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Advancements in rheumatoid arthritis therapy: a journey from conventional therapy to precision medicine *via* nanoparticles targeting immune cells

Anwesha Laha, [a] Simran Nasra, [a] Dhiraj Bhatia [b] and Ashutosh Kumar *[a]

Rheumatoid arthritis (RA) is a progressive autoimmune disease that mainly affects the inner lining of the synovial joints and leads to chronic inflammation. While RA is not known as lethal, recent research indicates that it may be a silent killer because of its strong association with an increased risk of chronic lung and heart diseases. Patients develop these systemic consequences due to the regular uptake of heavy drugs such as disease-modifying antirheumatic medications (DMARDs), glucocorticoids (GCs), non-steroidal anti-inflammatory medicines (NSAIDs), *etc*. Nevertheless, a number of these medications have off-target effects, which might cause adverse toxicity, and have started to become resistant in patients as well. Therefore, alternative and promising therapeutic techniques must be explored and adopted, such as post-translational modification inhibitors (like protein arginine deiminase inhibitors), RNA interference by siRNA, epigenetic drugs, peptide therapy, *etc*., specifically in macrophages, neutrophils, Treg cells and dendritic cells (DCs). As the target cells are specific, ensuring targeted delivery is also equally important, which can be achieved with the advent of nanotechnology. Furthermore, these nanocarriers have fewer off-site side effects, enable drug combinations, and allow for lower drug dosages. Among the nanoparticles that can be used for targeting, there are both inorganic and organic nanomaterials such as solid-lipid nanoparticles, liposomes, hydrogels, dendrimers, and biomimetics that have been discussed. This review highlights contemporary therapy options targeting macrophages, neutrophils, Treg cells, and DCs and explores the application of diverse nanotechnological techniques to enhance precision RA therapies.

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[a]*Biological and Life Sciences, School of Arts & Sciences, Ahmedabad University, Central Campus, Navrangpura, Ahmedabad 380009, Gujarat, India. E-mail: ashutosh.kumar@ahduni.edu.in*

[b]*Indian Institute of Technology Gandhinagar, Palaj, Gandhinagar – 382055, Gujarat, India*

1. Introduction

In the 1800s, while examining patients complaining of severe joint pain, Augustin Jacob Landré-Beauvais first described

Anwesha Laha

Anwesha Laha is a postgraduate in Biotechnology from St. Xavier's College, Kolkata. Having completed her Master's thesis in immunology from ICMR-NICED, she is now pursuing her doctoral studies at Ahmedabad University. Anwesha's research is centered on the development of nano-drug delivery systems aimed at targeting immune cells for the treatment of rheumatoid arthritis. She aspires to make significant advancements in the field, contributing to more effective and targeted therapies for this chronic autoimmune condition.

Simran Nasra

Simran Nasra is currently a doctoral student at Ahmedabad University. She obtained her Master's degree in Biochemistry from Nirma University. Her PhD focuses on Targeted Macrophage Re-Programming: Synergistic Therapy with Methotrexate and RELA siRNA Folate-Liposome in RAW264.7 Cells and Arthritic Rats. Her research in Dr Ashutosh Kumar's Nanobiotechnology Laboratory is focussed on exploring drug delivery targets for rheumatoid arthritis.

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RA.[1] It is now known to be an autoimmune disorder, which is chronic in patients and affects the synovial joint lining. The causes extend to environmental, genetic, or both.

Under normal body physiology, an acellular synovial membrane is found, composed of a fine layer of mostly macrophages and cellular components derived from fibroblasts.[2] These macrophages display an inflammatory and hypertrophic phenotype in RA.[3] The other effector immune cells involved in the pathophysiology are antigen-presenting cells (APCs) like dendritic cells and B cells. Neutrophils are also known for their immune roles in RA. All these cells secrete a plethora of chemical activators such as chemokines and cytokines that escalate the inflammation.[4]

RA, due to its effects, needs a proper diagnosis followed by immediate care and treatment. Research has shown that when RA is left untreated, patients subsequently lose their ability to work or move. Even in certain cases, the disease onset becomes so severe that the patients show symptoms of pulmonary granulomas and keratitis, which can prove fatal.[5,6] On the other hand, some therapies have been created to treat or lessen the effects of RA. The majority of them deal with anti-inflammatory issues. The conventional drugs are mostly effective and some of them have been named and described in Table 1.[7] However, studies have shown them to be endowed with a range of side effects (Table 1) and resistance in patients, owing to their non-specific action, excess, and repeated dosage.[8] This has paved the way for efforts to discover more cell-based therapies and natural compounds with fewer side effects.

To make drug targeting more specific, nowadays, nanotechnology comes in most handy. Nanostructures hold great promise as innovative delivery systems for drugs (DDSs) because they can be designed to deliver certain medication dosages to targeted locations. By enabling temporal regulation over the release kinetics of the drug and raising the biological availability of the medicinal component, they contribute to safe and effective DDSs. Nanotechnology usage in physiochemical therapies, like in the replacement of joints, photothermal therapy (PTT), and photodynamic therapy (PDT) are a few cutting-edge RA therapeutic techniques.[9] Biological nanoparticles are of greater importance pertaining to their high biocompatibility in the body and low toxicity. All these make nanotherapy an ideal choice in biomedicine. Diseases that are challenging to treat by conventional therapies due to the lack of specificity in targeting or regional bioavailability, like those in mitochondrial disorders, can be effectively treated by the advent of nanodrugs.[10] Stimuli-regulated nanozymes have also been used in photothermal therapy in tumor microenvironments to release reactive oxygen species (ROS) for killing cancerous cells.[11] Nanoparticles have also shown potential in the monitoring and detection of cancers such as colorectal cancer.[12] They can also be used in the theragnostics of cardiovascular diseases (CVD) with increasing opportunities for personalized medicines.[13] Similarly, this review discusses the advancements in RA therapy aided by nanotechnology.

In RA, many patients die due to a lack of information or awareness about the management of their symptoms. Hence, this review brings to the readers the current updates on the strategies being used or in the process of being developed for both managing the disease and stopping its progression. It takes the reader through conventional therapies, their side effects, recent therapeutics, and emerging solutions aided by nanotechnology for treating RA. It also aims to convey the various nanocarriers available and the potential advantages and disadvantages that come with them for the treatment of RA.

2. Role of macrophages in RA

Macrophages are immune cells that are found in three different phenotypes, depending on the physiological condition of the body.[14] M0 or naive macrophages are found

Dhiraj Bhatia

Dr Dhiraj Bhatia obtained his PhD from NCBS-TIFR in Bangalore, India, in DNA nanotechnology. Post PhD he went to the Curie Institute in Paris, initially as a Curie fellow and later as an HFSP long-term fellow, where he learnt about the cellular and biological applications of DNA nanodevices. In 2018, he moved to India to start his own laboratory at the Indian Institute of Technology Gandhinagar, where he is an Associate Professor. His lab focusses on translational aspects of DNA nanotechnology to develop tools to program biological systems for biomedical applications.

Ashutosh Kumar

Dr Ashutosh Kumar works as an Associate Professor in the Division of Biological and Life Sciences, School of Arts and Sciences, Ahmedabad University, Gujarat, India. His research group works at the intersection of biology and nanotechnology, with a specific emphasis on advancing nanomedicines tailored for the therapy of breast cancer and rheumatoid arthritis. His work focuses on harnessing the distinctive properties of nanoparticles to improve drug delivery specificity, minimize side effects, and enhance therapeutic outcomes.

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Table 1 Conventional drugs used in RA and their mechanism of action and side effects

Class of drugs	Mechanism of action	Side effects
Non-steroidal anti-inflammatory drugs (NSAIDs)	(a) Analgesic, antipyretic, and anti-inflammatory properties (b) Effects are caused by the suppression of inflammatory mediators produced by the cyclooxygenase (COX) pathway	I. Non-specific drugs II. Acute kidney ischemia III. Increased blood pressure IV. Increased bleeding V. Upper gastrointestinal complications VI. Rashes VII. Cardio-vascular effects
Glucocorticoids	(a) Anti-inflammatory activity pertaining to its action by binding to its receptor. (b) Glucocorticoid-receptor complex binds to *cis* elements called glucocorticoid response elements and results in the downstream effect	I. Cataract II. Metabolic disorders III. Peptic ulcers IV. Osteoporosis V. Diabetes
Disease modifying anti-rheumatic drugs (DMARDs)	(a) Disease-modifying agents, some of which, like methotrexate are chemotherapeutic in nature (b) Function by blocking molecular metabolisms like inhibition of purine or pyrimidine synthesis (c) Can also block cell signalling components or cell–cell interactions	I. Nephrotoxicity II. Gastro-intestinal disorders III. Retinal toxicity IV. Hepatic dysfunction V. Infections VI. Hematological disorders VII. Pneumonitis VIII. Leukopenia, neutropenia IX. Skin infections X. Central nervous system toxicity XI. Sepsis

under normal body physiology, which when intruded by pathogens or other potent harmful cells, get converted to activated or proinflammatory M1 macrophages, secreting inflammatory cytokines and other bioactive substances, to save their soul. These signals that convert M0 to M1 can be lipopolysaccharides (LPS), granulocyte macrophage colony stimulating factor (GM-CSF) or cytokines like interferon-gamma (IFNγ), and tumor necrosis factor (TNF). M1 macrophages are a repertoire of secreting inflammatory cytokines that lead to progressive joint erosion, namely interleukin 6, 12, 1β, and TNF.[15] Similarly, certain cytokines like IL-10 can get these M1 macrophages transformed into anti-inflammatory macrophages (M2), which then secrete signals and get converted to M0 macrophages, returning to normal body homeostasis. This is the cycle of polarization of the macrophages by the immune system to protect the body from diseases. However, under certain disease conditions, this homeostasis is jeopardized, and there is hyperactivation of pro-inflammatory macrophages, which overexpress cytokines, attacking the own body tissues and cells, like in autoimmune diseases like RA.[16] In RA, NF-κB, MAPK, JAK/STAT, Notch, and other signaling pathways control the M0–M1 phenotype conversion. Additionally, this process is aided by metabolic reprogramming, whereby M2 macrophages employ oxidative phosphorylation while M1 macrophages prioritize glycolysis.[17] Maintenance of homeostasis is regulated by different receptors, one of which is colony stimulating factor 1 receptor (CSF1R).[18] Thus, these long-lived macrophages, which are tissue-resident cells, play an important role in determining inflammatory tissue priming with the infiltration of lymphoid and myeloid immune cells, secreting effector proteins, namely antibodies, cytokines, and vesicular structures, that can regulate systemic functions.[19]

In macrophages and monocytes, tumor necrosis factor receptor-associated factor 1 (TRAF1) is thought and found to have an inhibitory role in the expression of pro-inflammatory cytokines, inflammasome-mediated IL1 secretion, and NF-κB activation. Thus, it is hypothesized that macrophages in RA lack TRAF1, but conducting conclusive experiments is difficult due to the polymorphisms found in TRAF1.[20] An adipokine, resistin, has the potential to hyperactivate macrophages by adenylate cyclase associated protein 1 (CAP1), which leads to perivascular adipose tissue damage (PVAT), leading to cardiovascular diseases (CVD), one of the leading causes of death in RA.[21] Double positive macrophages, that are both CD4 and CD8 positive macrophages, are markers of inflammation and are involved in inflammation of the Th1 type.[22] Secretion of the soluble form of A proliferation inducing ligand (APRIL) from macrophages induces the viability and formation of B cells, leading to B cell-mediated auto-immunity. An Ig-like lectin family protein, Siaglec1, that can bind sialic acid, undergoes activation in macrophages, leading to an increase in C-reactive protein (CRP) and IgM – rheumatoid factor. Allograft inflammatory factor 1 is overexpressed in RA which initiates and maintains inflammation in the RA synovium.[23] NF-κB signalling is crucial to the pathophysiology of RA. The involvement of NF-κB in the synthesis of the chemokine IL-8 and macrophage inflammatory protein-1α supports this claim.[24]

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In the joint environment, monocytes are activated and polarized into pro-inflammatory M1 macrophages, which is a part of the pathophysiology of RA.[25] Chemoattraction of monocytes to the arthritic joint is mediated by proinflammatory cytokines, such as IL-1, TNF and IL-6, produced by resident cells, such as macrophages and FLSs. By connecting to their receptors, these cytokines stimulate monocytes, which increases the expression of adhesion molecules and chemoattractant receptors on the surface of the cells. Consequently, the monocytes migrate into the synovial tissue and cling to the blood vessel endothelium. CD80 and CD86 and other markers present on the surface, which enable interactions and improve the presentation of the antigen *via* T cells, are expressed at higher levels by activated monocytes, along with CD14 and CD16.[26]

In RA, there is decreased autophagy in macrophages, which leads to ROS production. Peroxisome proliferator-activated receptor γ (PPARG) accelerates autophagy and prevents ROS-mediated macrophage polarization and "NOD-like" receptor protein (NLRP3) inflammasome activation, thus reducing reactive oxygen species (ROS) production and their accompanying stress.[27]

In murine collagen-induced arthritis (CIA) and synovial biopsies from RA patients, macrophages in the secondary lymphoid organs (SLOs) and synovial ectopic lymphoid-like structures (ELSs) were found to produce peptidyl arginine deiminase 4 (PAD4). Intracellular citrullinated histone release and macrophage extracellular trap formation (METosis) were demonstrated by activated murine and synovial fluid macrophages. Hence, lymphoid tissue macrophages have a role in the synthesis of anti-citrullinated protein antibodies (ACPAs) and the citrullination of self-antigens, suggesting that focusing on them specifically can help treat autoimmune diseases that depend on citrullination.[28] Thus, the various changes in macrophage physiology make them a good target for RA (Fig. 1). Various molecular markers of RA are being targeted to deliver a cell-based therapy, some of which have been cited in the table below (Table 2).

3. Role of neutrophils in RA

Neutrophils are a key player implicated in RA pathophysiology. Overexpression of Fcγ receptors is found on the surface of activated neutrophils. A plethora of bioactive inflammatory molecules are secreted by them. Some of them are IFNγ, TNFα, IL1β, IL6 and G-CSF, which are produced when immune cells interact with synoviocytes, causing synovitis.[43] This can also lead to osteoclastogenesis *via* IL10, TGF-β, and IL6. The situation is further aggravated when these osteoclasts act as APCs and lead to the activation of T_h and T_c cells.[44,45]

Neutrophils are also associated with the release of degradative enzymes.[46] Myeloperoxidase (MPO) is one such enzyme that activates T cells and DCs and is linked with the consumption of nitric oxide (NO), leading to the generation of nitrite ions (NO_2^-).[47,48] Another serine protease named neutrophil

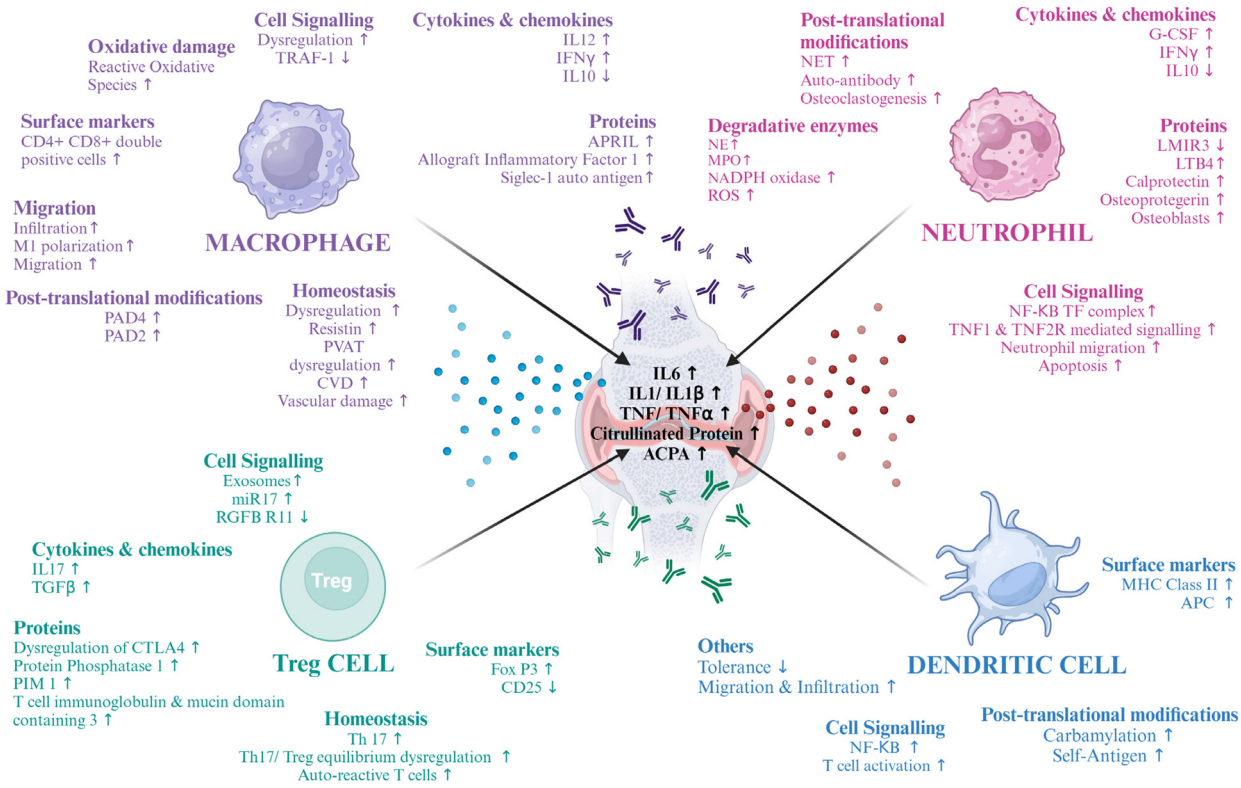

Fig. 1 Role of immune cells in RA – the potential dysregulations in the normal metabolic and cellular pathways in macrophages, neutrophils, regulatory T cells and dendritic cells that lead to RA and can be potential targets for therapeutics. The image was created with BioRender.com.

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Table 2 Recent treatment strategies targeting macrophages

Targets	Outcomes	Ref.
TRAF1	An increase in the expression of TRAF1 or infiltration of macrophages with expressed TRAF1 can have a therapeutic effect	20
Resistin	Inhibition of resistin can control PVAT, thus lowering CVD	21
Iguratimod	Inhibits activation of the IL-4/STAT 6 signalling pathway and has anti-fibrotic effects and prevents chronic kidney disease (CKD), inhibits macrophage infiltration, M1 polarization, and RAW264.7 migration	29–31
CSF1 & IL34	Can regulate macrophage homeostasis *via* CSF1R	18
APRIL	Inhibiting APRIL can lead to the lowering of B cell-mediated autoimmunity. Atacicept is an antagonist of APRIL.	32
Siaglec-1	Downregulation of this can decrease the CRP and IgM – rheumatoid factor and reduce inflammation	33
Allograft inflammatory factor 1	Inhibition of this can stop the proliferation of inflammatory macrophages	34
Pro-inflammatory cytokines	Reduction in the levels of IL12, TNF, IL1β, IL6, and IFNγ can help control immune reactions. A potent TNF antagonist is infliximab	35
CTLA4	Inhibitor of cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) shows antigen presentation by macrophage-T cell cooperation mediated by cell–cell contact	36
PPARG	Reduces ROS production in macrophages	27
Neutrophil cytosolic factor 4 (NCF4)	Cysteine peptides are kept in an oxidized crosslinked state by NCF4-dependent intracellular ROS, which shields against autoimmune arthritis by preventing the non-tolerized T cells from the presentation of peptides	37
JAK inhibitors	JAKi can increase MAFB expression, and it also promotes macrophage reprogramming toward the acquisition of a more anti-inflammatory/pro-resolution profile	38
Bruton's tyrosine kinase (BTK)	Inhibition of this might have potential therapeutic effects on RA	39
Total glucoside of Paeonia (TGP)	Modulates various cell signalling pathways to control inflammation	40
Peptidylarginine deiminase 4 & 2 (PAD4 & PAD2)	Inhibition of these can lead to a decrease in the citrullination of peptides and reduce the formation of autoantigens	28 and 41
Acetylcholine	Dose-dependent inhibition of pro-inflammatory cytokine release from macrophages	42

elastase (NE)[49] activates proteinase activating receptors (PARs)[50,51] and leads to cartilage destruction.[52] NADPH oxidase is also produced by neutrophils, which produces superoxide radicals, thus increasing the burden of reactive oxygen species (ROS).[53] In RA, neutrophils are reported to decrease apoptosis, which is preceded by an increase in the upregulation of NF-κB transcription factor complexes. This leads to the upregulation of the TNF 1 and 2 receptors, and this mediates the migration of neutrophils in the RA synovial fluid. A chemoattractant leukotriene B4 (LTB4) can lead to increased neutrophil activation and recruitment.[54] The upregulation of RANKL increases the formation of neutrophil extracellular traps (NETs), which are composed of a network structure containing granular enzymes and chromatin that not only traps bacteria but also increases the quantum of autoantigens, as NETs are composed of citrullinated proteins mediated by PAD4. These NETs are then counter-attacked, generating autoantibodies, *i.e.*, anti-citrullinated protein antibodies (ACPAs). NETs also increase osteoclastogenesis which leads to elevated bone erosion.[55] NETs are found to be carbamylated, which is associated with signalling for rapid osteoclast formation.[54] Thus, neutrophils are important in the pathophysiology of RA (Fig. 1) and are important targets for therapy, and some of the molecular targets are mentioned below in Table 3.

4. Role of Tregs in RA

FoxP3 expressing Tregs are known for their immunosuppressive functions.[66] The prevention of autoimmunity and main-

Table 3 Recent treatment strategies targeting neutrophils

Target	Outcomes	Ref.
NETs by inhibiting PAD4	Inhibiting the formation of NETs by inhibiting PAD4, can prevent bone erosion and the generation of autoantibodies. Inhibiting carbamylation can also be a target	56–58
Apoptosis	Inducing apoptosis can help in downregulating signalling *via* the NF-κB pathway, helping in reducing inflammatory responses. Celastrol is a drug that can be used for this	59 and 60
TNFα	Inhibition of these can help reduce osteoclastogenesis and neutrophil migration	43
IL6 receptor	Inhibiting this can reduce osteoclastogenesis	43 and 61
MPO, NE, NADPH oxidase & glutathione peroxidase 3 (GPX3)	Inhibiting these degradative enzymes can help in decreasing the chemokines and ROS burden in the synovium	43 and 62
LTB4 receptor (BLT1)	Inhibiting this receptor can slow down bone erosion	63
Leukocyte mono-immunoglobulin-like receptor 3 (LMIR3)	It controls inflammation negatively and is highly expressed in neutrophils. Dehydroandrographolide can bind to LMIR3 and prevent neutrophil activation	64
Prostaglandin E2 (PGE2)	Inhibition of PGE2 can decrease NETosis and neutrophil infiltration	65

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taining tolerance are their primary functions. However, there is a drop in their number as well as their function in RA.[67,68] The levels of cytokines like IL6 and TNFα are upregulated, which has important implications for the improper expression of FoxP3, which leads to a deficiency in the function of Tregs. This regulation is there at both protein and gene levels and passes *via* cell signalling pathways.[69,70] IL1β is another cytokine implicated in this.[71] IL2 and IL21 are also important for maintaining the homeostasis of Tregs that are dysregulated in RA.[72] The reduction of T-cell immunoglobulin and mucin-domain containing-3 was found to play a role in the dysfunction of Tregs.[73] Wang L. *et al.* found that a microRNA, miR-17, targets the TGFBRII receptor, thus leading to the suppression of Treg differentiation. This miRNA was found to be transferred *via* exosomes.[74] In RA, Tregs and Th17 compete with one another to create a dynamic equilibrium. One important cause of RA is an imbalance in this immunological balance.[75,76] Consequently, rectifying the Treg/Th17 cell imbalance, decreasing the number of Th17 or IL-17A levels, and raising peripheral blood Tregs in RA patients may be essential to treating the disease (Fig. 1). Some of the other therapeutic targets are mentioned in Table 4.

5. Role of dendritic cells in RA

The interaction between the antigens generated in the body and the adaptive immune cells is regulated by DCs. By cross-presenting antigen to CD8+ T cells, stimulating the generation of B cell antibodies, and activating and priming the effector CD4+ T cells, DCs serve as a link between the two types of immune systems in the body.[90] Additionally, DCs are regarded as important in preserving immunological tolerance. It is believed that in RA, DCs activate Tfh or inflammatory T cells which react with self-epitopes and, subsequently, B cells, which in turn stimulate autoantibodies.[91,92] The DCs are found in the center of clusters of T cells in the RA synovium, which express different receptors like CD80, CD86, adhesion molecules, and CCR7, which helps in Th1 and Th2 phenotype formation from T cells, producing various cytokines. In turn, the synovium of RA also promotes differentiation of the DCs.[93] It is said that the hypoxic conditions in the RA environment, along with increased glycolysis and anabolism, lead to the reprogrammed metabolism of the inflammatory DCs, which leads to their hyperactivation.[94] Thus, switching the DCs to catabolism can have therapeutic potential in RA.

DCs are attracted in large quantities to the tissues and synovial fluid of RA patients' joints.[95] The majority of these synovial DCs are mature, and there is overexpression of NF-κB. Disease activity and nuclear RelB expression are correlated, suggesting that DCs are susceptible to local inflammatory PAMPs, DAMPs, and/or cytokines, such as TNF.[96] RA synovial tissue contains several subsets of MHC class II+ APCs, such as MHC class II^{hi} fibroblast-like synoviocytes, CD11c + CD20+ activated B cells, and cells with activated Toll-like receptor (TLR), myeloid in origin.[97] Multiple APC types may therefore continue to present synovial fibroblast or cartilage autoantigens, such as type II collagen (CII) and HCgp130, to primed migratory memory T cells of the synovium after inflammatory arthritis has begun.[98] Self-epitopes found on autoantigens can be citrullinated to enhance binding to the shared epitope (SE) on HLA-DR alleles. Subsequently, this mechanism promotes autoreactive T-cell proliferation. Thus, neoepitopes add to the biological foundation of RA vulnerability, which is supplied by HLA-DR alleles that are SE-positive (SE+).[99] Furthermore, during periods of stress or infection, cross-presenting DCs that take up citrullinated necrotic antigens may be co-stimulated by CD4+ T cells specific to citrullinated antigens. This may help in the establishment of B cell germinal center (GC) differentiation and cytotoxic T lymphocytes (CTL) specific to citrullinated peptides and anti-citrullinated protein antibodies (ACPA+).

DCs play a significant role in peripheral tissues and the thymus' ability to maintain tolerance. Nevertheless, persistent DC ablation breaks down this self-tolerance in CD4+ T cells, which triggers autoimmunity.[100] DCs are therefore crucial

Table 4 Cellular targets in Treg that can be used for therapy and their outcomes

Target	Outcome	Ref.
IL 6 receptor	Inhibitor or anti-IL6 antibodies can increase the number of Tregs	77
IL2	Helps in the induction of Tregs	78
PI3K-Akt-mTOR signalling axis	Controlling this can help in controlling the regulation of Tregs. In this regard, rapamycin and all-*trans*-retinoic acid (ATRA) are potent candidates in the promotion of the proliferation of Treg cells	79
TNF	Administration of TNF blockers can help reduce inflammation by removing its suppressive function on the FoxP3 function	80
CTLA4	Inhibiting this using a CTLA4-Ig can help in controlling RA by inducing the formation of Treg cells	81
Treg	1. To restore quantity and function, Treg-based therapies can also serve as a potent therapeutic. 2. Transfer of functional Tregs has been seen to be effective. 3. Another strategy being used is the use of chimeric antigen receptors (CARs) for enhancing the inhibitory effect of Tregs on autoantigens. 4. Combination therapy of polyclonal Tregs and IL2 is also in pre-clinical trials. 5. Phosphatase and tensin homolog (PTEN) shows the potential to stabilize Tregs. 6. Bifidobacterium's polysaccharide A is a bacterial product that has the capability of inducing Tregs. 7. Vasoactive intestinal peptide (VIP) and immunoglobulin D (Immunoglobulin D, IgD)-Fc-Ig can stabilize the Th17/Treg equilibrium.	82–89

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Table 5 Cellular targets in DCs that can be used for therapy and their outcomes

Target	Outcomes	Ref.
TGP	Modulates various cell signalling pathways to control inflammation	38
NF κB/nuclear RelB	A decrease in this signalling can decrease DC activation	94, 101 and 102
Citrullinated peptides	A decrease in the levels of these can decrease the number of autoantigens in the body, which can decrease their presentation by the DCs	99, 101 and 103
TNF, IL1 & IL6	These cytokines are products of DCs and decreasing these can decrease the quantum of inflammation	23, 98, 101 and 102
Tolerogenic DC or immunometabolism of DCs	Making DCs tolerogenic by inducing apoptotic cell death or anergy is also a potent therapeutic for curing RA by producing high amounts of IL10 and TGF-β	92, 98 and 104
IL4	Modifying DCs to modify the production of IL4 is a therapeutic strategy to reduce the impact of RA	91 and 102
GM-CSF	Controlling their production can control the differentiation and migration of the DCs. Mavrilimumab is a monoclonal antibody and a potent drug for targeting GM-CSF	100, 102 and 105

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therapeutic targets in the management of RA, and some of the molecular components that can be used to target these cells are mentioned below in Table 5 (Fig. 1).

6. Potential nanoparticles for targeted drug delivery in RA

Nanotechnology is defined as the science of making structures that range in nanometers in terms of size. The smaller size of the particle not only helps in reaching regions that are deep-seated in the body but also increases the surface-to-volume ratio that allows us to functionalize the surface with different molecules. This functionalization is important for achieving very specific and targeted delivery. Functionalizations can be done using protein ligands, aptamers, or antibodies specific to the cells to which they are targeted. Moreover, nanoparticles show the properties of controlled release of drugs, enhanced circulation time, and reduced drug clearance. Based on these advantages, the dosage of the drugs can be reduced, which potentiates their reduction of toxicity and hence side effects along with negating off-target anomalies. The immune cells' role in RA and their molecular components for therapeutic targets have been discussed in the earlier sections. This section talks about some inorganic and organic nanoparticles that are in use and have the potential to be used for RA therapeutics, along with their advantages and disadvantages in the subsequent sections (Fig. 2).

For passive targeting, at the inflammatory site, due to the leaky vasculature and increased macrophage infiltration, the enhanced uptake and retention effect can select nanodrugs in the synovial tissue and retain them.[106] Specifically, particles of size 100–200 nm are favorable as they are neither taken up by the spleen nor flushed out by the phagocytic system.[107] Active targeting, however, is easy, as only the receptor for the cells needs to be known.

6.1. Nanoparticles to target macrophages

Macrophages, as discussed in section 2, are important mediators of RA. The molecular targets in macrophages that can help in the therapy have already been discussed. In this section, various nanomaterials that can encapsulate the target drug for macrophages and be used for targeted delivery will be discussed.

Polyethylene glycol is used for making stealth nanoparticles, enhancing their retention at the targeted site. A diblock copolymer named PEG-*block*-poly(propylene sulphide) was synthesized and loaded with celastrol, which was ROS responsive. This nanoparticle prevented Notch1 and NF-κB activation, along with the suppression of proinflammatory cytokines like IL-1β, TNF-α, and IL-6. It also aided in the enhancement of anti-inflammatory cytokines like M-CSF and TGF and suppressed M1 macrophage activation.[108] Cel has also been delivered using albumin-coated nanoparticles.[109] Heo *et al.* synthesized PEGylated dexamethasone palmitate nanoparticles that showed high permeability at the inflammatory site, and dexamethasone palmitate helped in TNFα inhibition and monocyte chemoattractant protein (MCP1) inhibition in macrophages. They were also retained for a longer time due to PEGylation.[110] An approach for downregulating BTK in macrophages was using siBTK delivered using cation lipid assisted nanoparticles (CLAN), which overcame the disadvantages of poor permeability and stability of siRNA due to the EPR effect.[111] Amphiphilic PEG analog F127 (PEO-PPO-PEO) was used by scientists to modify lipidoid nanoparticles that delivered siIL-1β.[112] Chitosan nanoparticles have been used to deliver siRNA for inhibiting the Notch pathway, preventing bone erosion.[113] Researchers have designed polymerosomes functionalized with mannose for targeting macrophages. This can be used for the delivery of different drugs to macrophages to reduce inflammation, one of which is hydroxychloroquine.[114] Polymeric nanoparticles are another group of nanoparticles that can be used in the treatment of RA.[115]

Nowadays, biomimetic nanoparticles are of great importance as they mimic the natural cell membrane components, thus causing the least immunogenic reaction in the body and prolonging the circulation time in the body.[116] Scientists have used microvesicles, which are macrophage-derived, to decrease the host's ability to eliminate MNPs and extend their retention in the body. They can also detect CD44 or macrophage antigen

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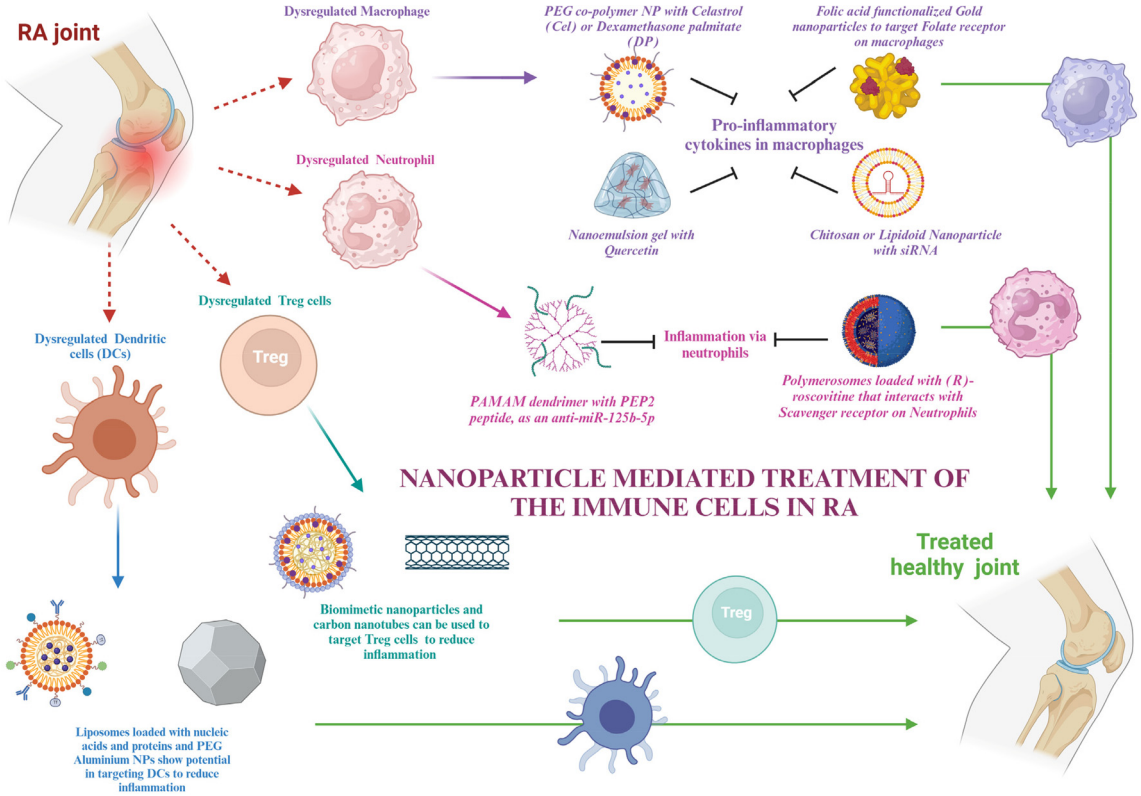

Fig. 2 Schematic representation of nanoparticle mediated treatment of the immune cells in RA – the schematic illustration shows the various nanomaterials that are used to treat the immune cells getting dysregulated in RA, *i.e.*, macrophages, neutrophils, Tregs and DCs. The image was created with BioRender.com.

1 (Mac-1), impersonate a macrophage to interact with M-CSF and the NF-κB ligand–receptor activator (RANKL) for the suppression of osteoclastogenesis and attach to the endothelium to target the inflammatory region.[117] Targeting the nanoparticles actively can also be a strategy by using the receptors of the macrophages, which are CD44, folate, and scavenger receptors. Their respective ligands can be used or antibodies against the receptors can also target the nanoparticles.[118] Through the use of AgNPs tagged with FA ligands, researchers were able to specifically target M1 macrophages and cause intracellular GSH to release Ag+. It improved efficacy by leading to the death of M1 macrophages and the removal of ROS, allowing M1-to-M2 repolarization and lowering inflammation.[119] The PEGylated liposome combined with folic acid (FA) may particularly target macrophages that are actively involved in using FRβ. Suppression of inflammatory cytokines and promotion of M1 macrophage polarization to M2 for RA therapy were achieved by the silencing of the canonical inflammatory signaling pathway, NF-κB p65.[117] Among the antiapoptotic B-cell lymphoma-2 (Bcl-2) protein family, the myeloid cell leukemia-1 (Mcl-1) protein was shown to be overexpressed in RA patients' synovial macrophages. By preventing the proapoptotic protein Bax from being activated, Mcl-1 shields macrophages against apoptosis. In order to treat RA, NPs mediate the suppression of the Mcl-1 protein's expression in activated macrophages, causing apoptosis. Researchers used the FR-mediated transport of nanoparticles to deliver Mcl-1/siRNA for inducing apoptosis.[120] Superoxide dismutase (SOD) can be used as a ROS scavenger and as a treatment for RA. For this, a cellobiose-coated nano-matrix (CNM) was made using a fiber disaccharide solution and a propylene sulfide nano-matrix. The targeted ligand FA was conjugated to SOD yielding F-SOD. After that, CNM was adsorbed to the F-SOD solution, resulting in the creation of cellobiose-coated FA-SOD NPs (FECNM). The porous cellobiose coating on the NPs provides the advantage of strong adsorption properties and thus proves to be an effective way to adsorb SOD.[121]

In Pandey *et al.*'s study, Au-NPs were modified with a thiolated dendritic polymer to produce nanogold core dendrimer NPs (Au-DEN-NPs). The –OH groups on the surface of the NPs were conjugated using methotrexate (MTX), and IR780, a near-infrared bioactive material, was enclosed to offer a photothermal advantage. MTX is an FA analog.[122] Owing to the side effects of MTX, a similar dendritic nanoparticle can also be used to target any of the potential targets on macrophages, as discussed in section 2. Gokhale *et al.* developed a nanoemulsion (NE)-based gel loaded with quercetin (QCT) (QCT-NE gel) to treat RA. QCT-NE was prepared by spontaneous emulsification techniques. Because of its high skin permeability, it also reduces the secretion of pro-inflammatory cytokines and can

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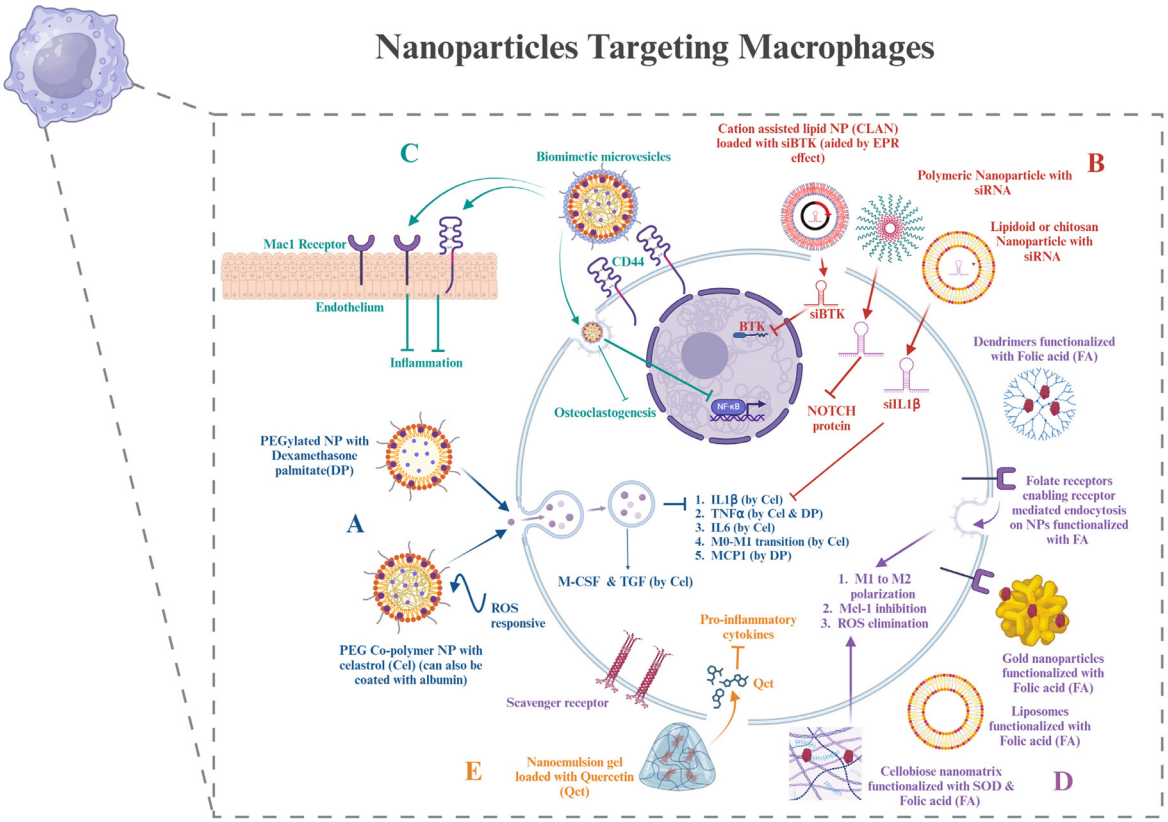

Fig. 3 Nanoparticles targeting macrophages – (A) PEGylated nanoparticles with different drugs loaded onto them and their downstream effects on cytokines and chemokines in macrophages. (B) Nanoparticles delivering different siRNAs targeted to the targeted cell signalling pathways. (C) Biomimetic nanoparticles covered with the macrophage membrane on the outside that help in efficiently prolonging the circulation time in the body and can bind to the CD44 receptor and the Mac1 receptor on endothelium cells as well. It also shows the downstream signalling the nanoparticles regulate. (D) Nanoparticles functionalized with folic acid (FA) on the surface to enter macrophages *via* folate receptors present on them, with their effects. Scavenger receptors belong to another class of receptors present on macrophages that can be used for targeting nanoparticles to macrophages. (E) Nanoemulsion gel that can be used for transdermal application, loaded with drugs, and its function. The image was created with BioRender.com.

be applied transdermally.[123] Hence, these are some strategies for targeting macrophages *via* nanotechnology for delivering cell-based therapeutics (Fig. 3).

6.2. Nanoparticles to target neutrophils

Although several chemokines and signaling pathways have been shown to be useful targets for manipulating neutrophils, which include altering their properties and influencing their infiltration and activation, anti-neutrophil treatments and neutrophil depletion have not proved successful in clinical trials. This is probably because they have an indiscriminate effect on neutrophils throughout the body and exhibit very little selectivity for the inflammatory site. To accurately manipulate and prevent disturbing the innate immune homeostasis, tailored distribution to neutrophils precisely in the inflammatory areas is necessary.[124] This section describes certain nanotechnological strategies that have been used to treat RA and can be used for delivering therapy to neutrophil targets, as discussed in section 3 (Fig. 4).

Neutrophil membrane-coated nanoparticles were created by fusing neutrophil membranes onto polymeric cores. These nanoparticles inherit the antigenic exterior and related membrane functions of the donor cells, making them perfect decoys for biological agents that target neutrophils. These nanoparticles have demonstrated the ability to target deep into the cartilage matrix, decrease synovial inflammation, neutralize proinflammatory cytokines, and offer robust chondroprotection against joint injury.[125] To modify the unfavorable microenvironment for RA remission, researchers have created a neutrophil membrane-cloaked, naturally occurring antiarthritic drug called leonurine (Leo) and a catalase (CAT) coloaded nanoliposomal system called Leo@CAT@NM-Lipo. It successfully reduced paw swelling, decreased the score for arthritis, lessened the damage to bone and cartilage, and cured several organ dysfunctions in rats with adjuvant-induced arthritis (AIA) by combining the synergistic actions of inflammation resolution, ROS scavenging, macrophage polarization, and hypoxia relief.[126] CD11b and Fcγ receptors are receptors overexpressed on activated neutrophils. Antibodies against

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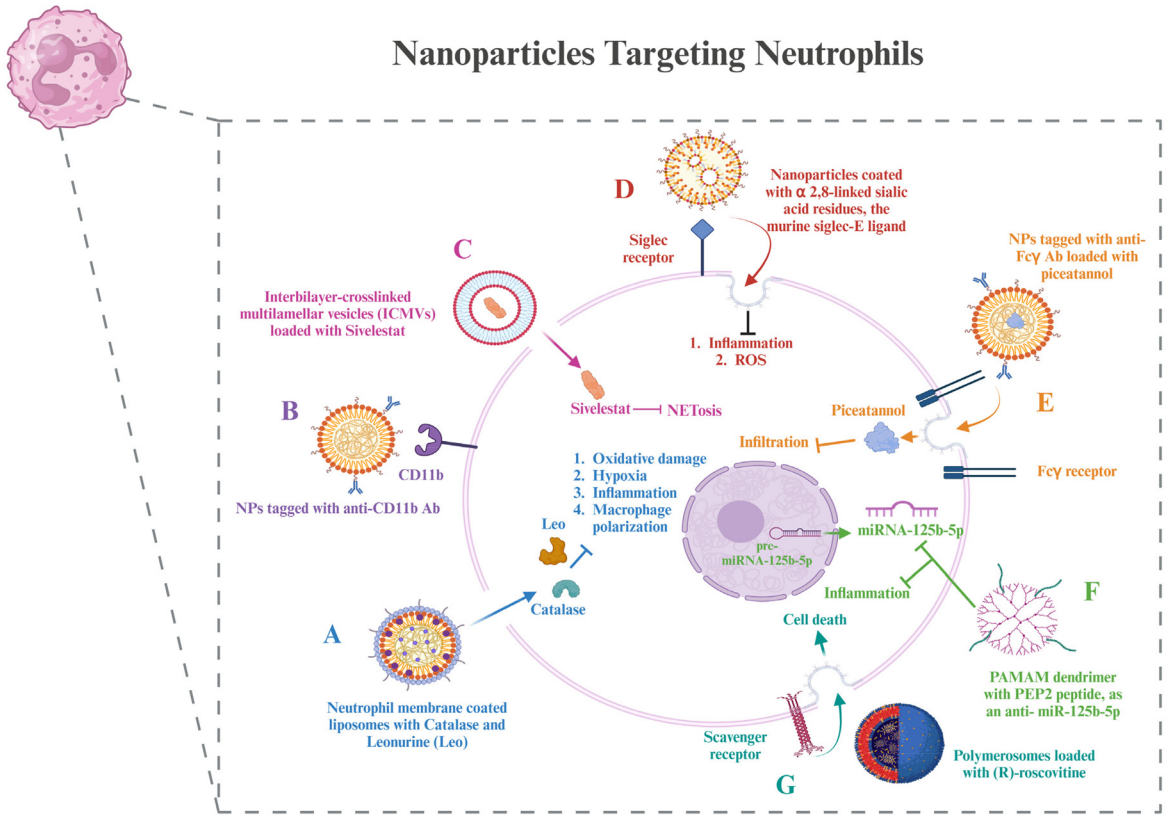

Fig. 4 Nanoparticles targeting neutrophils – (A) biomimetic nanoparticles coated with neutrophil membranes and loaded with drugs and their downstream effects. (B) Targeted nanoparticles to CD11b by coating them with the anti-CD11b antibody. (C) Multilamellar vesicles loaded with a drug to inhibit NETosis. (D) Siglec receptor-targeted nanoparticles and their effects downstream. (E) FcγR targeted nanoparticles loaded with a drug to inhibit neutrophil infiltration. (F) PAMAM dendrimers functionalized with a citrullinated peptide, PEP2, that can inhibit inflammation by inhibiting miRNA-125b-5p. (G) Polymerosomes loaded with drugs that can enter neutrophils *via* receptor-mediated endocytosis using scavenger receptors and lead to neutrophil death, reducing inflammation. The image was created with BioRender.com.

these can be coated onto different nanoparticles loaded with drugs to deliver them to neutrophils.[127,128]

Wang *et al.* administered piceatannol, a tiny chemical that inhibits "outside-in" β2 integrin signaling pathways in leukocytes, to active neutrophils in the bloodstream using albumin nanoparticles. The studies also showed that Fcγ receptors were required for albumin nanoparticle uptake by neutrophils connected to the inflammatory endothelium, which are highly expressed on activated neutrophils. Compared to free piceatannol, this method successfully separated adherent neutrophils from the endothelium, preventing neutrophil infiltration.[129] Delivery techniques based on nanoparticles provide tools to target NETosis for better therapeutic outcomes. Mice exposed to LPS-induced endotoxic shock were saved by sivelestat, an inhibitor of neural epithelial cells, which was given through interbilayer-crosslinked multilamellar vesicles (ICMVs).[130] A further investigation showed that siglec receptors can be targeted by nanoparticles coated with α2,8-linked sialic acid residues, the murine siglec-E ligand, which reduces inflammatory responses.[131] It is interesting to note that α2,8-sialylated nanoparticles reduced ROS in neutrophils, which in turn prevented NET formation.[132]

Scavenger receptors were required in one investigation for the polymersomes' transport of (*R*)-roscovitine to neutrophils.[133] After that, the polymersomes broke free of the early endosomes due to a pH-triggered disintegration process, which made it possible to transfer *R*-roscovitine into the neutrophil cytoplasm without stimulating the cells. *R*-Roscovitine induced neutrophil death, which reduced inflammation. PEP2, a citrullinated peptide, and an antisense oligonucleotide that targets a microRNA, anti-miRNA-125b-5p, were combined into two different kinds of nanoparticle formulations: chitosan-hyaluronic acid and PAMAM dendrimers. Both varieties of nanoparticles demonstrated high cell targeting efficacy and provided effective drug delivery vehicles.[134]

6.3. Nanoparticles to target Treg cells

Treg cells, as discussed in section 4, are important components for maintaining T cell homeostasis that gets dysregulated in RA. The quantity and function of Treg cells are both hampered in RA. Potential targets to resolve these issues have already been discussed. This section shows glimpses of certain approaches for targeting Treg cell therapies *via* nanotechnology. The creation of hybrid nanoparticles (NPs) that help B

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and T cells establish tolerance has been reported by researchers. The NPs are made up of a lipid monolayer that encloses a rapamycin-loaded PLGA core that stimulates the growth of regulatory T cells (Tregs). The lipid monolayer contains both the protein antigen and a ligand of the B cell inhibitory co-receptor CD22 (CD22L), which together block B cells from activating when they come into contact with the antigen. The outcomes demonstrate this adaptable NP platform's potential for reducing autoimmune illness and promoting immunological tolerance to a self-antigen.[135]

Functionalization with the right ligand to target the highest affinity receptor plays a very important role in nanoparticle design. Evidence that ApoB coating on nanoparticles increases their rate of uptake by liver epithelial cells came from such a study, showing that ApoB's higher affinity for its cognate receptor can enhance drug uptake compared to the bare nanoparticles or using any other ligand–receptor complex. It resulted in enhanced secretion of TGF-β after receiving an injection of the nanoparticle formulation, and this increased FoxP3+ Tregs in the lungs, thus showing their potential in allergy treatment.[136] Negatively charged particles may target LSECs due to the stabilin receptors on LSECs, which show preference for binding negatively charged particles.[137] Carambia *et al.*, for instance, produced anionic iron oxide nanoparticles with a poly(maleic anhydride-*alt*-1-octadecene) coat. Following intravenous injection, the particles were quickly removed from the plasma and gathered in LSECs together with their antigen load, which increased the number of Foxp3+ Tregs.[138] All these studies have been done on liver cells; however, these same strategies can be used to target synovium cells as well.

A biodegradable nanoparticle containing a small chemical glutamate receptor enhancer, *N*-phenyl-7-(hydroxyimino)cyclopropa[*b*]chromen-1a-carboxamide (PHCCC), was utilized to change the development of Th17 cells into Treg cells, as well as to reduce the drug's toxicity by 36 times and release 89% of the drug under regulated conditions.[139] FoxP3+ Treg plays a major role in the control of autoimmunity, and studies have shown that low doses of IL-2 can activate Tregs and enhance their capability of suppression.[140] Because of this, a number of studies were based on utilizing IL-2 *via* nanocarriers to affect autoimmune events and alter the biology of regulatory T cells. Horwitz *et al.* loaded PLGA nanoparticles with IL-2 and TGF-β in an experimental context and then coated them with anti-CD2/anti-CD4 antibodies to achieve T cell-specific targeting.[141] In a mouse

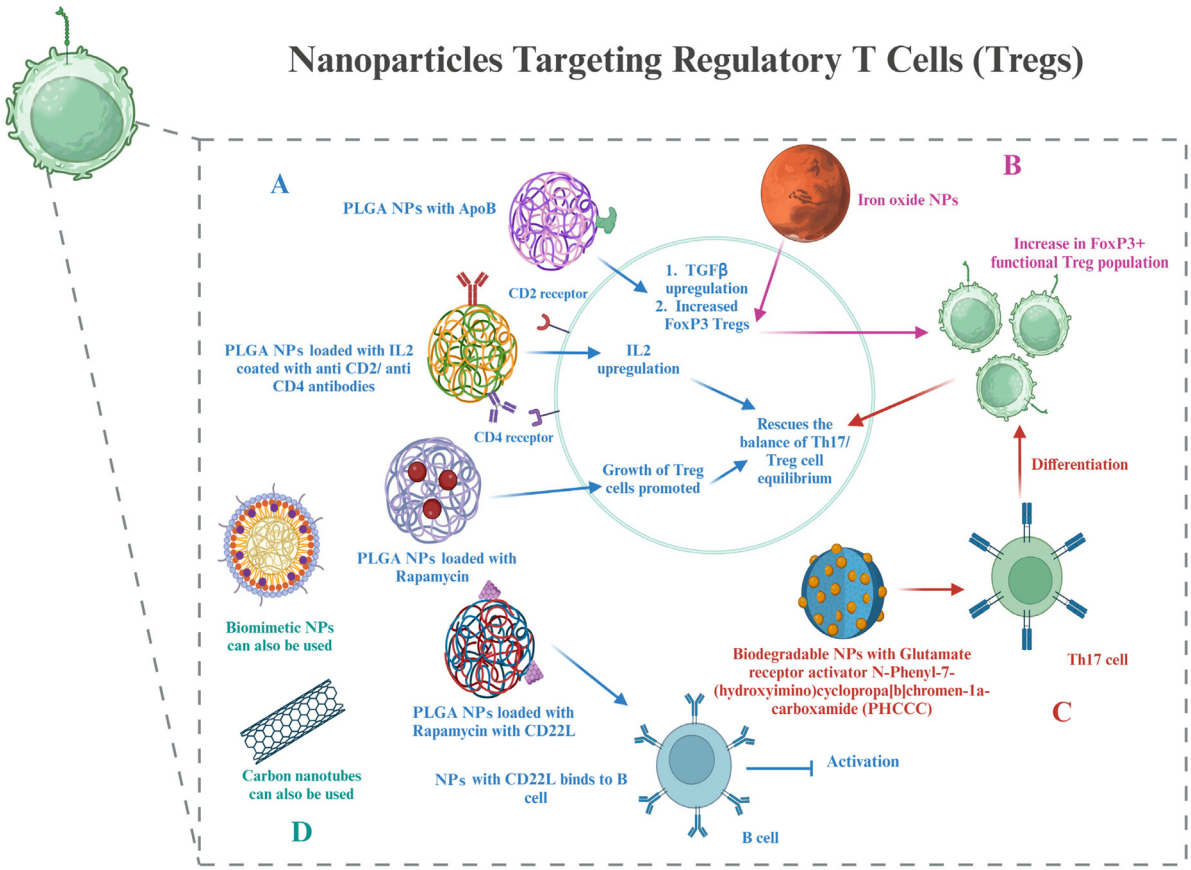

Fig. 5 Nanoparticles targeting Tregs – (A) PLGA nanoparticles loaded with drugs and their effects on cell signalling, cytokines, and B cell activation. (B) Iron oxide nanoparticles and their role in increasing FoxP3+ Treg cells. (C) Biodegradable nanoparticles and their interaction with Th17 cells to differentiate into FoxP3+ Treg cells. (D) Biomimetic and carbon nanotubes can be potentially used to target Tregs in RA, as in other diseases. The image was created with BioRender.com.

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model of lupus erythematosus, systemic treatment of these nanoparticles led to decreased disease activity *in vivo* and promoted the proliferation of Tregs both *in vitro* and *in vivo*. This same strategy can be used in the treatment of RA as well.

Biomimetic nanoparticles based on Treg cells have been synthesized and effectively used for immunomodulatory purposes.[142] Single-walled carbon nanotubes have also been successfully used to target Treg cells in tumor microenviron-

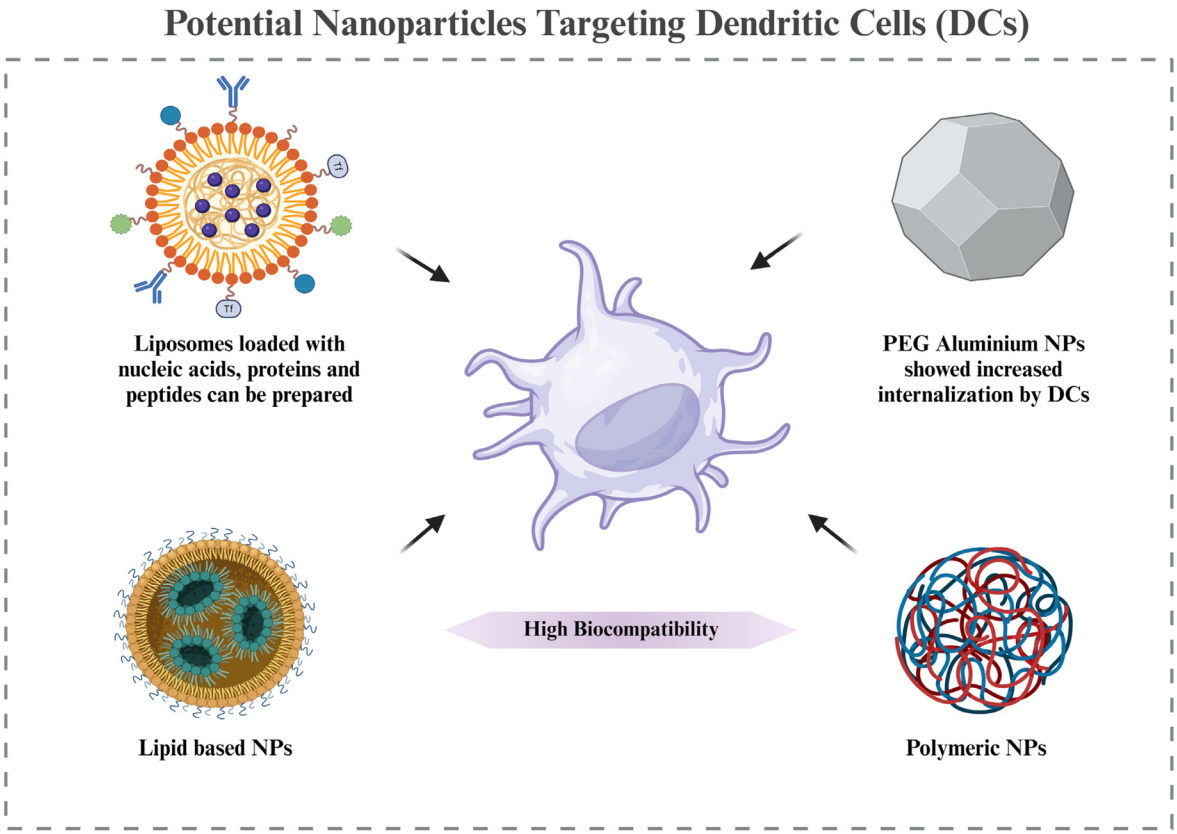

Fig. 6 Potential nanoparticles targeting DCs – it shows some potential nanoparticles with their advantages in targeting DCs that can be used to target them in the RA synovium. The image was created with BioRender.com.

Table 6 Administration routes, advantages, and disadvantages of inorganic nanoparticles

Nanoparticles	Administration route	Advantages	Disadvantages	Ref.
Metallic nanoparticles	Intra-articular, intravenous, intra-peritoneal injection	I. Can be functionalized with multiple groups II. Can be made of any size and shape III. Due to their electric and magnetic properties, they can be coupled with different radiations for photothermal or photodynamic therapy	I. Particle instability II. Toxicity in the human body III. Generation of the nanoparticles can build up toxicity IV. Many need triggers to release the cargo V. Poor solubility VI. Accumulation in the blood can block blood flow	151–156
Non-metallic nanoparticles	Intra-articular injection	I. High loading capacity II. Good biological degradability III. Silica has good surface properties enabling better functionalization	I. Poor solubility II. Biosafety is highly varied depending on the formulation	155
Cationic nanoparticles	Intra-articular injection	I. Improved pharmacokinetic properties II. Longer retention time	I. Cause systemic toxicity	157 and 158

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Table 7 Administration routes, advantages, and disadvantages of organic nanoparticles

Nanoparticles	Administration route	Advantages	Disadvantages	Ref.
Biomimetics	Subcutaneous injection	I. Used in targeted deliveries II. Can escape the immune system and hence are less reactive in the body III. Less irritability IV. High biocompatibility V. Prolonged circulation time in blood	I. Orientation of the nanomedicine with the membrane II. Membrane fragility	159–161
Liposomes	Intramuscular, subcutaneous, topical, pulmonary, nasal, oral, and intravenous routes	I. Biocompatible as their morphology is similar to cells of the body II. Versatility III. Targeting abilities IV. Controlled release V. Enhanced stability VI. Biodegradability VII. Scalability VIII. Encapsulation efficiency	I. Rancidification of lipids leading to a lower shelf life II. Instability at different pH values III. Expensive formulation	162–165
Hydrogel	Oral, intra-articular, intravenous, transdermal	I. Controlled release due to its structure II. Biocompatible and biomimetic, thus reducing immunogenicity III. Lubrication properties that protect joints from degradation and friction IV. Can used for long periods of time	I. Mechanical strength is low II. Handling is difficult III. Needs secondary dressing for securing it, as is non–adherent IV. Expensive	166–170
Solid–lipid nanoparticles	Targeted delivery can be achieved by topical or oral administration	I. Controlled release of drugs II. Enhanced delivery of hydrophobic and lipophilic drugs III. Zero irritability of skin IV. Highly stable V. Protected from degradation by enzymes VI. Very high tolerability *in vivo* VII. Higher penetration and permeability of drugs VIII. Targeted delivery	I. Composition can often lead to the uncontrolled release of drugs and drug leaching II. Low drug loading capacity III. More data are needed for confirmation of safety and toxicity.	171–177
Niosomes	Administration of the drug-loaded niosomes in the form of transdermal gels and patches	I. Enhanced shelf life II. High chemical stability III. Cost-effective in making IV. High skin penetrability and retention V. Decreased irritation and haemolysis VI. Enhanced residence time of drugs and controlled release	I. Can form aggregation II. Encapsulated drugs can leak	178–181
Ethosomes	Transdermal administration	I. Better skin penetrability due to their soft nature II. Higher alcohol content enhances the encapsulation capability	I. Yield is poor II. Chance of coalescing III. On transfer from organic to water media, may lead to the loss of product. IV. Skin irritation or dermatitis V. Needs adequate solubility of the drug	182–186
Transferosomes	Transdermal gels	I. Are elastic due to edge activators II. Can encapsulate both hydrophilic and hydrophobic drugs III. Show high skin penetrability due to their elastic nature	I. Expensive to manufacture II. Can be degraded oxidatively III. Phospholipids can undergo reorganization	187 and 188

Table 7 *(Contd.)*

Nanoparticles	Administration route	Advantages	Disadvantages	Ref.
Nanoemulsions	Transdermal gels	I. Increased bioavailability of insoluble and impermeable drugs II. Escape the first-pass mechanism due to small size III. Enhanced skin penetrability	I. Thermodynamically unstable II. Require external energy for formation	189–192
Polymeric micelles	Intravenous injection, infusion, oral, topical	I. Circulation time in the blood is prolonged II. Controlled drug release III. Protection of the inside content from degradation IV. Enhance the solubility of drugs V. Can be passively targeted	I. Complex characterization II. Low stability	193 and 194
Dendrimers	Intravenous injection	I. Easy movement across cell surfaces II. Good targetability III. Enhanced rate of cell entry IV. Monovalency V. Enhanced solubility VI. Good hemocompatibility and cytocompatibility	I. Can interact with cell membranes and disrupt them II. Can interfere with neuronal signalling III. Can lead to haemolysis IV. Can be toxic to the healthy cells of the body V. Can show gastro-intestinal, renal and hepatic toxicity VI. Highest toxicity is shown by cationic dendrimers	195–203

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ments.[143] Thus, even though not many nanoparticles targeting Treg cells have been used in RA treatment, all the above strategies can be used in the treatment of RA, which lies in the future scope (Fig. 5).

6.4. Nanoparticles to target DCs

Based on the discussion of the cellular targets of DCs in RA in section 5, this section discusses the possible strategies for targeting the DCs *via* nanomedicines. There is very little evidence of targeting DCs in RA *via* nanotechnology; however, the potential approaches by which DCs can be targeted for nanotherapy are being highlighted.

Adaptive antitumor immunity depends on DCs' capacity to collect, process, and present antigens to stimulate T cell priming. As a result, DC-targeting nanomaterials are thought to be a viable strategy for enhancing an effective and focused immune response against cancer. Additionally, multifunctional compounds are combined in nanomaterials to modify the antigen presentation in whole or in part.[144] Lipid-based and polymeric nanoparticles have been shown to have greater biocompatibility when used to create DC-targeted vaccinations for antiviral and anticancer therapies.[145,146] The potential of liposome-based nanoparticle encapsulating molecules such as heat shock proteins, OVA, and the trivalent influenza antigen to stimulate the immune system in the therapy of disease has been studied. In order to prepare DCs for later strategies that aim to directly activate them *in vivo*, it may be necessary to deliver protein, peptide, and nucleic acid antigens to them *via* nanomaterials. This could improve DC circulation and reduce DC breakdown *in vivo*. These antigens may trigger the right kind of immunological reaction.[147] Additionally, nanomaterials (such as gold or aluminum nanoparticles) likely improve internalization at the single-cell level.[148] Using PEG-stabilized nanoscale aluminum particles (100 nm) demonstrated increased internalization in antigen-presenting cells. Consequently, nanotechnology not only improves the bio- or physicochemical features of antigen formulations through antigen protection, quantity enhancement, function conjunction, and the presentation of antigens, but it also redefines the efficacy of conventional agents or materials with potentially novel functions in modulating antitumor immunity.[149,150] All of these benefits are directed toward the development of adaptive immunity against cancers.

In cancer, there is a requirement for upregulation of DC activation, for which the above examples are cited. However, in RA, we need to downregulate DC activation. Hence, this section is just to take note of the nanocarriers and their advantages that can be used for targeting DCs in RA. The therapeutic molecules and their expected downstream regulations will be different in RA compared to cancer. Further research in making nanocarriers targeted to DCs, specifically in RA, is required, while also noting the potential effects of already known DC-targeted nanoparticles used in other diseases, as that might give an idea of the pros and cons of each of the nanomaterials in RA targeting (Fig. 6).

The discussions on targeting immune cells in RA give a clear idea that using nanotechnology not only reduces the quantum of side effects but also increases its efficacy by many folds. But when a wide range of nanoparticles is available for researchers to choose from, it becomes essential to take note of the advantages and disadvantages of each nanoparticle before using them. It is also important to note the possible routes of administration for them to improve patient convenience, depending on the disease severity. Tables 6 and 7 enlist the administration routes, advantages, and disadvantages of inorganic and organic nanoparticles that can be used for RA therapy.

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7. Conclusion

The first description of the disease dates back to the 1800s. From defining it as primary asthenic gout to calling it rightly rheumatoid arthritis, research in this field has come a long way. Today, we have knowledge of most of the symptoms and common causes of the disease. Conventional treatments with which therapeutics in this field started are the most used ones to date. However, lately, these conventional treatments have started showing systemic side effects due to their repeated usage and off-target effects. Some patients show resistance to conventional drugs as well. Therefore, acquiring more knowledge of the specifics of the disease to devise more specific treatments, along with using nanotechnology to make the delivery of the drugs more targeted and controlled, ensuring the regulation of the dosage and retention time, was and will be the most suitable strategy in RA therapeutics. Organic nanoparticles like biomimetics and liposomes show good biocompatibility in the body due to their composition, which is very similar to the body's own cells, making them less immunogenic and giving more options for administration routes. However, there are certain shortcomings in nanotechnology as well, like scaling up production, unpredictability of the nanocarrier inside the system, and the difficulty of the synthesis of certain nanoparticles, claiming further research and developments in this field. There is a requirement to develop DC-targeted nanocarriers in RA. Also, despite well-established animal models of RA being useful, the human disease pattern is not always faithfully replicated in these animals. RA in humans has a far more complex pathogenic background than in animal models. More work is still required to progress the development of possible drug delivery methods for clinical trials and marketing in the RA treatment space. In the foreseeable future, we anticipate that treatments for RA and other autoimmune illnesses will advance quickly.

Author contributions

AL: writing and image curation, SN: conceptualization and editing, DB: editing, and AK: funding acquisition and conceptualization.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no competing financial interest and there are no conflicts of interest.

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