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REVIEW

Targeted-Immunomodulatory Nanomedicines for the Treatment of Autoimmune Diseases via Multiple Administration Routes

Bom Lee[1,2,*], Jeeeun Yoo[1,2,*], Han Sol Lee[3], Yonghyun Lee[1,2]

[1]College of Pharmacy, Ewha Womans University, Seoul, 03760, South Korea; [2]Graduate Program in Innovative Biomaterials Convergence, Ewha Womans University, Seoul, 03760, South Korea; [3]College of Pharmacy, Chosun University, Gwangju, 61452, South Korea

*These authors contributed equally to this work

Correspondence: Yonghyun Lee, College of Pharmacy, Ewha Womans University, 52 Ewhayeodae-Gil, Seoul, 03760, South Korea, Email y.lee@ewha.ac.kr

Abstract: The incidence and prevalence of autoimmune diseases are rising globally, presenting a significant health challenge. Current treatments focus on symptom management and immunosuppression, often resulting in side-effects such as increased infection risk and broad immunosuppression. Targeted immune modulation strategies, particularly through nanomedicines, offer promising advancements by enabling precise drug delivery and reducing systemic toxicity, risks, and pharmacokinetic issues. Nanocarriers, which are nanoparticles with drugs encapsulated, improve targeting to inflamed areas and lymphoid tissues, protecting therapeutic agents from degradation. Administration routes—intravenous, subcutaneous, intramuscular, and oral—offer distinct benefits for enhancing efficacy in treating autoimmune diseases. In this review, we explore autoimmune diseases and review the limitations of current treatment options. We also emphasize the importance of exploring various administration routes for innovative nanocarrier systems and discuss their effects on modulating immune responses and inducing immune tolerance in autoimmune diseases. In particular, we highlight numerous preclinical studies utilizing intravenous, subcutaneous/intramuscular, and oral nanocarrier formulations that demonstrate substantial improvements in therapeutic efficacy and dose reduction compared to conventional therapies, underscoring the translational potential of nanomedicines for autoimmune diseases. Finally, we discuss future research directions and challenges in the development of nanomedicines for autoimmune diseases.

Keywords: nanomedicine, passive targeting, EPR effects, active targeting, autoimmune diseases, lymph node delivery

Introduction

The prevalence and incidence of autoimmune diseases are rising rapidly, recording approximately 19.1% increase of incidences annually, which poses a substantial global health challenge.[1] Autoimmune diseases, caused by the breakdown of self-tolerance, are characterized by aberrant immune responses against self-antigens. Depending on the predominant immune mechanisms, they can be broadly categorized into Th1/Th17-driven inflammatory disorders and autoantibody-mediated diseases. The autoimmune disorders are chronic and often cause debilitating symptoms, leading to an increased focus on developing effective treatment strategies.[2] Current therapeutic approaches primarily target symptom management and involve immunosuppressive medications.[3] However, symptom management does not address the underlying causes of autoimmune diseases, and immunosuppressive therapies may result in severe systemic immune suppression and increased infection risk.[4] This has led to development of targeted immune modulation strategies that can selectively regulate immune responses at specific sites of interest.[4] Monoclonal antibodies (mAbs) target cytokines or immune cell antigens to selectively limit inflammation.[5] However, mAbs can also evoke hypersensitivity reactions and have pharmacokinetic challenges.[5] Nanomedicines, which are therapeutic agents encapsulated within or conjugated to nanoparticles to protect them from degradation and enhance targeting to inflamed areas or lymphatic organs, are a promising new therapeutic strategy.[6]

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Targeted delivery can improve efficacy while reducing toxicity, positioning nanoplatforms as a promising approach for managing autoimmune diseases.[6]

To ensure the effectiveness and safety of nanomedicines, careful attention must be paid to the design of nanocarriers, focusing on characteristics such as size, surface chemistry, stability, and biocompatibility.[7] Nanoparticle size affects targeting; intramuscularly/subcutaneously-administered particles above micrometer sizes remain localized, with drug release occurring over a prolonged period, while smaller particles (sub-microns in size) can reach immune cells in lymphoid tissues.[7] Surface charge and functionalization also influence targeting and immune responses.[7] For example, cationic particles non-specifically bind to cell membranes that typically having negative charges, while ligands functionalized on nanoparticles can enhance the targeting ability of nanoparticles; this is referred to as active targeting.[8] Biodegradability is also an important issue because treatment typically requires long-term usage.[9] For example, PLGA or lipid-based nanoparticles, which have low cytotoxicity and offer stable drug release, have been used in lipid-based SARS-CoV-2 mRNA vaccines.[10] Numerous review articles have highlighted that these physiochemical characteristics critically influence the targeting efficiency of nanoparticles, their uptake by immune cells, and the resulting modulation of immune responses; therefore, these aspects will not be discussed in detail in this review.

Another key aspect of nanomedicine usage in autoimmune disease treatment is the choice of administration route.[11] Common routes include intravenous (IV), subcutaneous (SC), intramuscular (IM), and oral (PO) each of which has unique benefits.[11] IV administration enables nanoparticles to accumulate in inflamed tissues, where increased vascular permeability allows for targeted anti-inflammatory effects, making this an route ideal for anti-inflammatory therapies.[11] When IV administered nanomedicines along with tolerogens are delivered into the spleen, immune tolerance can be induced.[12] SC and IM routes are advantageous for delivering nanomedicines to lymphatic organs such as lymph nodes, promoting immune tolerance through a process known as hyposensitization.[13,14] The oral route can deliver nanoparticles to Peyer's patches and the lamina propria, supporting both anti-inflammatory and hyposensitization strategies.[15] Orally administered nanomedicines can reach Peyer's patches and healthy lamina propria for effective oral tolerance and penetrate disrupted intestinal barriers, targeting inflammation directly in the intestines (Figure 1 and Table 1).[15]

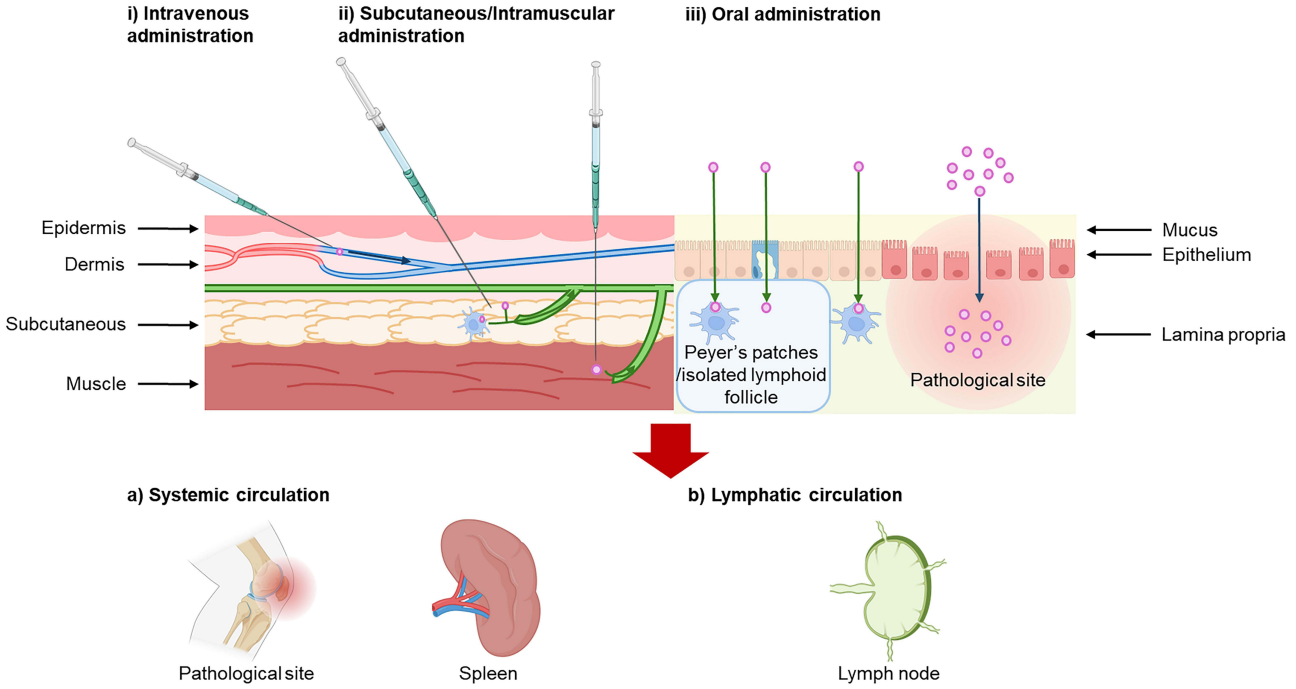

Figure 1 Targeted-immunomodulatory nanomedicine for treatment of autoimmune diseases. (Created with BioRender.com) i) Intravenous nanomedicine and iii) oral nanomedicine enter a) systemic circulation to reach pathological site through EPR effect or spleen. Meanwhile, ii) subcutaneous/intramuscular nanomedicine and iii) oral nanomedicine enter b) lymphatic circulation to reach lymph node.

Table 1 Mechanism of Immune Modulation, Advantages, and Disadvantages of Administration Routes

Administration Route	Mechanism of Immune Modulation	Advantages	Disadvantages
Intravenous (IV)	• Anti-inflammatory effect in inflammation site by EPR effect • Antigen-specific tolerance in spleen	• High bioavailability • Immediate distribution into systemic circulation	• Risk of side effects including local inflammation • Low patient compliance in case of long-time infusion
Subcutaneous (SC) /Intramuscular (IM)	• Antigen-specific tolerance in lymph nodes	• Convenient bolus shot leading to higher patient compliance • Long-lasting therapeutic effects	• Risk of side effects including local inflammation • Significant pain in IM injection due to deep injection
Oral	• Anti-inflammatory effect in disrupted intestinal barriers • Antigen-specific tolerance in lymph nodes of lamina propria	• Noninvasive and convenient route leading to patient preference • Appropriate for long-term treatment	• Low bioavailability • Requirement for resistance of nanoparticles to degradation

In this review, we explore autoimmune diseases and review the limitations of current treatment options. We also emphasize the importance of exploring various administration routes for innovative nanocarrier systems and evaluate their effects on modulating immune responses and inducing immune tolerance in autoimmune diseases. In particular, we highlight numerous preclinical studies utilizing intravenous, subcutaneous/intramuscular, and oral nanocarrier formulations that demonstrate substantial improvements in therapeutic efficacy and dose reduction compared to conventional therapies, underscoring the translational potential of nanomedicines for autoimmune diseases. Finally, we discuss future research directions and challenges in the development of nanomedicines for autoimmune diseases.

Traditional Treatments for Autoimmune Diseases

The immune system plays a crucial role in defending the body against pathogens while maintaining tolerance to self-antigens.[16] However, when the immune system mistakenly identifies self-antigens as foreign, autoimmune diseases result, which cause chronic inflammation and damage to organs and tissues.[17] This misrecognition often stems from the failure of self-reactive immune cells, such as T and B lymphocytes, to be effectively eliminated or regulated by central tolerance and peripheral tolerance mechanisms.[18] Autoimmune conditions can manifest through a variety of mechanisms, including antibody production against self-antigens, immune complex formation, and T-cell-mediated responses (macrophages and cytotoxic t-lymphocytes), which collectively lead to cellular dysfunction and tissue destruction (Figure 2).[19]

In autoimmune diseases, immune dysregulation arises from failures in both central and peripheral tolerance, which are essential for preventing self-reactivity.[20] Central tolerance develops in primary lymphoid organs—the thymus for T cells and the bone marrow for B cells—where self-reactive lymphocytes are eliminated or inactivated before entering the peripheral immune system.[18] In the thymus, immature T cells (thymocytes) interact with self-antigens presented by antigen-presenting cells (APCs).[18] Thymocytes that bind too strongly to these self-antigens undergo negative selection, resulting in apoptosis.[11,18] T cells with low to moderate binding affinity to self-antigens survive, maturing into T cells capable of responding to foreign antigens without targeting self.[16,18] Among them, T cells that recognize self-antigens with moderate affinity differentiate into regulatory T cells (Tregs), which help suppress immune responses to self-antigens.[16] In the bone marrow, immature B cells also undergo selection.[21] B cells that strongly bind to self-antigens may be deleted, undergo receptor editing, or become non-reactive.[21] This selection ensures that self-reactive B cells are eliminated or inactivated before leaving the bone marrow, maintaining self-tolerance.[22]

Peripheral tolerance occurs after lymphocytes have matured and migrated to secondary lymphoid organs and tissues, such as lymph nodes and the spleen.[23] This tolerance mechanism is vital for controlling self-reactive cells that escape central tolerance and for managing immune responses in peripheral tissues.[23] In the periphery, self-reactive T cells that recognize self-antigens without the necessary co-stimulatory signals (provided by APCs) may become anergic (functionally inactivated), undergo apoptosis, or be regulated by Tregs.[24,25] Tregs play a central role in peripheral tolerance by suppressing the activation and proliferation of self-reactive T cells and preventing inflammatory responses against self-antigens.[26] In the periphery, B cells that bind to self-antigens without T cell help may become anergic or undergo

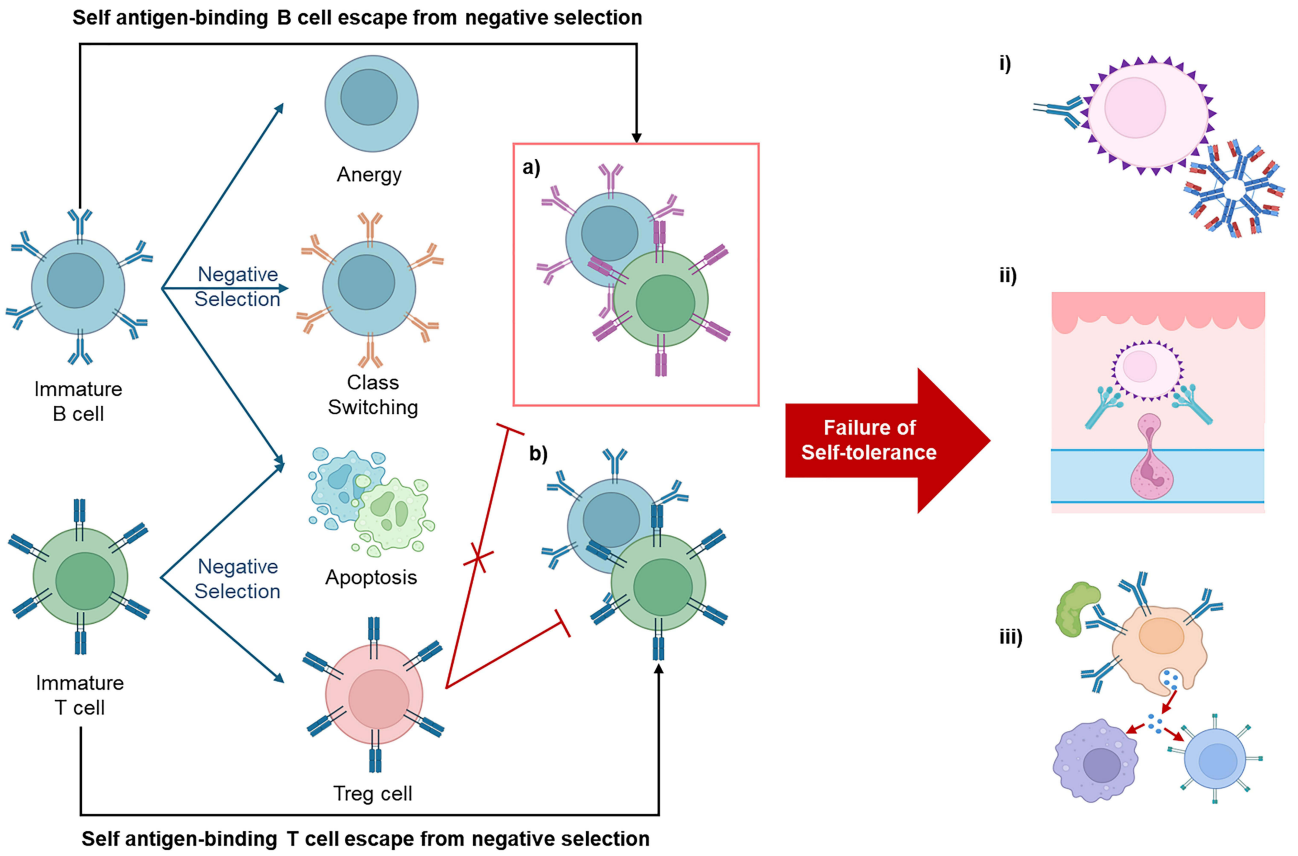

Figure 2 Immune tolerance and autoimmune diseases (Created with BioRender.com) (a) Some self-reactive B cells and T cells that escaped from negative selection cause failure of immune tolerance, (b) while the others are suppressed by T_{reg}. Autoimmune diseases following immune tolerance failure are characterized by i) antibody or immune complexes binding to self antigens on target cells (eg Grave's disease), ii) deposition of immune-complexes in tissues or blood vessels (eg Systemic lupus erythematosus), and iii) T_{h1} cells sensitized by self antigens activate macrophages and cytotoxic T cells (eg Type I diabetes).

apoptosis.[22] B cells also rely on Tregs and other regulatory mechanisms to prevent activation when they encounter self-antigens.[22,27]

Tregs are crucial for preventing autoimmunity by maintaining immune tolerance.[28] Natural Tregs (nTregs) and inducible Tregs (iTregs) both suppress immune responses against self and non-harmful antigens.[25,28] Natural Tregs (nTregs) develop in the thymus.[25] During T cell maturation, thymocytes that recognize self-antigens with moderate affinity differentiate into nTregs rather than conventional T cells.[25,28] These nTregs play a central role in self-tolerance, primarily by releasing anti-inflammatory cytokines like IL-10 and TGF-β, and by directly inhibiting other immune cells through surface receptors like CTLA-4.[29,30] This helps nTregs suppress potentially harmful self-reactive immune responses throughout the body.[29,30] Inducible Tregs (iTregs) are formed in peripheral tissues when naïve CD4+ T cells encounter specific antigens in a non-inflammatory environment, often in the presence of TGF-β and IL-2.[25] iTregs are essential for peripheral tolerance, particularly in tissues exposed to environmental antigens, such as the gut, where they suppress immune responses against harmless substances (eg, food and beneficial microbes).[31,32] Like iTregs, they release IL-10 and TGF-β and use inhibitory receptors (eg, PD-L1) to maintain immune balance.[31,32]

Autoimmune conditions like rheumatoid arthritis, type 1 diabetes, and psoriasis are characterized by persistent inflammation that often affects multiple organs.[33] Some diseases, such as Graves' disease, involve autoantibodies that bind to specific receptors, such as the thyroid-stimulating hormone receptor, leading to excess hormone production.[34,35] In other conditions such as rheumatoid arthritis, helper T cells activate macrophages and B cells, resulting in the production of autoantibodies and inflammatory responses that damage joint cartilage.[36] Different autoimmune diseases utilize similar mechanisms, either antibody- or T-cell-driven pathways, that disrupt tissue function and trigger chronic inflammation.[17,19]

Currently, autoimmune diseases are managed mainly through symptom management and immunosuppressive medications.[3] Some autoimmune diseases are managed with symptomatic treatments.[3] For example, analgesics and COX inhibitors may relieve pain in rheumatoid arthritis.[37] Hormone replacement therapies are often used for endocrine autoimmune disorders; for example, insulin is essential for managing type 1 diabetes,[38] while thyroid hormone inhibitors are used to treat Graves' disease.[35] However, these approaches are limited, as they do not target the major autoimmune response, address the underlying inflammation, or halt disease progression, and may lead to hormonal imbalances or resistance over time.[39] Glucocorticoids, such as cortisone, prednisone, and budesonide, are powerful immunosuppressants, inducing anti-inflammatory effects by broadly suppressing the immune system; however, they are associated with several adverse effects, including increased infection risk, osteoporosis, and systemic toxicity.[40] In addition, other immunosuppressive agents, including anti-metabolites (eg, mycophenolate mofetil, methotrexate, azathioprine), calcineurin inhibitors (eg, cyclosporine), and mTOR inhibitors (eg, sirolimus), are utilized to regulate immune cell proliferation or to induce apoptosis.[11] These agents have general toxicity due to broad immunosuppressant effects, can cause gastrointestinal disorders,[41,42] and are nephrotoxic.[43,44]

To overcome the limitations of conventional medications, monoclonal antibodies (mAbs) have been developed as targeted therapies for autoimmune diseases.[45,46] mAbs target specific antigens expressed on lymphocytes.[47] For example, rituximab, an anti-CD20 antibody, depletes B cells by targeting CD20,[48] while abatacept inhibits the interaction between CD28 on T cells and CD80/CD86 on MHC cells, which is essential for T cell co-stimulation.[49] However, these mAbs can still exhibit systemic toxicity due to their action on non-target immune cells expressing target molecules, resulting in broad immunosuppression.[49] Therefore, monoclonal antibodies (mAbs) targeting key inflammation-associated molecules have been developed, including those against tumor necrosis factor-alpha (TNF-α) eg adalimumab, golimumab, infliximab, and etanercept, which are used to treat rheumatoid arthritis, ulcerative colitis, and Crohn's disease.[50] Additionally, interleukin-targeting mAbs, such as anakinra (anti-IL-1) and tocilizumab (anti-IL-6), are utilized to treat rheumatoid arthritis.[51] These mAbs have shown unprecedented anti-inflammatory activity in autoimmune diseases with limited side effects.[52] Nonetheless, mAbs may elicit hypersensitivity reactions in certain organs and can provoke infusion reactions, as they are typically administered parenterally.[47] Furthermore, long-term use of antibody therapeutics can lead to the production of anti-antibody antibodies, resulting in a gradual decrease in therapeutic efficacy.[53]

Inflammatory diseases can also be treated through the induction of immune tolerance, a process that generates both humoral and cellular immunity.[11] This approach requires three critical steps: (1) the successful delivery of intact and active antigens (tolerogens) to target organs, such as the spleen, lymph nodes, lamina propria, or Peyer's patches;[54] (2) uptake of these antigens by antigen-presenting cells, particularly dendritic cells, at the target sites;[55] and (3) subsequent induction of tolerogenic immune responses.[56] Dendritic cells, under non-danger conditions, promote the transformation of T-cells into regulatory T-cells (iTregs), which circulate through the lymphatic and systemic blood systems to establish systemic tolerance.[57] This mechanism suppresses immune responses and can be effective at treating various inflammatory diseases.[57] Tolerogens can also be administered via various routes including oral, IV, and SC/IM routes, with the administration route affecting their local and systemic immune activity.[56,58] While this strategy has demonstrated clinical success, it faces significant challenges. One of the primary obstacles is the limited delivery efficiency of intact and active antigens to both target organs and antigen-presenting cells.[52] This inefficiency often results in poor induction of immune tolerance, reducing the overall effectiveness of the therapy.[11]

Thus, a nanomedicine approach, which can enhance the activity of drugs while minimizing toxicity, has gained attention.[59] By conjugating or encapsulating drugs within nanoparticles, target delivery, half-life, and stability of the drugs/tolerogens can be improved.[59] The targeting ability of the nanoparticles can be further enhanced through conjugation of various targeting moieties.[60] Nanoparticles also improve the precision of delivery by targeting specific cells such as dendritic cells with higher efficiency.[60] (Table 2) In the following sections, we will explore the potential of nanomedicines by categorizing different administration routes, including IV, SC/IM, and oral routes (Table 3).

Table 2 Comparison of Traditional Treatments and Nanomedicine Mediated Treatments of Autoimmune Diseases

Traditional Treatments	Nanomedicine Mediated Treatments
• Ameliorates initial inflammation but inadequate for acquiring long-term immune tolerance • Induces systemic toxicity and unintended immune depression • Short half-time and limited pharmacokinetic profiles	• Ameliorates inflammation and induces long-term immune tolerance • Reduces adverse effects of drugs by delivering cargo selectively to inflamed area or lymph nodes to induce antigen-specific tolerance • Elongated half-time and enhanced pharmacokinetic profiles

Table 3 Summarized Table of Immunomodulatory Nanomedicines for Treatment of Autoimmune Diseases

Nano Medicine	Size	Zeta-Potential	Admin. Route	Targeting Mechanism	Autoimmune Disease Model	Mechanism of Autoimmune Treatment
AZA-PHA (Azathioprine-poly (3-hydroxybutyrate-co -3-hydroxyvalerate-co -3-hydroxyhexanoate)	95.7nm	Unknown	IV	Passive	Systemic lupus erythematosus (SLE)	Delivering azathioprine to spleen
BRNP (Bilirubin nanoparticle)	110nm	Unknown	IV	Passive	Colitis	Delivering bilirubin to inflammatory colon
TCZ-PNP (Tocilizumab-polymer nanoparticle)	190 ± 5.6 nm	Unknown	IV	Passive	Rheumatic Arthritis (RA)	Delivering tocilizumab to inflamed ankle
FS14-NP/siRNA (Pluronic F127 Spermidine based Lipidoid nanoparticle/siRNA)	131.2nm	+21.4mV	IV	Passive	Rheumatic Arthritis (RA)	Delivering siRNA silencing IL-1beta to macrophages in inflamed joint
MPS/cRGD-CA-HPAP-aCD NP (Methylprednisolone/Cyclic arginine-glycine-aspartate-cinnamaldehyde-4-(hydroxymethyl) phenylboronic acid pinacol ester- α-cyclodextrin)	179nm	−30mV	IV	Active(RGD-αvβ3 integrin)	Rheumatic Arthritis (RA)	Delivering methylprednisolone to macrophages and synovial cells to promote transformation of M1-type macrophages to M2-type
Folate-conjugated MTX/siRNA-loaded liposome	170 nm	−23.6mV	IV	Active(Folate-Folate receptor)	Rheumatic Arthritis (RA)	Delivering NF-Kb-specific siRNA and methotrexate to macrophages
FA–PEG–R–NPs@siERN1 (FA (folic acid)-PEG -R(RKKRRQRRR)-NPs(ss-PBAA-PEI)@siERN1)	203.3nm	−13.7mV	IV	Active(Folate-Folate receptor)	Rheumatic Arthritis (RA)	Modulating calcium ion concentrations to induce polarization into M2 macrophage and inhibiting MyD88-dependent Toll-like receptor signaling
KGF-Neus (Keratinocyte growth factor-neutrophil-like liposome)	134.44 ± 2.36 nm	−2.38 ± 0.4mV	IV	Active (Neutrophil membrane coating)	Ulcerative colitis (UC)	Delivering keratinocyte growth factor to inflamed colon
PD-PLGA@Si-Ab/PDA-I(PSAPI) (Perfluorocarbon diclofenac- poly (lactide-co-glycolide)/ polydopamine-iodine)	190 nm	60mV	IV	Active(TSH receptor antibody-TSH receptor)	Grave's disease	Enhancing efficiency of HIFU and mitigating inflammation by co-delivering diclofenac
MSNs-DNA@SeC (Mesoporous silica nanoparticles-DNA@SeC)	161.3 nm	−16 mV	IV	Active(ctDNA-anti-dsDNA antibody)	Systemic lupus erythematosus (SLE)	Capturing and removing serum antibodies in nephritis
CD22L-NP(R)-OVA (CD22 Ligand-nanoparticle (rapamycin)-ovalbumin)	101.3± 14.2 nm	Unknown	IV	Active(CD22 ligand-CD22)	Rheumatic Arthritis (RA)	Delivering self antigen(GPI) and Treg stimulating rapamycin

(*Continued*)

Table 3 (Continued).

Nano Medicine	Size	Zeta-Potential	Admin. Route	Targeting Mechanism	Autoimmune Disease Model	Mechanism of Autoimmune Treatment
ITE+MOG35–55@PEGylated PLGA nanoparticle (2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester+ Myelin Oligodendrocyte Glycoprotein@Poly(Ethylene Glycol)ylated poly(lactide-co-glycolide) nanoparticle)	103.4± 28.3 nm	−24.9 ± 9.7 mV	SC	Passive	Autoimmune encephalomyelitis (EAE)	Delivering self MOG35-55 antigen and AhR agonist to lymph node to induce Treg cells
MOG-PLGA-PEG-NP (Myelin Oligodendrocyte Glycoprotein-Poly(Lactide-co-Glycolide)-Poly(Ethylene Glycol)-Nanoparticle)	286±11 nm	−23.2 ± 3.3 mV	SC	Passive	Autoimmune encephalomyelitis (EAE)	Delivering self MOG35-55 antigen to lymph node to induce antigen-specific tolerance
IL-10@PLGA/E100 nanoparticle (Interleukin-10@Poly(Lactide-co-Glycolide)/Eudragit E100)	800 nm	42.7 ± 1.1 mV	IM	Passive	Type 1 Diabetes (T1D)	Delivering anti-inflammatory IL-10 gene to lymphoid organs and bloodstream through muscle cells
MOG-QD (Myelin Oligodendrocyte Glycoprotein-Quantum Dot)	15.0 ± 0.24 nm~ 21.0 ± 0.63 nm	−17.6 ± 1.5 mV~ −4.2 ± 1.2 mV	SC	Active(CL4 ligand-MARCO)	Multiple sclerosis (MS)	Delivering self antigen MOG to MARCO-expressing macrophages in lymph node to induce tolerance
AbaCitDTN (Abatacept-Citrullinated peptide-Dexamathasone-Tannic acid nanoparticle)	100 nm	2mV	SC	Active (Abatacept-CD80 and CD86 receptor)	Rheumatic Arthritis (RA)	Delivering anti-inflammatory dexamethansone and inhibiting CD80 and CD86 to induce Treg
AbaLDPN-MOG (Abatacept modified polydompamine core nanoparticles loaded with MOG peptide and dexamethasone)	100 nm	−30mV	SC	Active (Abatacept-CD80 and CD86 receptor)	Multiple sclerosis (MS)	Delivering self antigen MOG to antigen presenting cell and inhibiting CD80/CD86 costimulatory signal
INF-PU-PEG (Infliximab-loaded polyurethane-based Poly(Ethylene Glycol) nanoparticles)	231.55 ± 49.72nm	−6.81 ± 2.67mV	Oral	Passive	Colitis	Delivering TNF-a inhibitor infliximab to inflamed colon
INF/LMSN@GE (Infliximab/Lipid-coated Mesoporous Silica Nanoparticles@Ginger Exosome)	284.6 nm	−12.1 mV	Oral	Passive	Colitis	Delivering TNF-a inhibitor infliximab to inflamed colon and inhibiting NLRP3 inflammasome pathway by ginger exosome
PLGA-CII (Poly(Lactic-co-Glycolic Acid)-Collagen Type II)	299.7 ± 4.9 nm	Unknown	Oral	Passive	Rheumatic Arthritis (RA)	Delivering self antigen type II collagen to Peyer's patch to induce tolerance
FK506@EHCh NP (Fujisawa Kenkogo 506 (Tacrolimus)@Ethyl Hydroxyethyl Chitosan)	118.7 ± 2.8 nm	22.2 ± 2.0 mV	Oral	Active (Hyaluronic acid-CD44)	Colitis	Delivering tacrolimus(FK506) to inflammatory cells while reducing systemic toxicity
HABN (Hyaluronic acid-Bilirubin nanoparticles)	86 ± 5 nm ~416 ± 9 nm	−35.6 ± 1.6 mV~ −46.2 ± 5.2 mV	Oral	Active (Hyaluronic acid-CD44)	Colitis	Delivering ant-oxidative and anti-inflammatory bilirubin to inflamed colon and immune cells

Intravenously Administered Nanomedicines for Autoimmune Diseases

Upon IV administration, nanomedicines preferentially accumulate at sites of inflammation[61] or in specific organs that play a crucial role in modulating immune responses, such as the spleen (Figure 3).[62]

Inflamed tissue creates an environment favorable for nanoparticle accumulation due to characteristics such as increased vascular permeability and immune cell activation.[63] Inflammation increases blood vessel permeability,

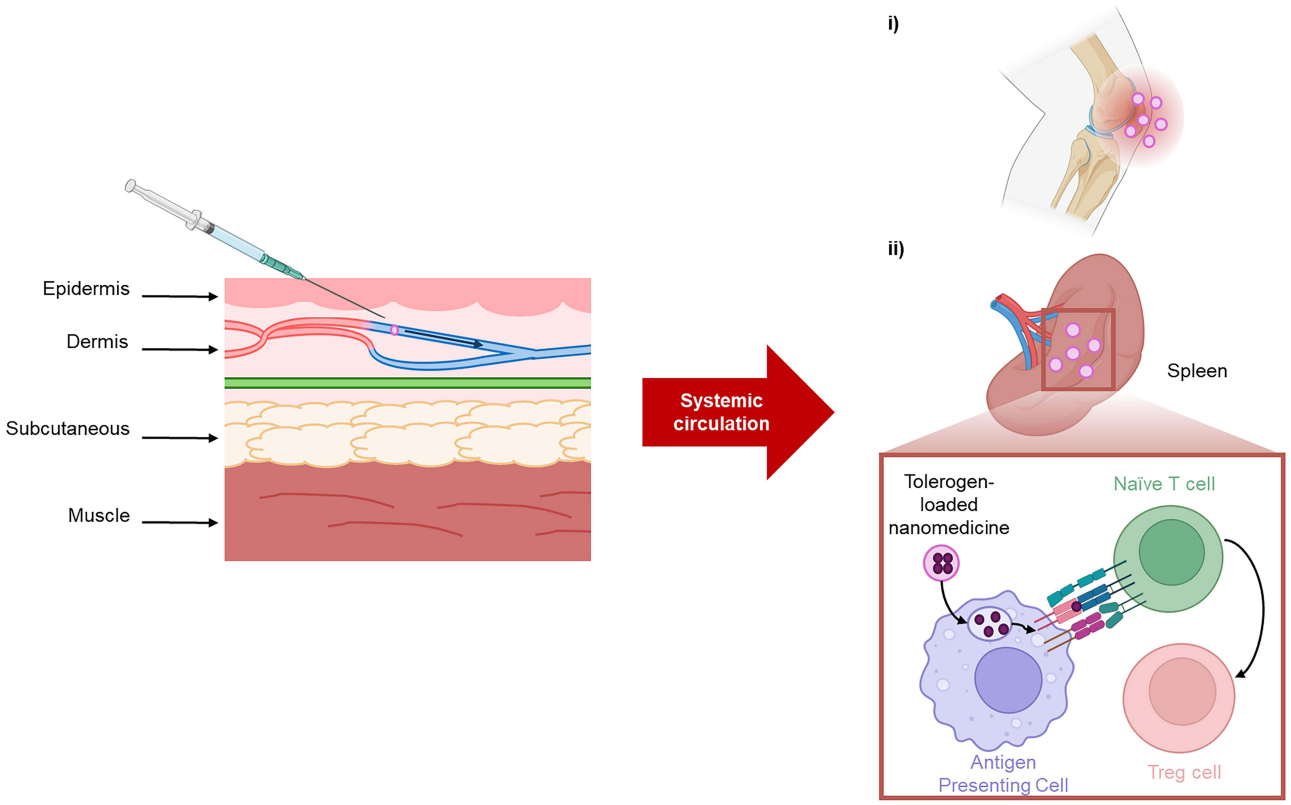

Figure 3 Intravenously administered nanomedicines for autoimmune disease. (Created with BioRender.com) Intravenous nanomedicines can i) drain into inflamed areas to exert anti-inflammatory effect or ii) induce antigen-specific tolerance in the spleen via the systemic circulation.

allowing nanoparticles to enter inflamed areas more easily.[58,59] This process, known as the enhanced permeability and retention (EPR) effect, is crucial for nanoparticle accumulation in inflamed tissues.[61] Additionally, inflammation activates immune cells, like macrophages and neutrophils, which can engulf nanoparticles and migrate toward the inflamed site.[64] Nanoparticles can be engineered for selective accumulation near these immune cells through active targeting, a technique that uses specific ligands to bind nanoparticles to immune cells.[65] This active targeting improves the accumulation of nanoparticles at inflamed sites by either directly targeting immune cells or facilitating migration of immune cell-bound nanoparticles to the inflamed area after binding to cells such as macrophages.[65] In addition, IV nanoparticles can promote immune tolerance by targeting lymphatic organs, such as the spleen.[66] Targeting ligands enhance this effect by improving nanoparticle delivery to immune cells and acting as costimulatory signals.[67]

Together, these physicochemical properties of nanoparticles and pathophysiological characteristics of inflamed tissue allow for effective accumulation of nanomedicines at inflammation sites, enabling targeted therapeutic effects.

Passive Targeting of IV-Administered Nanomedicines

IV administered nanomedicines can target inflamed sites through EPR-mediated passive targeting, leading to enhanced therapeutic efficacy while reducing the toxicity of the loaded drugs including conventional drugs, antibody drugs, and RNA-related drugs.[59]

For example, the immunosuppressant azathioprine has been formulated into a nanomedicine for the management of systemic lupus erythematosus (SLE).[68] Specifically, azathioprine was incorporated into a polyhydroxyalkanoate terpolymer known as poly(3-hydroxybutyrate-co-3-hydroxyvalerate-co-3-hydroxyhexanoate) (PHBVHHx), synthesizing AZA-PHA. IV administration of AZA-PHA demonstrated superior efficacy compared to the free drug or AZA-PLA (azathioprine encapsulated in poly-lactic acid nanoparticle), with increased accumulation in the spleen and reduced renal clearance. Furthermore, AZA-PHA exhibited no adverse effects in a murine MRL/lpr lupus model, indicating a favorable

safety profile.[68] These results suggest that nanomedicines loaded with azathioprine can effectively mitigate inflammation without the significant side-effects typically associated with azathioprine.

In addition to clinically used immunosuppressants, natural anti-inflammatory compounds such as bilirubin can be formulated into nanomedicines for treating autoimmune diseases.[69] For example, Lee et al designed bilirubin nanoparticles (BRNPs) using PEGylated bilirubin for the treatment of inflammatory bowel diseases.[70] Despite bilirubin's potent intrinsic antioxidant, cytoprotective, and anti-inflammatory properties, its biomedical application has been hindered by its hydrophobicity and associated toxicity.[71] To overcome these limitations and enhance its therapeutic potential, an amphiphilic PEGylated bilirubin-based nanomedicine was developed.[70] When administered IV, PEGylated bilirubin nanoparticles localized specifically to the inflamed colons of mice with DSS-induced colitis. The nanoparticles demonstrated reactive oxygen species (ROS)-scavenging and anti-inflammatory activities, leading to significant amelioration of colitis symptoms. These findings highlight the potential of nanoparticle formulations to enhance the therapeutic efficacy of drug candidates while simultaneously minimizing their associated toxicity.

Additionally, inorganic nanoparticles themselves can ameliorate inflammation without additional cargo loading. For example, Liu et al designed macrophage membrane-coated cerium oxide nanoparticles (RM-CeO_2), capable of scavenging cell free-DNA (cfDNA), ROS, and inflammatory cytokines, which interplay in the development of inflammatory diseases.[72] Upon IV administration in murine models of rheumatoid arthritis and autoimmune hepatitis, RM-CeO_2 exhibited prolonged circulation and preferential accumulation at inflamed sites.[72] Subsequently, the macrophage membrane component neutralized inflammatory cytokines, while the CeO_2 core scavenged ROS and degraded cfDNA, thereby addressing multiple factors involved in disease progression.

Nanoparticles also serve to protect monoclonal antibodies (mAbs) from degradation and facilitate their targeted delivery to sites of inflammation.[73] Given that mAbs are often recognized as foreign entities by the human immune system, they are susceptible to degradation and may inadvertently provoke the production of anti-mAb antibodies.[74] Furthermore, mAbs can also induce off-target side effects.[45] Nanoparticles can address these limitations, which has inspired investigation into the effects of loading or conjugation of mAbs.[75] For example, Chen et al synthesized theragnostic polymer nanoparticles (PNPs) by constructing a polymer composed of benzo[1,2-b:4,5-b′]dithiophene and dibromobenzo[1,2-c:4,5-c′]bis([1,2,5]thiadiazole), which was then nano-precipitated with DSPE-PEG and DSPE-PEG-COOH.[76] These PNPs were then conjugated with tocilizumab (TCZ-PNP), a widely utilized mAb for rheumatoid arthritis. Upon IV administration in a rheumatoid arthritis model mouse induced by collagen antibody and subsequent irradiation with a near-infrared II (NIR-II) laser, TCZ-PNP exhibited a strong signal at the inflammatory joints and effectively suppressed the expression of inflammatory cytokines. A notable aspect of this study is that the nanoparticles functioned as both therapeutic and imaging agents, enabling the detection of subtle inflammatory signals, which facilitated early diagnosis and comprehensive disease management.[77]

In addition to encapsulating conventional chemical agents or biologics, nucleic acids such as small interfering RNAs (siRNAs) that target immune-related genes can also be formulated into nanomedicines to attenuate immune responses during inflammation.[78] As an example, Song et al developed lipidoid-polymer hybrid nanoparticles (FS14-NPs) designed to deliver siRNA targeting IL-1β (siIL-1β) to macrophages.[79] FS14-NPs were synthesized by combining F127 (a copolymer of hydrophilic polyethylene oxide and hydrophobic polypropylene oxide) with S14 (a lipidoid) and subsequently incubating these nanoparticles with siIL-1β to facilitate loading through electrostatic interactions. FS14-NP/siIL-1β complexes were administered IV and effectively suppressed inflammation in a collagen antibody-induced arthritis model (CAIA mice). FS14-NP/siRNA complexes rapidly accumulated in macrophages within arthritic joints, leading to a reduction in levels of pro-inflammatory cytokines and alleviation of clinical symptoms such as ankle swelling, bone erosion, and cartilage destruction. Another example is lipid-based nanoparticles encapsulating siRNAs targeting the colony stimulating factor-1 (CSF-1) axis; administration of these yielded great anti-inflammatory responses in a myosin peptide induced-myocarditis model.[80] CSF-1 regulates monocytes derived from hematopoietic stem cells and to promote the differentiation of monocytes and macrophages, which play significant roles in inflammatory processes and the fibrotic scarring of cardiac tissue.[81] IV administration of siCSF-1-encapsulated nanoparticles in a mouse model of autoimmune myocarditis effectively targeted not only the inflamed cardiac tissue but also immune organs such as the spleen and bone

marrow.[80] This resulted in inhibition of myeloid cell accumulation and activation of tissue-resident immune cells within the heart, ultimately leading to a reduction in cardiac inflammation.

Beyond EPR effects, certain nanoparticles can be designed to remain in the bloodstream and exert therapeutic effects directly within the vascular compartment—targeting processes such as blood clotting, platelet aggregation, and histone release—without relying on passive accumulation via the EPR effect. Since NETosis and other intravascular inflammatory responses can be excessively activated under specific conditions, such as bacterial infections or COVID-19, leading to severe complications including sepsis, this strategy is highly relevant for managing the symptoms of these diseases.[82] For instance, Lee et al developed PEGylated nanoparticle albumin-bound (PNAB) formulations loaded with steroidal ginsenosides (Rg6 and Rgx365) as a therapeutic strategy to alleviate clinical complications observed in severe SARS-CoV-2 patients.[82] These PNAB-drugs effectively reduce histone H4 and NETosis-related factors in plasma, alleviate SREBP2-mediated systemic inflammation in PBMCs, suppress blood clot formation and vascular inflammation in an engineered blood vessel model, and mitigate tissue damage and cytokine storm in animal models, thereby improving survival rates. The findings suggest that PNAB-steroidal ginsenosides hold promise for treating coagulation and hyperinflammation symptoms in severe COVID-19 cases.

In summary, encapsulation of a diverse array of therapeutic agents ranging from small chemical compounds to macromolecular drugs has yielded stable, non-toxic nanomedicines with stable anti-inflammatory effects. When administered IV these nanomedicines can effectively target sites of inflammation or components of the immune system by circulating through the systemic bloodstream, thereby exerting immunomodulatory effects.

Active Targeting of IV-Administered Nanomedicines

IV nanomedicines can effectively target inflammation and the immune system.[59] Functionalization of ligands associated with immune cells can further enhance the targeting efficacy of these nanomedicines.[83] Consequently, there is a growing body of research focused on the development of IV nanomedicines that specifically target sites of inflammation and/or activated immune cells.[59]

For example, Lu et al conjugated nanomedicines with an RGD sequence to selectively target activated macrophages.[84] In more detail, these authors encapsulated methylprednisolone within pH/ROS dual-responsive nanoparticles designed for application in the microenvironment of rheumatoid arthritis. Methylprednisolone was incorporated into α-cyclodextrin, which was modified with cinnamaldehyde and 4-(hydroxymethyl) phenylboronic acid pinacol ester, both of which are activated by low pH and reactive oxygen species, which are characteristic of the arthritic microenvironment. Subsequently, α-cyclodextrin was coated with DSPE-PEG-RGD, allowing the RGD sequence to target avβ3/avβ5 integrins that are overexpressed on activated macrophages. IV administered nanoparticles resulted in a significant reduction in pro-inflammatory cytokines compared to the free drug in in vivo collagen-induced arthritis models. Notably, functionalization of the RGD sequence as a macrophage-targeting agent resulted in enhanced anti-inflammatory activity compared to other treatment groups. Importantly, the nanomedicines exhibited no significant toxicity or adverse effects either in vitro or in vivo.

Folate is another ligand that is frequently employed for active targeting of the folate receptor, which is overexpressed on activated macrophages.[85] Duan et al developed a nanoparticle system composed of calcium phosphate and liposomes encapsulating NF-kB-targeted siRNA and methotrexate (MTX).[86] These nanoparticles were further functionalized with folate to facilitate targeting of the folate receptor on LPS-activated macrophages. In a collagen-induced rheumatoid arthritis model, the IV administered nanomedicine specifically targeted activated macrophages at the inflammatory joints passively (by EPR effects) and actively (by folic acid). This nanomedicine therefore exhibited high therapeutic efficacy through inhibition of the NF-kB pathway due to NF-kB-targeted siRNA and inhibition of the metabolism of inflammatory immune cells with a significant reduction in the side-effects of both drugs. Additionally, Feng et al developed a nanomedicine functionalized with folic acid comprising cationic polyethylenimine (PEI) and poly(β-amino amine) (PBAA)-encapsulated siRNAs targeting the endoplasmic reticulum to suppress the *endoplasmic reticulum to nucleus signaling 1* (*ERN1*) gene (siERN1).[87] IV administration of the siERN1 nanomedicine targeted activated macrophages at pathological sites due to interactions between folic acid and the folate receptor, leading to polarization of activated

macrophages into an anti-inflammatory M2 phenotype by modulation of calcium ion concentrations and inhibition of MyD88-dependent Toll-like receptor signaling.

Another example of active targeting is the thyroid-stimulating hormone (TSH) receptor, which is overexpressed on activated thyroid tissue. For instance, Wang et al developed a thyroid-targeted nano-bomb system (PD-PLGA@Si-Ab/PDA-I, PSAPI) to enhance high-intensity focused ultrasound (HIFU) therapy for the treatment of Graves' disease.[88] PSAPI consists of a core that encapsulates the phase-transition material perfluorohexane and the anti-inflammatory agent diclofenac within a PLGA and silica shell. Following IV administration, PSAPI accumulates in the thyroid and specifically targets overactive thyroid cells via interactions between the TSH receptor antibody on the nanoparticle surface and TSH receptors on thyroid cells. Upon internalization, the expansion of perfluorohexane gas leads to rupture of the silica shell, thereby amplifying the thermal and mechanical effects of HIFU. Additionally, diclofenac mitigates local inflammation following ablation, enhancing both the therapeutic efficacy and safety of the HIFU treatment.

Integrating nanomedicines with entire immune cell membranes offers a promising strategy to actively target inflamed sites by mimicking the behavior of immune cells.[89] For example, Zhao et al developed neutrophil-mimicking nanoparticles to target the inflamed colon in a mouse model of DSS-induced colitis.[90] Specifically, keratinocyte growth factor (KGF), known for its therapeutic effects on colitis, was encapsulated within liposomes that were then fused with neutrophil membrane vesicles (NEMs) extracted from activated neutrophils, resulting in neutrophil-mimicking nanoparticles termed KGF-Neus. KGF-Neus selectively targeted the inflamed colon by mimicking the natural recruitment of neutrophils to inflammatory sites owing to the targeting ability of NEM-associated proteins. This process involved binding to inflammatory vascular endothelial cells, enabling precise delivery of the therapeutic payload. By employing immune cell-mimicking nanocarriers, this approach demonstrates how nanomedicines can actively target inflamed tissues and display enhanced anti-inflammatory effects, thereby offering a novel and effective avenue for treating inflammatory diseases.

Nanoparticles administered IV can induce immune tolerance by targeting lymphatic organs like the spleen via blood vessels.[62] To enhance spleen targeting, specific targeting ligands can be used.[62] These ligands not only improve targeting efficiency toward immune cells but can also serve as costimulatory signals through their binding interactions.[91] For example, Brzezicka et al developed hybrid nanoparticles to induce immune tolerance in a K/BxN serum-transfer arthritis (STA) model by presenting self-antigens while activating inhibitory signals.[92] These nanoparticles featured a lipid monolayer encapsulating a PLGA core with rapamycin to promote regulatory T cells (Tregs). These nanoparticles also presented glucose-6-phosphate isomerase (GPI), a self-antigen relevant to rheumatoid arthritis, and a CD22 ligand to inhibit B cell activation. When administered IV, the nanoparticles targeted B cells in the spleen, inducing B cell tolerance as measured by low anti-GPI antibodies and decreased cell populations as well as T cell tolerance as measured by increased Tregs, thereby aiding in the recovery of joint damage.

In summary, targeting of inflamed tissues can be enhanced by functionalizing nanomedicine surfaces with immune cell-specific ligands.[93] IV delivery directs nanomedicines to pathological sites, where active targeting enables their binding to immune cells. Additionally, ligands that engage inhibitory signals on immune cells show improved targeting efficiency and can further modulate immune responses.[94]

Nanomedicines Administered Subcutaneously and Intramuscularly for Autoimmune Diseases

SC and IM routes are commonly used methods for drug delivery.[95] In SC and IM routes, drugs are initially deposited into the surrounding tissue before they diffuse into the bloodstream or lymphatic system.[58] These methods allow for targeted drug delivery with specific advantages based on particle size.[96] Nanoparticles behave differently depending on their size: those smaller than 5 nm partially enter the bloodstream and partially move to lymph nodes, while nanoparticles in the 5–50 nm range are directed primarily toward lymphatic vessels. Larger nanoparticles typically remain at the injection site, where they slowly release their contents into the bloodstream and lymphoid organs.[97–99] Larger nanoparticles, which are not appropriate for lymphatic delivery, can still reach lymphoid organs by being taken up by APCs, such as macrophages and dendritic cells, facilitating the delivery of their cargo to lymphoid organs (eg lymph nodes) and potentially inducing immune tolerance.[97,100,101] Overall, SC and IM administration routes enable lymphatic organ (eg

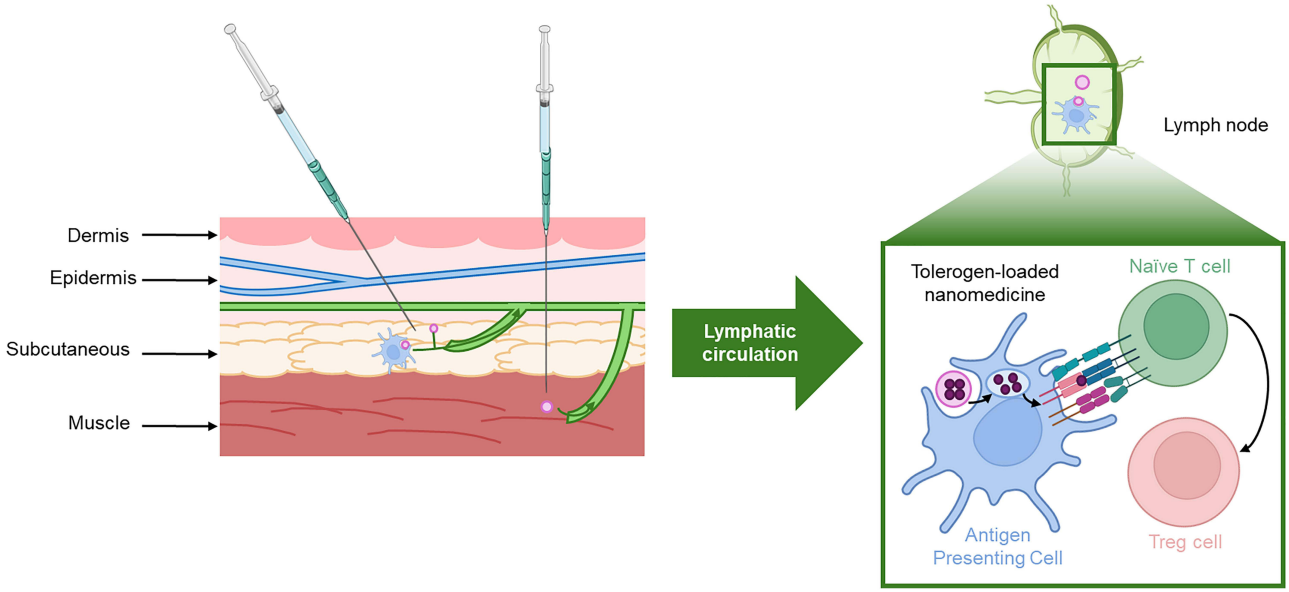

Figure 4 Subcutaneously and intramuscularly administered nanomedicines for autoimmune diseases. (Created with BioRender.com) Subcutaneous or intramuscular nanomedicines enter lymphatic circulation by themselves or by dendritic cells to induce antigen-specific tolerance in lymph nodes.

lymph nodes)-targeted drug (eg antigens, and immune modulators) delivery, particularly of nanoparticles, facilitating the induction of immune tolerance (Figure 4).

Passive Targeting of SC/IM-Administered Nanomedicines

Nanomedicines administered via SC and IM routes possess the ability to target lymphoid organs by either directly draining into lymphatic vessels or by recruiting dendritic cells and macrophages.[102] Consequently, these nanomedicines can facilitate immune tolerance by stimulating anti-inflammatory immune cells within lymphoid organs.[103] Notably, these nanomedicines do not merely induce transient immune suppression; rather, they are designed to continuously modulate immune cell activity to address autoimmune diseases, thereby promoting effective remission of such conditions.[104]

Traditional immunosuppressants can be targeted to lymphoid organs to enhance immune suppression and reduce side effects by using nanoparticle-based SC and IM administration.[11] For example, Park et al developed methotrexate-loaded PLGA nanoparticles (MTX-NPs) for lymphatic organ delivery of MTX for the treatment of arthritis.[105] SC administered MTX-NPs targeted the spleen and modulated T and B cell responses in a collagen-induced arthritis model, ameliorating arthritis at lower doses than those typically used in clinical settings. MTX-NPs were shown to increase regulatory T cell (Treg) populations in the spleen while simultaneously reducing levels of interleukin-6 (IL-6) and interleukin-17A (IL-17A), both associated with the development of Th17 cells. Furthermore, the nanoparticles enhanced the presence of regulatory B cells (Breg) in splenocytes compared to free methotrexate.

SC administration of nanomedicines also promotes the recruitment of immune cells, such as dendritic cells and macrophages, to the injection site, followed by their migration to the lymph nodes.[102] When these nanomedicines carry antigens associated with autoimmune diseases to the lymph nodes, they can induce antigen-specific tolerance, resulting in effective treatment of autoimmune diseases.[11] In a study by Kenison et al, nanoliposomes were loaded with the aryl hydrocarbon receptor (AhR) agonist 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) and a T cell epitope derived from myelin oligodendrocyte protein (MOG35–55).[106] The AhR agonist facilitated immune modulation, while MOG35–55 served as a self-antigen to induce antigen-specific tolerance. SC injected nanoliposomes loaded with the AhR agonist and MOG35-55 antigen targeted lymph nodes after uptake by APCs, thereby expanding the population of MOG35–55-specific Treg cells, reducing MOG-specific effector T cell activity, and decreasing effector T cell infiltration into the central nervous system in a murine model of autoimmune encephalomyelitis induced by MOG35–55 or PLP139–151. This resulted in the amelioration of experimental autoimmune encephalomyelitis. As

another example, Li et al induced antigen-specific immune tolerance in a model of autoimmune multiple sclerosis induced with the MOG35-55 peptide through the SC administration of PEGylated poly(lactide-co-glycolide) (PLGA) nanoparticles containing the autoantigen peptide MOG35–55, without the use of tolerogenic drugs.[107] The study emphasized the significance of PEGylation, which facilitated the ability of the SC administered nanoparticles to promote an antigen-specific immune response. Notably, PEGylation did not directly diminish the activation of inflammatory dendritic cells; rather, it contributed to the establishment of a more anti-inflammatory microenvironment at the injection site by attenuating complement activation and neutrophil recruitment. Concurrently, PEGylated nanoparticles facilitated the local recruitment of dendritic cells, which subsequently migrated to lymphoid organs to promote T cell tolerance.

Amelioration of immune responses by blocking dendritic cell activation without nanoparticle-mediated self-antigen presentation is another promising strategy. For example, Li et al developed a cationic lipid–assisted PEG–PLGA nanoparticle (CLAN) platform for the targeted co-delivery of siRNAs against CD40 and LKB1, which are involved in the stimulation and metabolism of dendritic cells.[108] Following subcutaneous administration in an experimental autoimmune encephalomyelitis model, CLAN preferentially targeted splenic CD11c+ dendritic cells, achieving over 60% siRNA uptake, suppressing Th1/Th17 differentiation, and promoting Treg induction.[108]

Large nanoparticles administered SC and IM tend to remain at the injection site and release drugs in a controlled manner over a prolonged time period.[109] For example, PLGA and Eudragit 100-based nanoparticles ~800 nm in size were fabricated using a W/O/W emulsion/solvent evaporation technique and loaded with plasmid DNA encoding IL-10.[110] Notably, these nanoparticles remained at the injection site and were internalized into muscle cells, producing IL-10, an anti-inflammatory cytokine that promotes the differentiation of regulatory T cells (Tregs) in lymphoid organs and the bloodstream. Thus, this IM administered nanomedicine resulted in a reduction of blood glucose levels in a model of streptozocin-induced autoimmune type 1 diabetes. These results prove the feasibility of using cationic PLGA/E100 nanoparticles for IL-10 gene delivery for the prevention of autoimmune diabetes.

In conclusion, both SC and IM delivery of immune-modulating nanomedicines can result in the effective delivery of loaded drugs such as antigens/immunomodulatory drugs into lymphoid organs such as lymph nodes by directing these drugs toward lymphatic vessels or via APC-mediated lymphoid organ delivery,[102–104] leading to effective induction of immune tolerance.

Active Targeting of SC-/IM-Administered Nanomedicines

Active targeting of SC or IM-administered nanomedicines has the potential to improve the capacity of loaded drugs to target immune cells at the site of injection or within lymph nodes.[111] Notably, antigen-presenting cells such as dendritic cells are increasingly being recognized as critical targets for the induction of antigen-specific immune tolerance due to their ability to phagocytose, present antigens to T cells, and facilitate T-cells priming in lymph nodes.[112] In this context, conjugation of ligands that improve the binding affinity of nanoparticles to antigen-presenting cells is associated with a more effective induction of immune tolerance compared to passive targeting strategies.[111]

As an example, Hess et al developed myelin self-peptides displaying quantum dots (QDs) conjugated with the CL4 ligand to target MARCO-expressing macrophages in lymph nodes for tolerance induction against multiple sclerosis.[113] SC administered nanoparticles demonstrated enhanced lymph node targeting ability due to their macrophage-binding capability, resulting in the induction of tolerance against myelin through expansion of myelin specific-regulatory T cells.[113] This resulted in a significant reduction of disease severity in a murine model of multiple sclerosis induced with MOG.[113] Notably, the density of myelin molecules presented on QDs was shown to be highly associated with the induction of immune tolerance; specifically, a higher quantity of QDs displaying lower levels of myelin self-peptide proved to be more effective than a lower quantity of QDs exhibiting a high density of myelin self-peptide.[113]

Conjugation of antibodies that target co-stimulatory signals on the surface of dendritic cells not only enhanced their binding affinity but also facilitated the reprogramming of immune cells into a tolerogenic phenotype.[112,114] For example, Wu et al developed a tannic acid-based tolerogenic nanovaccine, CitDTN, to deliver citrullinated self-antigen and dexamethasone.[115] This formulation was further modified with abatacept, an antibody targeting CD80 and CD86 on dendritic cells, resulting in the formation of AbaCitDTN. Upon SC injection, AbaCitDTN effectively targeted CD80/86-expressing skin dendritic cells, was internalized by these cells, and subsequently drained into lymph nodes in a collagen

induced-rheumatoid arthritis model. Dexamethasone suppresses inflammation, while tannic acid served as both the core nanomaterial and an antioxidant agent. Within lymph nodes, dendritic cells that phagocytosed AbaCitDTN presented the citrullinated peptide antigen to T cells. As a result of this process, abatacept inhibited the co-stimulatory signals induced by CD80 and CD86, promoting the induction of regulatory T cells and leading to the amelioration of collagen induced-rheumatoid arthritis. Similarly, abatacept-modified polydopamine core nanoparticles loaded with MOG peptide and dexamethasone (AbaLDPN-MOG) were also developed.[116] These nanomedicines specifically targeted dendritic cells, migrated to lymph nodes, and inhibited the interaction between CD80/CD86 on antigen-presenting cells and CD28 on T cells, which facilitated the maturation of regulatory T cells. The nanomedicine described above significantly mitigated the symptoms associated with multiple sclerosis in a murine multiple sclerosis model induced by MOG. Furthermore, SC injection of this nanomedicine not only prevented but also alleviated autoimmune encephalitis, suggesting its potential as a therapeutic tolerogenic nanovaccine for autoimmune disorders.

Numerous studies have illustrated that SC or IM nanomedicines can actively target immune cells by conjugation of ligands that bind to surface markers on cells or the utilization of ligands that facilitate the internalization of the nanomedicines.[11] Notably, by targeting surface markers on dendritic cells, nanomedicines administered SC or IM can traffic to lymph nodes through endocytosis, even if their size does not conform to the typical range for lymphatic drainage.[112] Targeting ligands can also block the interactions between dendritic cells and T-cells.[117] This allows for effective drainage into lymph nodes and the presentation of self-antigens, thereby facilitating antigen-specific tolerance and addressing the underlying causes of autoimmune diseases.[114]

Oral Nanomedicines for Autoimmune Diseases

Oral administration is widely recognized as the most convenient medicine administration method for patients, which has prompted extensive research into the development of oral nanomedicines that are both effective and user-friendly.[118] Orally administered nanomedicines can be utilized for anti-inflammation therapy and hyposensitization therapy.[119] Orally administered nanomedicines can reach the inflamed intestine through leak intestinal barrier (passively) and by actively targeting immune cells such as macrophages, resulting in anti-inflammatory activity for the treatment of intestinal inflammation-associated diseases such as inflammatory bowel disease.[119,120] In addition, orally administered nanomedicines can specifically deliver tolerogens to dendritic cells at the healthy lamina propria and Peyer's patch after internalization of nanomedicines by M-cells.[121] This has been shown to induce immune tolerance and therefore have therapeutic efficacy against various autoimmune diseases (Figure 5).

Passive Targeting of Orally Administered Nanomedicines

Orally administered nanomedicines can passively target inflamed intestinal tissue through a leaky intestinal barrier, thereby exhibiting anti-inflammatory activity for the treatment of intestinal inflammation-associated diseases such as inflammatory bowel disease.[119,122] In addition, orally administered nanomedicines can reach Peyer's patch through M-cells non-specifically, leading to the induction of immune tolerance against various autoimmune diseases.[118]

Anti-TNF-α antibodies, which are widely used as biologic-targeted therapeutics for the treatment of inflammatory bowel diseases, exhibit instability in the harsh gastrointestinal environment.[123] To address these limitations and enhance the therapeutic efficacy of the drugs, numerous studies have focused on encapsulating anti-TNF-α antibodies within nanoparticles.[124] For example, Pabri et al developed infliximab-loaded polyurethane-based nanoparticles as an oral nanomedicine to treat colitis.[125] The orally administered nanomedicine exhibited enhanced accumulation and penetration in the inflamed colon compared to the free drug, indicating successful targeted delivery of infliximab to the inflamed colon. Consequently, this nanomedicine demonstrated excellent anti-inflammation activity in a murine DSS-induced colitis model. Similarly, Mao et al developed infliximab-encapsulating mesoporous silica nanoparticles coated with ginger-derived exosomes as an oral nanomedicine to treat colitis.[126] This formulation exhibited stability within the gastrointestinal tract, targeted delivery to the colon, and high permeability across the inflamed colon epithelium. This nanomedicine showed good therapeutic efficacy in a murine DSS-induced colitis model due to the synergistic anti-inflammation activity of infliximab and the ginger exosome capable of inhibiting the NLRP3 inflammasome.(Clinical trial number: not applicable).

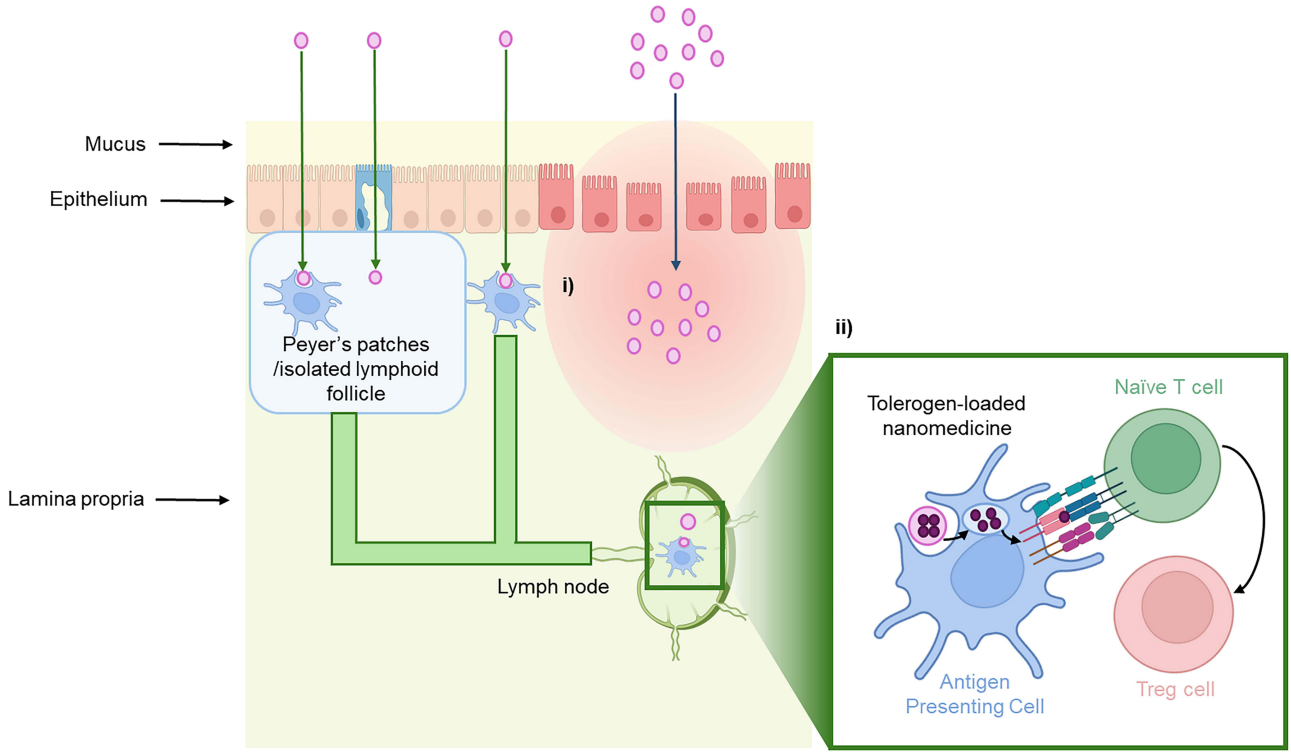

Figure 5 Orally administered nanomedicines for the treatment of autoimmune diseases. (Created with BioRender.com) Oral nanomedicines can i) penetrate through the disrupted intestine barrier to ameliorate inflammation or ii) be taken up by dendritic cells in the lamina propria to induce antigen-specific tolerance in lymph nodes.

In addition, Park et al constructed nanoassemblies composed exclusively of a mesalamine prodrug that conjugates 5-ASA with a mucoadhesive and cathepsin B-cleavable peptide.[127] Upon oral administration in a murine IBD model, the nanomedicine demonstrated enhanced accumulation at inflamed sites via the EPR effect and precise macrophage polarization by cathepsin B-triggered mesalamine release.[127] As a result, the nanomedicine showed outstanding therapeutic efficacy in inhibiting local inflammation and suppressing systemic inflammation in IBD model.[127]

Furthermore, Kim et al demonstrated the induction of antigen-specific tolerance in a collagen-induced arthritis model through the oral administration of a PLGA nanomedicine encapsulating type II collagen (PLGA-CII).[128] Fourteen days post-administration of PLGA-CII, many nanoparticles were detected in Peyer's patches. In the Peyer's patches, the nanomedicine delivered tolerogens to immune cells, leading to the induction of immune tolerance, as evidenced by a noted decrease in serum IgG anti-CII antibodies and CII-specific T cells, alongside an increase in TGF-beta mRNA expression. Consequently, the oral administration of PLGA-CII successfully induced antigen-specific tolerance in Peyer's patches, thereby mitigating the severity and incidence of arthritis.

In conclusion, orally administered nanomedicines have the potential to suppress inflammatory responses in pathological intestines and promote immune tolerance by penetrating into Peyer's patches or the lamina propria.

Active Targeting of Orally Administered Nanomedicines

The efficacy of oral nanomedicines can be enhanced by active targeting strategies.[129] Active targeting enhances the targeting ability of oral nanomedicines by allowing them to bind to molecules overexpressed on cells such as inflamed epithelium and immune cells (eg macrophages) at inflamed sites in addition to the inherent passive targeting ability of the nanoparticles through disrupted intestinal barriers.[122] This enhances the accumulation of nanomedicines at inflamed sites. One study demonstrated that nanomedicines functionalized with active targeting ligands specifically targeted CD103+ dendritic cells and Peyer's patch through M-cells induced tolerance.[119]

Cai et al developed tacrolimus-loaded beta-cyclodextrin coated with positively charged chitosan, CD44-targeted hyaluronic acid, and pH-responsive Eudragit S100 for anti-colitis therapy.[130] This Eudragit S100 coating enabled the nanoparticles to

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specifically target the impaired intestinal barrier in a pH-responsive manner, facilitating drug release exclusively in the inflamed colon.[130,131] Furthermore, the hyaluronic acid coating enhanced the targeting ability of the nanomedicine to macrophages via hyaluronic acid-CD44 interactions.[130,132] Finally, this nanomedicine exhibited dramatic therapeutic efficacy in a murine DSS-induced colitis model as exhibited by a significant reduction in inflammatory cytokines such as TNF-α, IL-1β, and IL-6 alongside improved restoration of colon tissues.[130] Furthermore, Lee et al developed a hyaluronic acid-bilirubin nanomedicine (HABN) by conjugating anti-oxidative/immune modulatory bilirubin with CD44-targeting hyaluronic acid for targeted modulation of the gut microbiome, intestinal barrier, and immune system in colitis.[133] The nanomedicine targeted inflamed colonic epithelium and pro-inflammatory macrophages via CD44-hyaluronic acid interactions. HABN beneficially target-modulated the gut microbiome while restoring intestinal barrier functions and inducing anti-immune responses, leading to strong anti-inflammation activity in a murine DSS-induced colitis model.

Moreover, antibodies can be utilized to actively-target inflamed tissues.[134] Xiao et al developed an oral hydrogel encapsulating single-chain CD98 antibody (scCD98)-functionalized nanoparticles loaded with CD98 siRNA (siCD98).[135] To prepare this nanomedicine, chitosan was conjugated with uranoic acid-PEG-maleimide and scCD98, resulting in the formation of scCD98-PEG-UAC, which was then combined with PEI and siRNA through a complex coacervation technique. Hydrogels of these nanoparticles protected the antibody-based-targeting ligand, which is susceptible to enzymatic degradation under harsh GIT conditions. scCD98-functionalized siCD98-loaded nanoparticles specifically targeted CD98, which is overexpressed by inflamed colon tissue and macrophages. In a murine DSS-induced colitis model, these nanoparticles effectively reduced CD98 levels and those of inflammatory cytokines (including tumor necrosis factor α, interleukin-6, and interleukin-12), thereby exhibiting dramatic therapeutic efficacy.

To enhance the internalization of tolerogenic nanomedicines into dendritic cells within Peyer's patches and the lamina propria, ligands that actively target M cells and dendritic cells can be utilized.[136] For example, Chen et al developed chitosan nanoparticles designed to deliver the antigen heat shock protein 65–6×P277 (H6P).[137] These nanoparticles were modified with the M cell-targeting peptide arginylglycylaspartic acid (RGD) and the dendritic cell-targeting ligand mannose. Following oral administration of H6P-loaded nanoparticles once weekly for 7 weeks to non-obese diabetic (NOD) mice, significantly enhanced H6P uptake by dendritic cells was observed.[137] This led to the induction of antigen-specific T cell tolerance through immune deviation (shifting from a Th1 to Th2 response) and the expansion of CD4+CD25+FOXP3+ regulatory T cells. As a result, diabetes onset was successfully prevented in all treated NOD mice. These findings emphasize the potential of active targeting of dendritic cells and M cells with nanoparticles to induce antigen-specific tolerance and mitigate autoimmune diseases.

The aforementioned examples illustrate that active targeting of oral nanomedicines can be accomplished by coating nanoparticles with materials that exhibit affinity for specific receptors or by conjugating nanoparticles with targeting ligands.[138] By enhancing the targeting capabilities of oral nanomedicines, it is possible to facilitate efficient delivery to the intended site, leading to enhanced therapeutic efficacy.[139]

Perspective, Challenges, and Future Research Directions

Autoimmune diseases are becoming increasingly prevalent, presenting significant global health challenges.[140] Current treatments, which focus on symptom management and immunosuppression, have limitations, such as failing to address disease causes and increasing infection risks.[141] Emerging targeted immune modulation strategies aim to selectively regulate immune responses.[142] Monoclonal antibodies (mAbs) show promise in limiting inflammation, but can elicit hypersensitivity reactions and have pharmacokinetic issues.[143]

Nanomedicines that encapsulate nanoparticles are innovative solutions for delivering therapeutic agents due to enhanced targeting, reduced drug degradation, and reduced systemic toxicity.[144] The choice of delivery method plays a crucial role in determining the nanoparticles' final destination, enabling targeted delivery to inflamed sites for anti-inflammatory effects or to lymphoid organs to promote immune tolerance.[145] Thus, the administration route significantly influences treatment outcomes.[145] IV nanoparticles can accumulate in inflamed tissues due to enhanced vascular permeability and deliver tolerogens to the spleen to induce immune tolerance. The spleen's critical role in immune regulation makes it a valuable target for IV-administered nanoparticles, which when targeted to the spleen facilitate immune modulation and minimize off-target effects. SC and IM routes are ideal for delivering nanomedicines to lymph

nodes, promoting immune tolerance through hyposensitization. Oral delivery targets Peyer's patches and the lamina propria for anti-inflammatory effects and tolerance induction in intestinal inflammation. Furthermore, the conjugation or coating of nanoparticles with active targeting ligands that target receptors on immune cells or pathological sites can enhance the immunomodulatory effects of these nanomedicines.

Despite the potential of immunomodulatory nanomedicines in treating autoimmune diseases, several challenges remain to be addressed to be commercialized in clinical practice since only a limited number of immunomodulatory nanomedicines have progressed to Phase II or III clinical trials for autoimmune diseases. First, drug regimens, dose, and drug (tolerogens)-release kinetics should be considered to develop effective approaches to induce immune tolerance and anti-inflammation activity while ensuring long-term safety. For example, the dose of antigen plays a critical role in shaping immune responses in oral nanomedicines.[146] High antigen doses can lead to immune anergy or deletion rather than protective immunity, emphasizing the need to deliver appropriate doses for effective immune protection.[147] Conversely, repeated administration of low antigen doses can induce a regulatory T cell (Treg)-based tolerogenic response, promoting immune tolerance.[148] This balance between dose and immune outcome is crucial for designing effective oral nanomedicine strategies. Second, since in most cases treatment of autoimmune disease requires long-term treatment, the long-term toxicity of nanomedicines should be evaluated.[11] Third, recent studies have shown that the gut microbiome plays a crucial role in the induction, development, severity, and treatment of various diseases.[149] Thus, the gut microbiome could be an important target of orally administered nanomedicines and this should be considered when developing oral nanomedicines. Finally, since many nanomedicines have complex structures, there are issues associated with large-scale manufacturing of nanoparticles and associated quality control, which has significantly hindered their clinical translation.[150] Even if industrial manufacturing issue is addressed and supplied to patients in clinical practice, nanomedicines may be still much more expensive than traditional agents, leading to patient compliance issue.[151] Therefore, establishing clear regulatory frameworks and cost-effective manufacturing strategies will be essential for the successful clinical translation of anti-inflammatory nanomedicines.

In conclusion, immunomodulatory nanomedicines have shown promising results in preclinical and early clinical studies. Since the worldwide success of COVID-19 vaccines, interest in immunomodulatory nanomedicines has significantly increased. While their clinical translation remains challenging, continued progress in addressing the factors discussed above, especially, scalability of production, regulatory challenges, cost, patient compliance, and long-term safety could pave the way for more effective and safer nanomedicine-based therapies for autoimmune diseases in the future.

Abbreviations

AhR, Aryl hydrocarbon Receptor; APC, Antigen-Presenting Cell; AZA, Azathioprine; BSA, Bovine Serum Albumin; CAIA, Collagen Antibody-Induced Arthritis; CD, Cluster of Differentiation; COX, Cyclooxygenase; cRGD, Cyclic Arginine-Glycine-Aspartate peptide; CSF, Colony Stimulating Factor; CTLA, Cytotoxic T-Lymphocyte Associated protein; CII, Type II Collagen; DSS, Dextran Sodium Sulfate; EPR, Enhanced Permeability and Retention effect; ERN, endoplasmic reticulum to Nucleus signaling; FDA, Food and Drug Administration; GPI, Glucose-6-Phosphate Isomerase; HIFU, high-intensity focused ultrasound; IL-1,2,6,10, Interleukins; ITE, 2-(1′H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester; IV / IM / SC / PO, Intravenous / Intramuscular / Subcutaneous / Per Os; KGF, Keratinocyte Growth Factor; mAb, Monoclonal Antibody; MOG, Myelin Oligodendrocyte; mRNA / siRNA, Messenger RNA / Small Interfering RNA; MRL/lpr, MRL mouse strain with the lpr (lymphoproliferation) mutation; MTX, Methotrexate; NETosis, Neutrophil Extracellular Trap formation induced cell death; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NP, Nanoparticles; PBMCs, Peripheral Blood Mononuclear Cells; PD-L1, Programmed death-ligand 1; PBAA, Poly(β-amino amine); PEG, Polyethylene Glycol; PEI, Polyethylenimine; PLGA, Poly(lactic-co-glycolic acid); QD, Quantum Dot; ROS, Reactive Oxygen Species; SLE, Systemic Lupus Erythematosus; SREBP2, Sterol Regulatory Element-Binding Protein 2; STA, Serum-Transfer Arthritis; TGF-b, Transforming Growth Factor beta; TNF-α, Tumor Necrosis Factor alpha; T_h / T_{reg} / iT_{reg} / $nT_{reg\ T}$, helper / Regulatory T / Induced Treg / Natural Treg cells; TSH, Thyroid-Stimulating Hormone.

Data Sharing Statement

Data availability is not applicable to this article as no new data were created or analyzed in this study. No datasets were generated or analysed during the current study.

Ethics Declarations

This article does not contain any studies with human participants performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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