery is situated close to digestive organs, it not only offers support but also behaves as a conduit for the transmission and progression of diseases.[3] Furthermore, the homeostatic role of the mesentery, rich in blood and lymphatic vessels, also introduces the risk of distal and systemic diseases associated with the organ. In this section, we discuss mesentery-related diseases, such as Crohn's disease, colorectal cancer, and volvulus, as well as the corresponding features of the diseases (Fig. 4a).

3.1. Crohn's disease

Crohn's disease is a chronic, recurrent inflammation of the intestine and a secondary mesenteric disorder, typically caused by external factors. Studies have suggested that the mesentery is involved in the pathogenesis of Crohn's disease, with one of the common manifestations being mesenteric fat wrapping and fibrosis around the inflamed intestine and peristaltic fat (Fig. 4b).[42] This occurrence may be a protective effect of the mesenteric fat associated with the inflammatory site, with the degree of intestinal fat wrapping and the thickness of the mesenteric wall increasing in response to exacerbated mesenteric inflammation.[43] It is also worth noting that fibrocytes, pro-inflammatory cells, are recruited to the serosal intestinal surface in pathological states of mesenteric inflammation.[44] Another possibility is that the mesentery plays a negative role in the pathogenesis of Crohn's disease. The mesentery and the intestine are joined at the serosa, and, during mesentery inflammation, which is often accompanied by transmural inflammatory and mucosal ulcer manifestations of the adjacent intestine, lymphoplasmacytic inflammation can occur deep in the mucosa, leading to the separation of

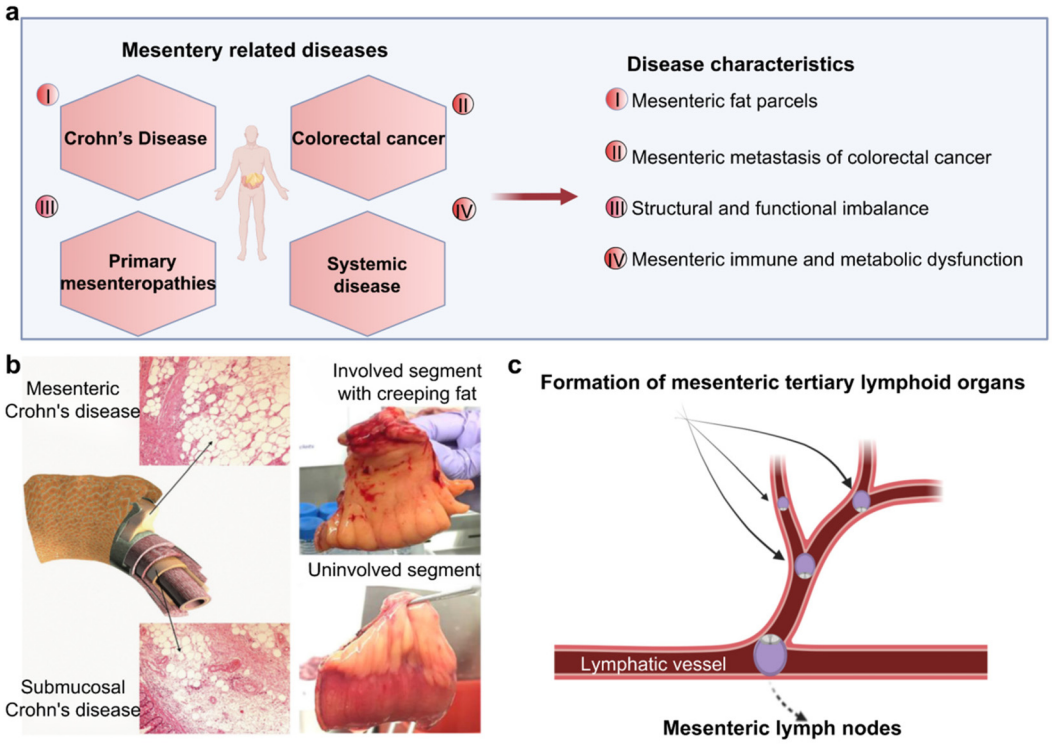

Fig. 4 (a) Mesentery related diseases. (b) Features of Crohn's disease and the accumulation of creeping fat in the intestinal segment. Reproduced with permission.[41] Copyright 2019, Elsevier. Reproduced with permission.[42] Copyright 2020, Elsevier. (c) Mesenteric lymphatic vessel remodeling and formation of new mesenteric lymph nodes.

crypt cells and the muscularis mucosae (Fig. 4b). It has been hypothesized that mesenteric inflammation may exacerbate the symptoms of Crohn's disease. This is supported by the observation that the severity of ulcers does not increase in patients with Crohn's disease when the inflamed bowel is adjacent to normal mesentery tissue.[41,45] At the cellular level, an increased number of mesenchymal cells leads to abnormal proliferation of the intestinal mesothelium, associated with the encapsulation of fat and infiltration of innate lymphocytes in the mesenteric lymphatic vessels.

Increased translocation of bacteria to mesenteric adipose tissue and mesenteric lymph nodes is another characteristic of Crohn's disease, which leads to a thickening and hypertrophy of the mesenteric fat, resulting in the production of the C-reactive protein by adipocytes.[40] Several studies have demonstrated that, in the presence of mesenteric inflammation, IL-6 and TNF-α synergistically increase the secretion of monocyte chemoattractant protein-1 and macrophage inflammatory protein-1 in adipose tissue, resulting in the storage of macrophage precursors in adipose tissue and further increasing the production of the C-reactive protein by adipocyte in Crohn's disease.[46,47]

The enlargement of mesenteric lymph nodes in adipose tissue is another common feature in patients with Crohn's disease, with abnormal interactions between lymphocytes in the lymph nodes and perinodal adipocytes, resulting in an increase of the lymph node-containing adipose tissue. This may be a result of mesenteric lymph remodeling driven by intestinal inflammation, generating a new, third lymphoid organ, comprising mesenteric lymph nodes at the branches of lymphatic vessels (Fig. 4c).[48] These recent advances in mesenteric anatomy and physiology have enabled a deeper understanding of the treatment of mesenteric tissue in Crohn's disease. In particular, experimental clinical surgery has been conducted to assess the potential effects of resectioning of the connected mesentery during bowel resection in Crohn's disease. For instance, a recent study reported the considerable decrease in the rate of reoperation after mesenterectomy in Crohn's disease.[49]

3.2. Intestinal malignancy

Normally, the mesenteric lymph vessels are directly connected to the intestine, and malignant tumors in the intestine can have various effects on the adjacent mesentery. Most notably, cancer cells can spread through the lymphatic system, penetrating the intestinal wall and metastasizing to the mesenteric wall and lymph nodes outside the mesentery, dispersing into the adipose tissue surrounded by fascia. A seminal study revealed that the location of malignant tumors is linked to metastatic patterns, the injection of colon cancer cells into the mesentery and antimesenteric sides of the colon leads to infiltration and metastasis of cancer cells in different areas of the bowel wall.[50] Currently, lymph node dissection serves as a crucial approach in colorectal cancer surgery, with the mesenteric location of lymph nodes believed to be a risk factor for

patients with colorectal cancer.[51] Moreover, it has been documented that colorectal cancer can alter the immune response in the mesentery, influencing the type and number of immune cells in mesenteric lymph nodes and altering the production of cytokines, angiogenesis, and the tumor immune microenvironment.[39]

3.3. Intestinal volvulus and malrotation with volvulus

Intestinal volvulus is a medical condition in which the intestine rotates around the mesentery or itself, leading to the formation of a coil between the intestine and the mesentery.[52] This disorder is most commonly observed in the small intestine and is caused by the lengthening of the intestinal loop and the mesentery, as well as strenuous exercise or physical labor after a meal.[23] The symptoms of volvulus include acute and severe abdominal pain, paroxysmal colic, abdominal distension, and lack of bowel movements.[53] If the mesentery is tightly twisted or the intestine is excessively dilated, it will not only cause intestinal obstruction but also cause local ischemia, a dangerous and rapidly progressing condition. Prevention of volvulus can be guided by understanding the unique structure and location of the mesentery; the unique structure and location of the mesentery provides guidance for the prevention of volvulus. For example, solving torsion can be achieved by flattening the mesentery's attachment to the bowel wall, as torsion generally occurs in the mobile area of the mesentery. This is evidenced by the lower frequency of cecal and sigmoid volvulus compared to small bowel volvulus.[25]

During the development of the intestine, the rotation of the intestine, always counterclockwise in healthy embryos, is regulated by increased expression of the Pitx2 transcription factor.[54] However, in the case of intestinal malrotation, the position of the intestine is changed or the mesenteric attachment is abnormal due to lesions in the mesentery.[23,55] This is a serious condition that can lead to volvulus, intestinal obstruction, necrosis, or even death. Intestinal malrotation is most commonly found in newborns, accounting for around 80% of cases. In adults, the disease may be caused by genetic factors or chronic inflammation due to intestinal malignant tumors. For example, a 60-year-old woman from India with invasive adenocarcinoma and cecal metastasis was found to have intestinal malrotation associated with cecal mass and dilatation and thickening of the terminal ileum.[56] The primary treatment for intestinal malrotation is Ladd's procedure of resection of the affected intestinal segment.

3.4. Other diseases

In addition to Crohn's disease and colorectal cancer, mesenteric hiatus hernia is another mesentery-related disease. This rare type of intestinal hernia, accounting for approximately 8% of all internal hernias, can be either congenital or acquired, and is usually caused by local defects in the mesentery after intestinal resection.[57] Symptoms of this condition include abdominal colic, and in severe cases, intestinal ischemic necrosis or obstruction.[58] Mesenteric cysts, another rare condition of the mesentery, are caused by enlarged lymphatic spaces and can lead to nausea, abdominal pain, and distension.[59,60] Treatment is usually by surgical resection.[61] Mesenteric vascular occlusion can be divided into mesenteric artery embolism or thrombosis, mesenteric vein occlusion, and combined occlusion of the mesenteric artery and vein.[23,62] This condition is typically caused by cardiovascular diseases, such as endocarditis or atherosclerosis, and can be life-threatening.[63] Symptoms include abdominal pain, vomiting, and hematochezia.[64]

Sclerosing mesenteritis is a condition that can cause varying degrees of mesenteric inflammation, fibrosis, and non-specific fat necrosis. Possible causes of the disease include mesenteric bacterial infection, abdominal surgery, or trauma.[65,66] The mesentery is composed of a surface mesothelium, which is distinct from mesodermal mesentery cells, and can be transformed into mesenchymal stem cells, thus influencing the number of mesenchymatous cells in the mesentery. A hallmark of sclerosing mesenteritis is abnormal mesothelial proliferation due to inflammation.[67] Patients typically present with symptoms such as inflammation and abdominal pain, and are at risk of developing various complications.

In addition to separating the abdominal digestive organs from the exterior of the abdominal cavity and preventing abdominal bacterial penetration, the mesentery is capable of regulating the level of C-reactive protein.[68] Moreover, the mesentery contains mesenteric lymphatic vessels that facilitate the transport of chylomicrons, cholesterol, and gastrointestinal (GI) hormones, thus linking the organ to systemic metabolic diseases, such as atherosclerosis and obesity.[3]

4. Nano–mesentery interactions

As mentioned above, engineered nanomaterials have permeated various aspects of daily life, including food additives, medicines, and GI tract imaging agents, thus increasing the risk of human oral exposure.[69–71] In comparison to microplastics in the air or cosmetics making more contact with the skin, GI tract imaging agents, food additives and antibacterial materials in food packaging have more potential to enter the mesentery and consequently cause more risk to human health due to their easier ingestion into the gut. The different properties of nanoparticles, such as particle size, surface charge, and surface modification, can affect their translocation behavior, fate, and subsequent biological effects in hosts (Fig. 5a and Table 1). To date, most toxicological studies of nanomaterials in the body have mainly focused on distal organs (the liver, spleen, lungs, *etc.*),[10] overlooking the initial route of entry through the intestine. Due to the close proximity of the mesentery and the intestinal lymph, nanoparticles may cross multiple levels of intestinal barriers to reach the mesentery, thus entering the systemic circulation through the abundant vascular and lymphatic vessels in the organ.[72] Investigating the interactions between nanomaterials and the mesentery is essential for understanding the *in vivo* dynamic behavior of nanomaterials, thus facilitating the intelligent design of nano-based systems targeting the mesentery. In this section, we

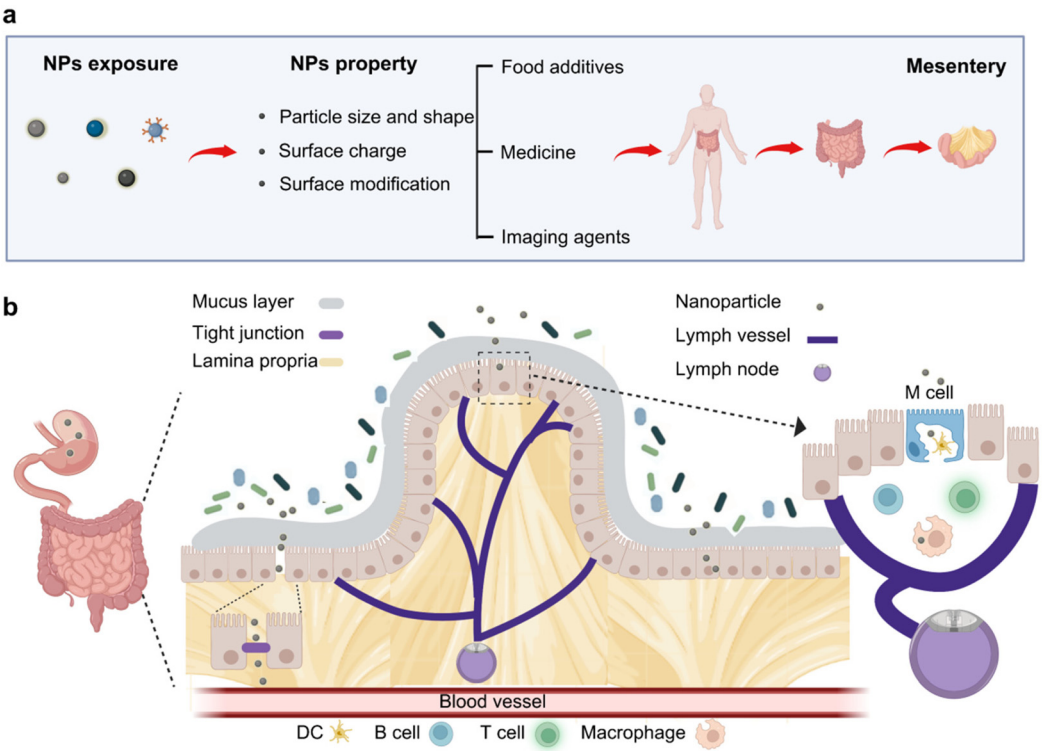

Fig. 5 (a) Key factors influencing the biological effects of nanoparticles. (b) Nanoparticles translocate the multi-level barrier of the intestine to reach the mesentery.

Table 1 The potential biological effects of nanomaterials on mesentery

Nanomaterials	Parameter (size)	Model	Exposure route	Distribution	Potential effects	Ref
Polystyrene	50 nm 500 nm 1 μm	SD rats	Oral administration	Mesentery lymph network	Inducing lymphatic leakage and fat accumulation	73
Ag_2S QDs	30.0 ± 2.0 nm 72.5 ± 5.3 nm 63.4 ± 4.9 nm 89.9 ± 8.8 nm	C57/Bl6 mice	Oral administration	Mesenteric veins	Transportation through the superior mesenteric vein into the hepatic portal vein causes an increase in the C-reactive protein concentration	11
Bile-acid-conjugated Polystyrene	100 nm 250 nm	SD rats	Oral administration	Mesenteric lymph node	Damaging the germinal center of mesenteric lymph nodes	74
SiO_2	50 nm	SD rats	Oral administration	Mesenteric lymph duct and node	Damaging the valve of the lymphatic collecting duct; impairing the function of the lymph nodes and inducing lymphatic reflux	75
CeO_2	191 ± 77 nm	SD rats	Intratracheally instillation	Mesenteric micro-vasculature	Affecting the function of mesenteric microvessels; causing endothelial dysfunction and excessive vasoconstriction	76

discuss the ability of nanomaterials to translocate from the intestine to mesentery, the effects of nanomaterials on the mesentery, and propose the potential mesenteric interception of nanomaterials.

4.1. The translocation of nanomaterials from the intestine to the mesentery

Thus far, several studies have demonstrated that various nanomaterials are able to translocate across the intestinal lumen and enter the mesentery.[11,73] For example, polystyrene (PS) microspheres of different sizes and charges enter the mesentery through the lymphatic system and accumulate in the capillaries and lymph nodes.[73] Another report of *in vivo* nanomaterial entry into the mesentery demonstrated that Ag_2S quantum dots enter the superior mesenteric vein after oral gavage.[11] Interestingly, fluorescent magnetic microcapsules injected at the branches of the superior mesenteric artery in rats, attached to mesenteric microvessels under a magnetic

field.[77] Specifically, a proportion of the fluorescent magnetic microcapsules either accumulated along the walls and curvature of mesenteric vessels or entered the vein by translocating across vascular endothelial cells. In addition, chylous particle-modified mesoporous silica nanoparticles can facilitate oral drug absorption through the lymphatic transport process in the intestinal villi.[75] Together, these findings indicate that nanomaterials are capable of crossing the mesenteric vessels and making their way into the circulatory system.

Although qualitative evidence has confirmed that nanomaterials can penetrate the intestinal barrier into the mesentery, the specific pathways responsible for this phenomenon remain to be fully elucidated. A plausible pathway is that nanomaterials translocate the multi-scale intestinal barrier, including the bacterial barrier and the mucus layer, disrupting the tight junctions of the epithelial barrier, and the immune layer, before being absorbed *via* endocytosis by M cells or collected by dendritic cells, and finally captured by the mesenteric lymph nodes to enter the systemic circulation.[12,78] Another possible route is the direct translocation of nanomaterials across the small intestine and entry into the mesenteric vein *via* clathrin-mediated endocytosis and/or micropinocytosis (Fig. 5b).[11]

4.2. The influence of nanomaterials on the structure and function of the mesentery

Because the structure of mesenteric tissue is mainly composed of arterial branches, small venous vessels, lymphatic vessels, and lymph nodes, the architecture is relatively thin and thus susceptible to nanoparticle accumulation. It has been shown that exposure to nanomaterials, such as CeO_2 nanoparticles, can impair the dilation of mesenteric arterioles in a dose-dependent manner.[76] Nanomaterials can induce vascular injury through two pathways: endothelium-dependent and endothelium-independent mechanisms. Endothelium-dependent injury is often caused by the release of vasodilator or vasoconstrictor factors by vascular endothelial cells,[79] while endothelium-independent injury is closely related to the function of vascular smooth muscle. In the latter, nanomaterials can affect the function of mesenteric microvessels, resulting in endothelial dysfunction and excessive vasoconstriction.

Mesenteric lymphatics have been identified as factors in the occurrence and development of Crohn's disease; inflammation of these lymphatics can cause disruption of the microstructure and leakage of the lymph fluid (Fig. 6). Although the lymph collecting ducts in the mesentery differ from those in the intestinal wall, the mesenteric ducts nonetheless contain smooth muscle cells. Damage to these cells by nanomaterials can thus interfere with the mesenteric lymph collecting vessels. A recent study described nano-drug delivery systems that target the mesenteric lymphatic system, thus alleviating structural damage to the lymphatic vessels and the mesenteric immune microenvironment.[80] This nanoformulation comprised mesoporous silica nanoparticles conjugated with long-chain fatty acids, coated with the intestinal membrane, and loaded with the small molecule drug, laquinimod. The nanoparticles targeted the mesenteric lymphatic vessels to deliver

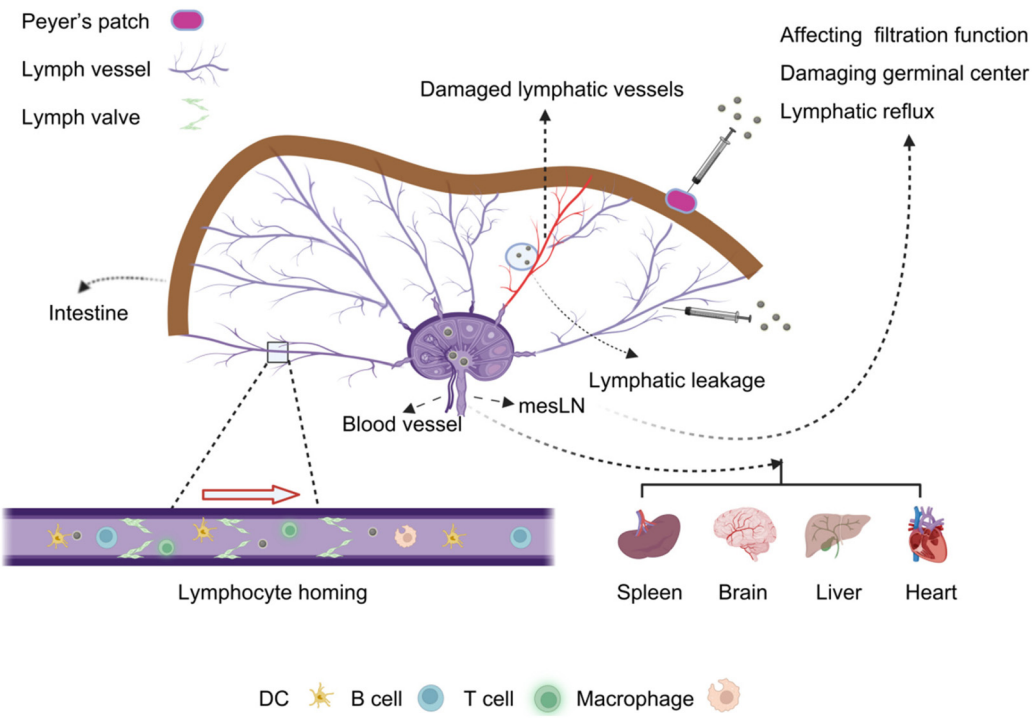

Fig. 6 Nanoparticles enter the mesentery, causing lymphatic damage and lymphatic reflux. When nanomaterials accumulate in mesenteric lymph nodes, they can provoke an increase in the number of immune cells, as well as damage the germinal center of lymph nodes, impair the filtration capability of lymph nodes, and induce lymph reflux.

the drug and repair the structure of the mesenteric lymphatic vessels.

4.3. The influence of nanomaterials on mesenteric immunity

Anatomically, the lymphatic vessels connected to the lamina propria, submucosa, and muscularis of the intestinal wall are involved in the transport of immune cells into the mesentery and the terminal mesenteric lymph nodes.[81] Therefore, the integrity of these vessels is central to the homeostasis of the mesenteric immune system. When the mesenteric lymphatic vessels are damaged or lost, dendritic cells are unable to migrate from the gut to the mesenteric lymph nodes. The efferent lymphatics connected to the mesenteric lymph nodes will transport a large number of lymphocytes and other cargo into the bloodstream.[82] This pathway provides a route for nanomaterials to modulate the mesenteric immune microenvironment. Although there is a gap in our knowledge of the effects of nanomaterials on the mesenteric immune microenvironment, this transport route represents a new research direction to examine the interaction between nanomaterials and the mesentery.

During intestinal inflammation, a third lymphoid organ is formed in the inflamed area of the mesentery near the ileum,[82] where the proportion of B cells and T cells is higher than that in other lymphoid organs. Importantly, this third lymphoid organ may prevent lymphatic drainage between the intestinal wall and mesenteric lymph nodes. Generally, intact immune cell homing is essential for intestinal immune equilibrium, and macrophages in the mesenteric collecting ducts may ingest nanoparticles into the mesenteric lymph nodes (Fig. 6). Furthermore, the mesentery is associated with intestinal inflammation, and nanomaterials or nano-drug delivery systems may interact with the mesenteric immune system at the onset or throughout the treatment of inflammation. Consequently, further studies are required to explore the connection between nanomaterials and mesenteric immunity. These interdisciplinary studies are necessary to further advance immunotherapy targeting the mesentery.

4.4. The influence of nanomaterials on various cell types of the mesentery

At the cellular level, the mesentery is composed of vascular endothelial cells, lymphocytes, adipocytes, and fiber cells. Nanomaterials can affect mesenteric cells in two ways. First, they can indirectly influence the physiological state of mesenteric cells by altering the intestinal flora.[83] For instance, TiO_2 NPs and Ag NPs can alter the structure and diversity of the gut microbiota, thus affecting the mesenteric adipose tissue and the transformation of mesentery mesothelium into mesenchymal cells.[42,84] Second, nanomaterials can directly interact with mesenteric cells after entering the mesentery through pathways such as lymphatic uptake. It is commonly accepted that the interaction between nanomaterials and mesenteric cells can contribute to the development of mesenteric tissue cells and the phenotypic transformation of immune cells in the mesentery.

4.5. The influence of the mesentery on the biodistribution of nanomaterials and the mesenteric interception effect

The mesentery's rich lymphatic channels and large surface area have a significant influence on the systemic distribution and transport of nanoparticles after their entry into the mesentery. Furthermore, the mesenteric biocontext can have an effect on the physicochemical properties of nanomaterials.[85] Essential proteins in the blood of the mesenteric capillaries may attach to the nanoparticles, forming a protein corona and altering their size. Additionally, the abundance of immune cells in the mesenteric lymphatic vessels may secrete enzymes, such as myeloperoxidase, which can break down invading nanomaterials. Consequently, the components of the mesentery are essential for influencing the properties of nanomaterials and their subsequent distribution.[86] As the absorption of nutrients in different intestinal segments is different, the mesenteric lymphatic vessels connecting different parts of the intestine also have variable effects on the distribution of nanomaterials in the mesentery. Although there appear to be no studies examining the general distribution of nanomaterials in the mesentery, some studies have investigated the transport and distribution of nanoparticles in the mesentery by injecting nanoparticles into the Peyer's patch and mesenteric lymphatic vessels.

When nanoparticles enter the mesentery from various routes, there can be damage to the lymphatic vessels, resulting in a retrograde lymph flow or leakage into the mesenteric interstitium (Fig. 6).[34] The lymphatic endothelial cells in the mesenteric lymphatic vessels sense pressure changes in the mesenteric interstitium, which provides a signal for controlling the opening of lymphatic valves.[72] Additionally, nanoparticles internalized by cells or entering the mesentery through pathways that bypass cells may agglomerate in the mesenteric lymphatic vessels and capillaries, leading to the obstruction of the third lymphatic organ and coverage by creeping fat, thus underscoring the mesentery as an organ uniquely suited to mediate the entry of nanomaterials into the body.[42] Importantly, mesenteric lymph nodes act as a filtering barrier and couple with lymphatic vessels to promote immune responses. The interaction between nanomaterials and the mesentery may activate immune cascade reactions, thus blocking the entry of nanomaterials into the body.

5. Conclusions and perspectives

It is now clear that the mesentery is a distinct organ that performs structural, immune, and metabolic functions, thus influencing the adjacent abdominal organs. The mesentery works in tandem with other organs to maintain the overall health and homeostasis of the human body. Moreover, the mesentery clearly plays a crucial role in the pathogenesis and progression of various diseases, especially intestine-related diseases (Crohn's disease, colorectal cancer, and volvulus). Of note is that the abundance of lymphatic vessels linking the mesentery is associated with systemic metabolic diseases

including atherosclerosis and obesity; this might be attributed to the lymphatic vessels' capacity to transport cholesterol.

The intricate connective networks between the mesentery and the intestine are both biological barriers and important conduits for the entry of exogenous substances/particles through the oral route.[31] Upon entering the intestine, nanoparticles may penetrate the mesentery and alter its structure or function. For instance, these particles may traverse cellular bypass pathways or active cellular transport pathways and interact with adipose tissue and lymphocytes, potentially obstructing lymphatic or blood vessels, leading to the formation of a third immune organ, and thereby altering the mesenteric immune microenvironment. Apart from the effects of nanoparticles on the mesentery, the mesenteric components may reciprocally influence the physicochemical properties of nanoparticles. These components, including immune cells, antibodies, enzymes, and proteins, can alter the size, morphology, particle state and surface charge through adsorption, degradation, or transformation. Therefore, it is essential to conduct a comprehensive study of nano–mesentery interactions in order to establish a framework for assessing the biological safety of nanoparticles in the human gut.

In addition, nanomaterials and nano-drug delivery systems have utility in the monitoring and treatment of various diseases, such as enteritis.[87] Therefore, it will be beneficial to improve the safety of nanomaterials and develop more effective nano-drug delivery systems to target the mesentery for the treatment of mesentery-related diseases, including Crohn's disease and colorectal cancer.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgements

This work was supported by the National Key Research and Development Program of China (2021YFA1200900, 2022YFC2409701, 2021YFE0112600), the National Natural Science Foundation of China (32271460), the Youth Innovation Promotion Association of the Chinese Academy of Sciences (2023042), the Research and Development Project in Key Areas of Guangdong Province (2019B090917011), and the Key-Area Research and Development Program of Guangdong Province for Guangdong High Level Innovation Research Institute (2020B0909010001).

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