Review

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Revitalizing therapies in autoimmune diseases: nanoparticles as alternative therapeutic tools

Revitalizando las terapias en enfermedades autoinmunes: Nanopartículas como alternativa de tratamiento

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Abstract

Autoimmune diseases, such as systemic lupus erythematosus (SLE), are complex disorders characterized by an abnormal immune response. In these diseases, the immune system mistakenly identifies different body components as foreign, leading to chronic inflammation and damage to multiple organ and tissue systems. Traditional treatments typically involve immunosuppressive drugs that broadly suppress the immune system. Although these medications can help control symptoms, they also carry significant side effects due to their nonspecific nature. Nanotechnology, through nanomedicine, plays a crucial role in treating diseases, improving drug therapeutic efficacy, and minimizing toxicity. This technology allows for better bioavailability of medications, more precise distribution in the body, and more precise control over drug release. Nanoparticles (NPs) are essential in this process, capable of overcoming biological barriers and directing drugs directly to the affected sites, increasing their effectiveness and reducing side effects. This approach is especially promising in treating autoimmune diseases and cancer. NPs can target specific cells, such as macrophages, monocytes, dendritic cells, and B lymphocytes, to deliver treatments more effectively, with less toxicity and adverse effects. Research in nanotechnology continues to advance, offering hope for more effective and personalized treatments.

Keywords: autoimmunity, B lymphocytes, immunomodulation, monocytes, macrophages, nanoparticles

Resumen

Las enfermedades autoinmunes son trastornos complejos caracterizados por una respuesta inmune anormal. En estas enfermedades, el sistema inmune identifica erróneamente diferentes componentes del propio organismo como extraños, lo que provoca inflamación crónica y daño en múltiples sistemas de órganos y tejidos. Los tratamientos actuales suelen implicar el uso de fármacos inmunosupresores que suprimen ampliamente la respuesta del sistema inmune. Aunque estos medicamentos pueden ayudar a aminorar los síntomas, también conlleva importantes efectos secundarios debido a su naturaleza inespecífica. La nanotecnología, a través de la nanomedicina, juega un papel crucial en el tratamiento de estas enfermedades, mejorando la eficacia terapéutica de los fármacos y minimizando su toxicidad. Esta tecnología permite mejorar la biodisponibilidad

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de los medicamentos, una distribución más precisa en el cuerpo y un control más exacto sobre la liberación de los fármacos. Las nanopartículas (NP) son fundamentales en este proceso, capaces de superar barreras biológicas y dirigir los medicamentos directamente a los sitios afectados, lo que aumenta su eficacia y reduce los efectos secundarios. Este enfoque es especialmente prometedor en el tratamiento de enfermedades autoinmunes y cáncer, donde las NP pueden dirigirse a células específicas, como los macrófagos, los monocitos, células dendríticas y linfocitos B, para entregar tratamientos de manera más efectiva, con menos toxicidad y efectos adversos. La investigación en nanotecnología continúa avanzando, ofreciendo esperanza para tratamientos más efectivos y personalizados.

Palabras clave: autoinmunidad, inmunomodulación, linfocitos B, macrófagos, monocitos, nanopartículas

INTRODUCTION

Under normal circumstances, the immune system acts as a sentinel that only activates defense mechanisms against foreign invaders such as bacteria, viruses and other potentially harmful agents. However, in the case of autoimmune diseases, this system mistakenly identifies cells, structural components or modifications of the body itself as foreign and initiates an attack (Figure 1). This erroneous attack by the immune system causes widespread inflammation and damage to various body tissues, resulting in a range of debilitating symptoms.

For an autoimmune disease to be triggered, a combination of factors is required that may vary according to the specific type of disease. However, there are several common elements that play a crucial role in the development that, although multifactorial, involves a complex interplay between genetic, environmental, immunological and regulatory factors in the context of chronic inflammation (Figure 1). Understanding these processes is crucial for the development of therapeutic strategies aimed at preventing or treating these conditions (Kumar et al., 2019).

The symptoms of autoimmune diseases vary greatly depending on the disease and the systems of the body affected by the immune response. For example, lupus can cause fatigue, joint pain and skin rashes; rheumatoid arthritis is characterized by painful joint inflammation; multiple sclerosis can cause muscle control and vision problems, while ulcerative colitis causes long-lasting inflammation and ulcers in the gastrointestinal tract.

PREVALENCE AND IMPACT

According to the *American Autoimmune Related Diseases Association*, there are more than 100 types of autoimmune diseases that affect approximately 5-10% of the world's population. These conditions, which include lupus, rheumatoid arthritis, and type 1 diabetes, tend to be chronic and can significantly decimate the quality of life (Joseph et al., 2024; Wang et al., 2024). In addition to collectively affecting millions of people worldwide, autoimmune diseases involve a considerable investment for healthcare systems due to their chronic nature and need for long-term treatment.

In Latin America, the prevalence of autoimmune diseases is also significant. According to the World Health Organization (WHO), non-communicable diseases, including autoimmune diseases, are responsible for up to 80% of deaths in the region. However, comprehensive data on the prevalence of specific autoimmune diseases in Latin America are lacking due to variability in disease definition, diagnostic criteria, and reporting practices in different countries (Medina-Ramirez et al., 2024).

In Colombia, autoimmune diseases are increasingly recognized as an important health problem. The "Community Oriented Program for Control of Rheumatic Diseases" (COPCORD)-Colombian Association of Rheumatology reported a significant prevalence rate of autoimmune diseases in the country. In Colombia, rheumatoid arthritis and systemic lupus erythematosus were among the most common autoimmune disorders identified. In reports of patients with systemic lupus erythematosus (SLE) between January 2012

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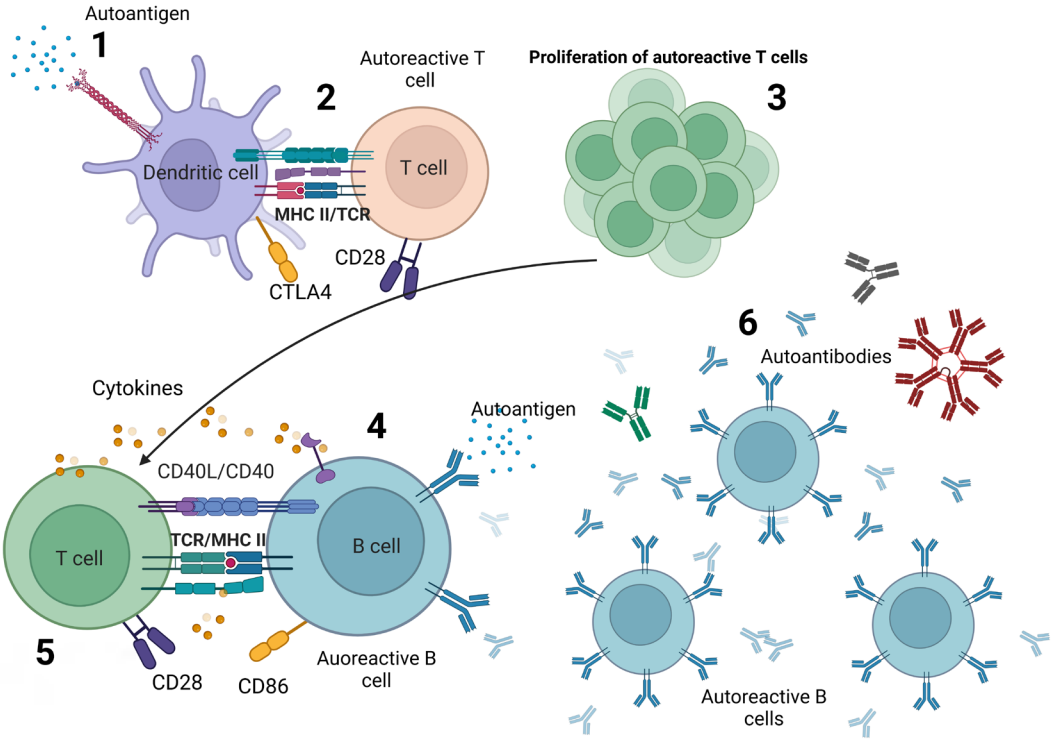

Figure 1. The establishment of autoimmunity requires that a self-molecule that has been modified by environmental factors and is in excess, can be recognized by a dendritic cell (**1**), which will digest and present to a self-reactive T cell some peptide components inducing its activation (**2**) and proliferation or clonal expansion (**3**). This T cell must, in turn, have escaped regulatory mechanisms (tolerance breakdown). The autoantigen is also recognized and presented by B cells (**4**) to the autoreactive T cells that expanded in (**3**) that, in turn, cooperate for the activation, proliferation and differentiation of B cells to autoantibody-producing plasma cells.

and December 2016, the prevalence of the disease was estimated to be 91.9 per 100,000 people (with a total population of 47,663,162), being more frequent in women (89% cases). The regions of the country with the highest prevalence of the disease are Bogotá, Antioquia and Valle del Cauca. However, as in the rest of Latin America, research on autoimmune diseases in Colombia is still limited. More epidemiological studies are needed to obtain a more accurate picture of the burden of these diseases and to inform public health strategies. These efforts would be crucial to manage and mitigate the impact of autoimmune diseases on individuals and health systems in Colombia, Latin America and the rest of the world.

THE CURRENT TREATMENT LANDSCAPE

Despite significant advances in biomedical research, fully effective treatment strategies remain elusive (Table 1). Current treatment strategies focus on controlling symptoms, reducing immune system activity and maintaining body functions. The increasing prevalence of these diseases underscores the need for further research to better understand these complex conditions and to develop more effective prevention and treatment strategies.

The nonspecific and broad-spectrum nature of current treatments, such as anti-inflammatory or immunosuppressive drugs, often results in side effects. This overview underscores the need for targeted treatments, highlighting the potential role of nanoparticles (NPs) to offer a more precise and less harmful approach in the management of autoimmune diseases.

Further research is imperative to better understand these complex disorders and to develop more effective and targeted treatments (Li et al., 2022). Different compounds are used to treat these diseases including corticosteroids, immunosuppressants, biologic agents, disease-modifying drugs, nonsteroidal anti-inflammatory

drug (NSAID) therapy, and targeted biologic agents. Examples of these drugs are shown in Table 1 (Chandrashekara, 2012).

These drugs are administered by different routes that require high systemic concentrations to achieve bioavailability and effect the afflicted organs, but also have side effects that affect unafflicted organs and tissues. For example, corticosteroids are fat-soluble compounds with low availability (approximately 60% when administered orally). In the case of prednisolone, it has been described that after an intravenous dose of this drug of 0.66 mg/kg in humans, the bioavailability is only about 62% (Garg & Jusko, 1994). This shows the need to develop strategies to improve availability.

Table 1. Types of drugs and examples of use in the treatment of autoimmune diseases.

Corticosteroids	Like prednisone, these are used to reduce inflammation and suppress the immune response.
Immunosuppressants	Examples include methotrexate, azathioprine, cyclosporine and mycophenolate mofetil, which inhibit an excessive immune response.
Biological agents	Includes drugs such as infliximab, adalimumab, etanercept and rituximab, which target specific molecules involved in the immune response.
Disease-modifying drugs	Examples include sulfasalazine and leflunomide, which are used to treat autoimmune diseases such as rheumatoid arthritis.
Therapy with nonsteroidal anti-inflammatory drugs (NSAIDs)	Examples include ibuprofen and naproxen, which can help control inflammation and pain associated with some autoimmune diseases.
Targeted biological agents	Examples include tocilizumab and abatacept, which target specific immune system targets to modulate the immune response.

TYPES AND FUNCTIONALIZATION OF NANOPARTICLES

For their potential in the therapy of autoimmune diseases, various NPs, including liposomes, polymeric NPs and dendrimers, have been studied (An et al., 2023; Gad et al., 2021; Yang & Santamaria, 2021). Each type has unique properties that influence their interaction with the immune system and therapeutic delivery (Lemos et al., 2015; Mitarotonda et al., 2022; Zolnik et al., 2010).

Functionalization with specific molecules, such as antibodies or peptides, improves the specificity of NPs, allowing them to target specific immune cells or tissues, thus minimizing off-target effects (Lemos et al., 2015; Mitarotonda et al., 2022; Zolnik et al., 2010).

NPs offer a promising avenue by improving efficiency in inducing antigen-specific tolerance, a critical aspect in the management and therapy of these disorders (Yang & Santamaria, 2021). These small carriers may improve drug pharmacokinetics, amplify therapeutic effects, and mitigate side effects often associated with long-term medication for autoimmune disorders (Zhu et al., 2022). Given the chronic and inflammatory nature of autoimmune diseases, the role of NPs in driving advances in treatment methods marks a significant shift towards more targeted and effective therapeutic interventions (Zhu et al., 2022).

NPs and their role in the treatment of autoimmune diseases involve multifaceted approaches that target various aspects of the immune system to restore balance and mitigate disease symptoms. Their application in the treatment of autoimmune diseases is based on their ability to modulate immune responses, deliver therapeutic agents directly to affected sites or compromised cells, and induce tolerance. Key aspects of how NPs

contribute to the management and treatment of autoimmune diseases are detailed below. We describe their mechanism of action, the strategies used to target a particular cellular subpopulation (involved in the immunopathology) of autoimmune diseases, and experimental evidence demonstrating their therapeutic potential in these diseases.

MECHANISMS OF ACTION: HOW NANOPARTICLES INFLUENCE THE IMMUNE RESPONSE

NPs offer a unique approach to modulate the immune system, essential for the treatment and management of autoimmune diseases. Their interaction with the immune system can be broadly classified into two main mechanisms:

Immunostimulation. NPs can be designed to elicit an immune response, either by direct stimulation of antigen-presenting cells or by delivery of antigens to specific cellular compartments, thus aiding in the fight against infection or disease (Zolnik et al., 2010).

Immunosuppression. By binding to polymers such as polyethylene glycol (PEG), NPs can protect themselves from immune recognition or can carry immunosuppressive molecules to specifically inhibit immune responses. This is particularly useful in autoimmune diseases where the immune system attacks the body's own cells (Li et al., 2022; Zolnik et al., 2010).

In the following, we describe some of the cells involved in the immunopathology of autoimmune diseases and highlight the importance of some NP preparations to stimulate or suppress the action of these cells as potential therapeutic tools for these diseases.

TARGETED DELIVERY AND IMMUNE MODULATION

By modulating the immune system, NPs can suppress or stimulate immune responses as needed. For example, NPs can generate macrophages with regulatory functions, beneficial for the treatment of other autoimmune diseases besides type one diabetes or induce regulatory T cells (Tregs) to restore immune balance (Li et al., 2022; Mitarotonda et al., 2022).

Intervention on regulatory T cells. One of the applications of NPs is the induction of antigen-specific Tregs without suppressing the entire immune response, but rather, through physiological mechanisms, modulating the immune system and promoting tolerance to antigens. These strategies focus on taking advantage of the unique properties of NPs to target and deliver specific antigens together with molecules that promote T-cell differentiation towards a regulatory phenotype (Treg, Figure 2) (Quintana, 2013).

In a study of type 1 diabetes in mice, NPs coated with major histocompatibility complex molecules and peptides (pMHC-NP, Figure 3) were used to expand a special type of Treg cells in the body. Treg cells help prevent the immune system from mistakenly attacking the body itself. The NPs contained disease-specific proteins and were injected into the mice at specific doses and times to stimulate the activation and expansion of Treg cells. The resulting T cells regulated the activation of other T cells that could cause harm to the body, without adversely affecting the immune system. This therapy was shown to be effective in diabetic mice, suggesting that it could be useful in the treatment of autoimmune diseases such as type one diabetes (Tsai et al., 2010).

Some authors have designed polylactic-co-glycolic acid (PLGA) NPs functionalized with anti-CD2/CD4 antibodies that contained IL-2 and encapsulated TGF-β. Intraperitoneal administration of these NPs in mice with lupus induced expansion of CD4+ and CD8+ Treg cells and marked suppression of anti-DNA antibody production and reduced renal disease (Horwitz et al., 2019).

Intervention on B lymphocytes. B lymphocytes are a fundamental component of the adaptive immune system and play a crucial role in protecting the body against pathogens (Wang et al., 2022; Yap & Chan, 2019). However, in the context of autoimmunity, B lymphocytes may play counterproductive roles and contribute to the development and progression of autoimmune diseases (Comi et al., 2021; Hampe, 2012; Nashi et al., 2010). B lymphocytes are responsible for the production of antibodies, which normally bind to specific antigens to neutralize or mark them for destruction. In autoimmune diseases, B lymphocytes may misrecognize components of the body's own as if they were foreign antigens, leading to the production of autoantibodies. These

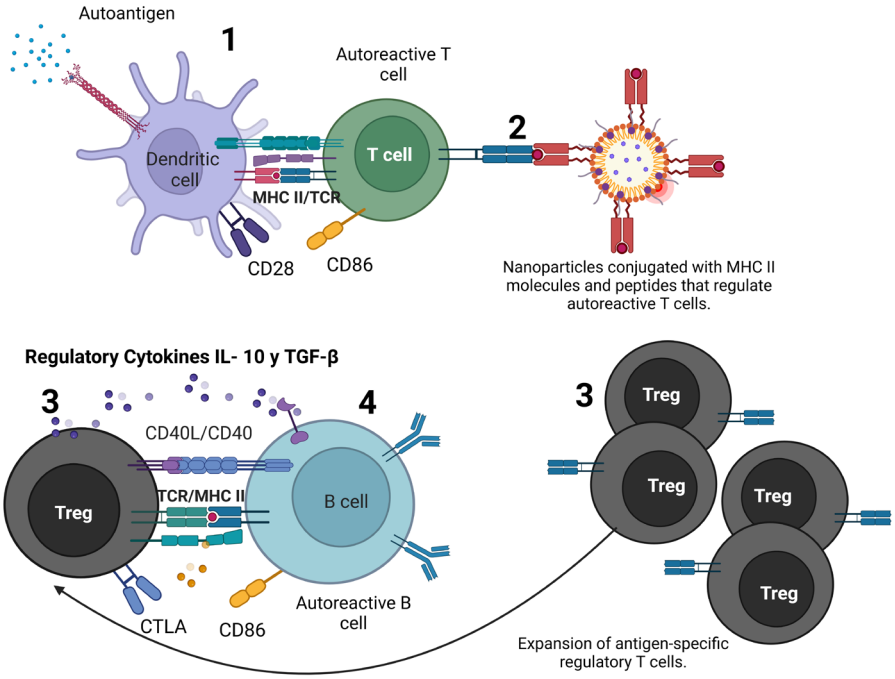

Figure 2. The self-antigen is recognized by dendritic cells and presented to T cells. To prevent the expansion of autoreactive T cells, nanoparticles decorated on their surface with segments of the major histocompatibility complex and the autoreactive peptides have been designed (Quintana, 2013), but this nanoparticle diverts the behavior of T cells towards a regulatory phenotype (**3**) that prevent the proliferation of B cells into autoantibody-producing cells (**4**).

autoantibodies bind to healthy tissues and cells, eliciting an inflammatory response that can result in tissue damage and organ dysfunction (Comi et al., 2021; Hampe, 2012; Nashi et al., 2010).

In addition to the production of autoantibodies, B lymphocytes also influence autoimmunity through their function as antigen-presenting cells. B lymphocytes can process and present self-antigens to T lymphocytes, activating them and thus perpetuating the immune response against the body's own tissues (Silverman & Carson, 2003; Yap & Chan, 2019). B lymphocytes are also producers of cytokines and chemokines, such as TNF-α, IL-6, IL-4, CCL22, and CCL17 (Wang et al., 2022), contributing to prolong the inflammatory phenomenon characteristic of these diseases.

Another important facet is their role in regulating the immune system. Regulatory B cells are a cellular subpopulation that can secrete anti-inflammatory cytokines and play a role in suppressing immune responses. In autoimmunities, it is believed that the balance between effector and regulatory B lymphocytes may be altered, leading to an exacerbated immune response.

The detailed study of how B lymphocytes contribute to autoimmune diseases is driving the development of targeted therapies. These therapies seek to moderate the activity of pathogenic B lymphocytes without compromising their ability to defend the body against genuine infections. Thus, B lymphocytes represent both a source of pathology and a therapeutic target in the management of autoimmunity.

One way to modulate the immune system is to directly intervene antibody-producing cells. In an *in vitro* study, Nile red (NR)-labeled poly-l-l-lactic acid (PLA) NPs were synthesized and loaded with a drug called Baricitinib, which targets specific proteins (JAK1 and JAK2) in B lymphocytes, proteins critical in the activation and differentiation processes of these cells, among other processes. This was done to determine whether NPs could help control the function of B lymphocytes, which are important in autoimmune diseases (Alvarez et al., 2023). NR-PLA NPs loaded with Baricitinib bind specifically to B lymphocytes without interacting with other types of immune cells.

NR-PLA NPs loaded with Baricitinib produced interesting results, as they were better at

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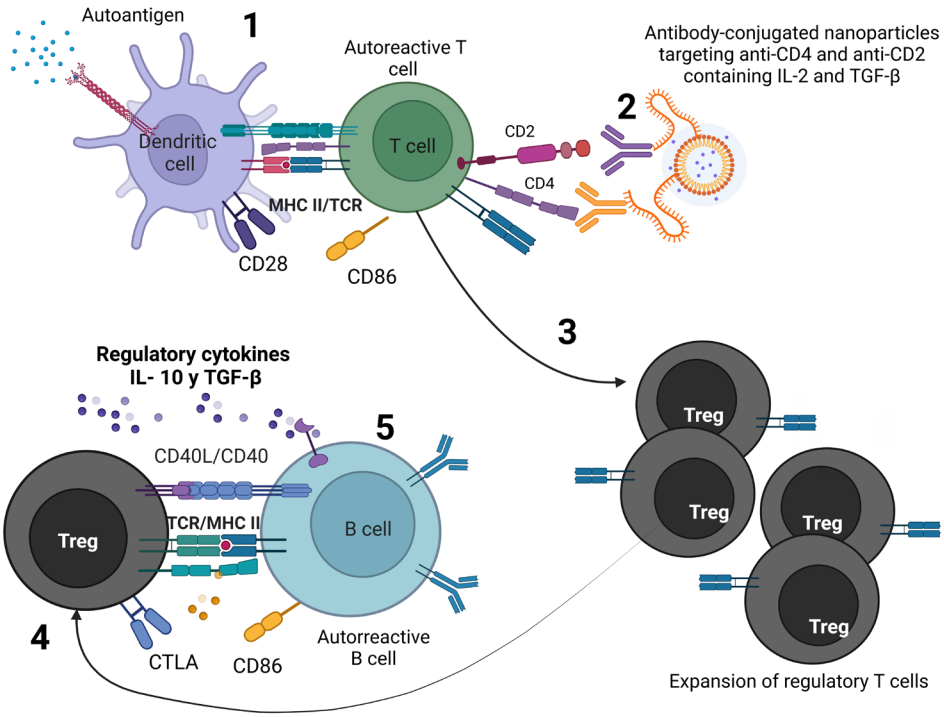

Figure 3. To prevent the expansion of autoreactive T cells (**1**), nanoparticles decorated on their surface with antibodies directed against CD2 and CD4 containing IL-2 and TGFß (**2**) have been designed to induce the expansion and of T cells and their deviation toward the regulatory phenotype (Horwitz et al., 2019) but this nanoparticle diverts the behavior of T cells towards a regulatory phenotype (**3**) that prevent the proliferation of B cells (**4**) into autoantibody-producing cells (**5**).

reducing the activity, growth and transformation of B lymphocytes into plasma cells compared to the unencapsulated Baricitinib drug. NR-PLA NPs loaded with Baricitinib also stopped the production of certain immune system signals called cytokines, which are often overactive in autoimmune diseases. This work suggests that PLA NPs could be a promising way to control overactive B cells that contribute to autoimmune diseases such as systemic lupus erythematosus (Figure 4). This could open up an exciting new avenue for the development of treatments for these diseases (Alvarez et al., 2023).

Intervention on monocytes and macrophages. Monocytes and macrophages are essential cells of the immune system that play crucial roles in the body's defense against pathogens and in the regulation of inflammatory processes (Ginhoux et al., 2020). However, these cells also play a significant role in the development and progression of autoimmune diseases).

Monocytes are circulating leukocytes that can differentiate into macrophages or dendritic cells once they enter tissues. Macrophages are tissue-resident phagocytic cells that play a key role in the innate immune response by digesting pathogenic microorganisms and dead or damaged cells. Macrophages also act as antigen presenters, a process that is essential for the activation of adaptive immune responses.

In the context of autoimmunity, monocytes and macrophages can contribute to the development of an immune response against the body's own components. This can occur when these cells present self-antigens to autoreactive T cells, which can lead to a chronic inflammatory response and tissue damage. In addition, macrophages can secrete a variety of proinflammatory mediators such as cytokines and chemokines that exacerbate inflammation and damage associated with autoimmune diseases (Burbano et al., 2014; Funauchi et al., 1993; Smiljanovic et al., 2018; Wu et al., 2017).

Importantly, the activation state and environment in which macrophages are found may influence their role in autoimmunity. Macrophages can ac-

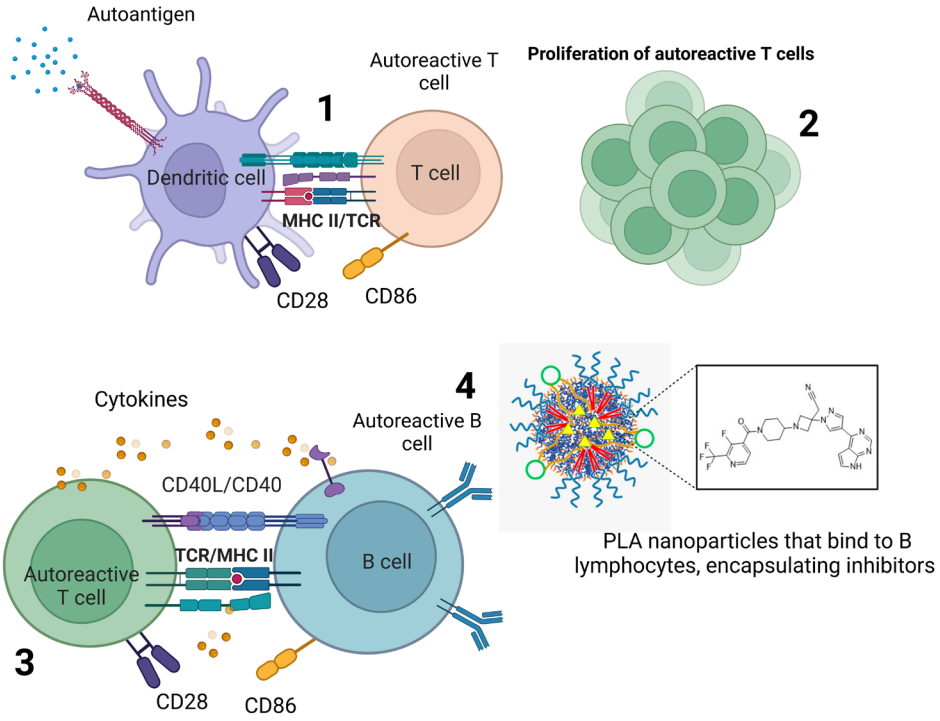

Figure 4. Although autoantigens can be recognized by dendritic cells (1) and presented to a self-reactive T-cell that activate and proliferate to (2) interact with B-lymphocytes that recognize the autoantigen and (4) interact with T-cells (3) for the production of autoantibodies. PLA nanoparticles containing specific inhibitory drugs of B cell metabolic pathways can block autoantibody production (Alvarez et al., 2023).

quire different phenotypes depending on signals from the microenvironment; some of these phenotypes may have proinflammatory properties that promote autoimmunity, while others may be regulatory and contribute to the resolution of inflammation.

In summary, monocytes and macrophages play complex roles in autoimmune diseases. On the one hand, they can perpetuate inflammation and tissue damage through inappropriate antigen presentation and the release of proinflammatory mediators. On the other hand, they also have the potential to moderate the immune response and promote resolution of the inflammatory process. A better understanding of their role in autoimmunity is crucial for the development of targeted therapies that can modulate their activity for therapeutic benefit.

The intervention of monocytes with drug-containing NPs represents a significant advance in nanomedicine and opens up new perspectives in therapeutic strategies to combat complex diseases, including autoimmunity (Alvarez & Rojas, 2023). Monocytes have a great capacity to migrate through tissues and have been identified as ideal vectors to transport therapeutic agents directly to areas affected by pathologies.

This innovative technique takes advantage of the intrinsic properties of monocytes to target areas of inflammation or infection and tumor environments, where these phagocytes often accumulate as part of the immune response. By intervening monocytes with drug-loaded NPs, a controlled and targeted release of treatment is achieved, which may increase its efficacy by concentrating drug action at the desired site and reducing side effects associated with systemic dosing (Marco-Dufort et al., 2021; Sivamaruthi et al., 2022; Smolensky & Peppas, 2007).

Another advantage of this therapeutic modality is the possibility of modifying the NP surface to improve their interaction with monocytes and optimize their biodistribution. In addition, NPs can be designed to respond to specific stimuli within

the pathological environment, such as changes in pH or the presence of certain enzymes, allowing even more precise targeting of the therapeutic agent.

The potential applications of this technology are vast, ranging from treating inflammatory and autoimmune diseases to fighting infections and targeting solid cancers. As research progresses, monocyte intervention with drug-containing NPs is expected to establish itself as a fundamental tool in personalized medicine, with the potential to significantly improve clinical outcomes in a variety of pathological conditions.

Interaction with dendritic cells. Dendritic cells are crucial components of the immune system, acting as lookouts that detect the presence of pathogens and trigger immune responses (Merad et al., 2013). However, in the context of autoimmune diseases, the role of these cells is twofold and complex (Ganguly et al., 2013). On the one hand, dendritic cells are essential for maintaining immune tolerance (i.e., the ability of the immune system to distinguish between self and non-self and to prevent attack on the body's cells and tissues). On the other hand, they can contribute to the development of autoimmunity when this tolerance is broken (Figure 5).

Under normal conditions, dendritic cells capture antigens and present them to T cells in a context that promotes tolerance. However, in autoimmune diseases, this balance can be altered by genetic, environmental or infectious factors. Dendritic cells can present autoantigens (normal components of the body) by activating T cells, resulting in an immune response against the individual's tissues (Ganguly et al., 2013).

In addition, it has been observed that, in certain autoimmunity's, dendritic cells may be in a state of chronic activation or may express abnormally high levels of co-stimulatory molecules that promote T-cell activation. This may lead to an amplification of the immune response and tissue damage characteristic of these diseases.

Therefore, by better understanding the role of dendritic cells in the pathogenesis of autoimmune diseases, therapeutic strategies specifically aimed at modulating their function could be developed.

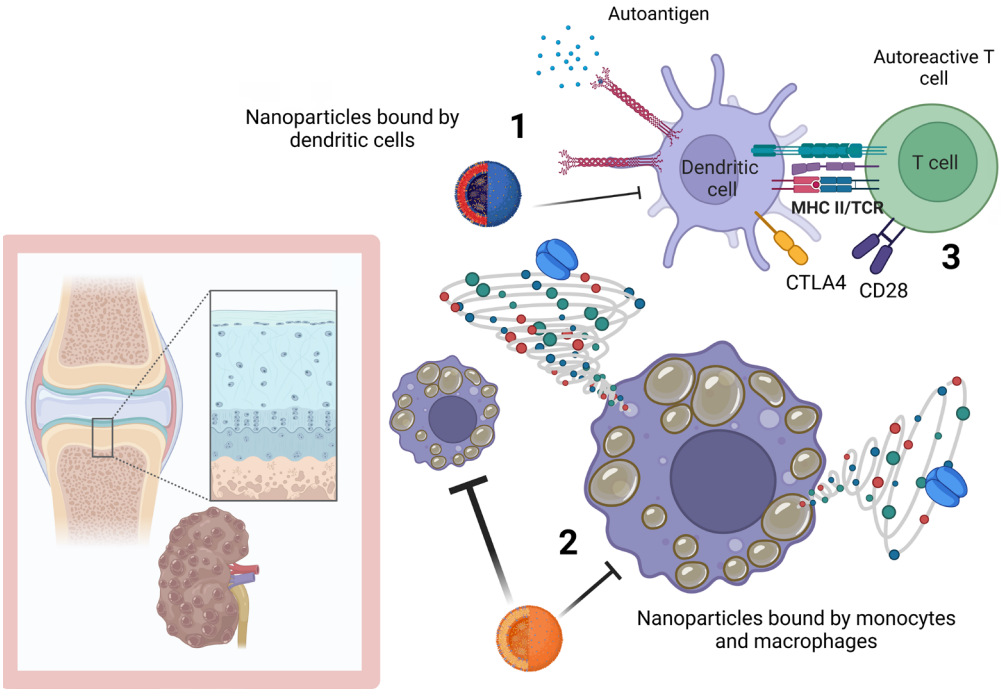

Figure 5. Early nanoparticles can interact with dendritic cells and divert their phenotype towards suppressor dendritic cells expressing CTLA-4 (**1**), so that they modulate autoreactive T cells. At the site of inflammation where lymphocytes monocytes and macrophages are mediating the chronic inflammatory response can also be reached by nanoparticles interacting with these cells.

This could include treatments that seek to restore immune tolerance or inhibit the inappropriate presentation of autoantigens, to mitigate or prevent the progression of these pathologies.

The activation state of dendritic cells is crucial. NPs can control the induction of tolerogenic dendritic cells, which are essential for inducing immune tolerance. NPs offer the possibility to deliver controlled amounts of autoantigens and tolerogenic agents simultaneously to dendritic cells, targeted by specific targeted ligands of these cells. However, this effect can be overridden by proinflammatory modulators (Li et al., 2022).

Some authors have shown that after subcutaneous administration of liposomes containing a peptide constituting a segment of ovalbumin and calcitriol, the active form of vitamin D, the liposomes were phagocytosed by PD-L1hi dendritic cells from mice previously immunized with OVA/QuilA. Such uptake reduced the expression of MHC class II and CD40. OVA323-339 /calcitriol liposomes suppressed the expansion, differentiation and function of effector T and induced peripheral Foxp3+ and IL-10+ regulatory T in an antigen-specific manner. Additionally, they generated liposomes in which disease-specific peptides and calcitriol were encapsulated to determine the response of endogenous autoreactive T cells in murine models of rheumatoid arthritis and vasculitis. These liposomes decreased the clinical manifestations of the disease and suppressed the differentiation and function of antigen-specific memory T cells. Consequently, the uptake of peptide/calcitriol liposomes by dendritic cells promotes the upregulation of antigen-specific T cells and induces antigen-specific tolerance in inflammatory autoimmune diseases (Galea et al., 2019).

CHALLENGES AND FUTURE DIRECTIONS

Despite the promising therapeutic potential of NPs in the treatment of autoimmune diseases, challenges such as scalability, cost-effectiveness and potential toxicity need to be addressed. Ongoing research aims to overcome these hurdles and fully exploit the potential of NPs in clinical settings (Lemos et al., 2015).

The Scripps Research Institute has reported initial success with a nanotechnology-based strategy that targets only the immune system cells that provoke an autoimmune reaction, highlighting the potential for highly specific and effective treatments (Brzezicka et al., 2022).

This section highlights the pivotal role of NPs in advancing the treatment and management of autoimmune diseases, offering hope for more specific, effective and less toxic therapeutic options.

DESIGN CONSIDERATIONS AND CHARACTERISTICS OF NANOPARTICLES

The properties of NPs, including size, shape, charge and stiffness, significantly influence their interaction with the immune system. These characteristics affect cellular uptake, circulation time, and overall immune response, making it crucial to tailor NPs specifically for each therapeutic application (Mitarotonda et al., 2022; Zolnik et al., 2010). Understanding these mechanisms is vital for developing safer and more effective NP-based therapies for autoimmune diseases, which highlights the importance of ongoing research in this area (Mitarotonda et al., 2022; Zolnik et al., 2010).

Safety. Despite therapeutic potential, NPs can sometimes cause unwanted immunostimulation or immunosuppression, leading to safety concerns, such as increased susceptibility to infections, inflammatory disorders, or even cancer (Zolnik et al., 2010).

Vectorization of therapy to specific sites. NPs can be functionalized with different molecules allowing effective targeting of treatment to cells or tissues involved in the immunopathology of various diseases, increasing the concentration of the drug in the affected area and improving its therapeutic efficacy (Lee et al., 2021).

Improved treatment efficacy. Targeted drug delivery by monocytes can improve treatment efficacy by ensuring that a greater proportion of the therapeutic agent reaches the desired site of action, reducing the need for higher doses that may be necessary when the drug is administered systemically. Since monocytes can uptake circulating NPs and then migrate to sites of inflammation in response to chemotactic signals,

allowing efficient drug arrival at these sites.

Reduced side effects. By targeting drugs specifically to the sites where they are needed, exposure of healthy tissues to the treatment is reduced, which can significantly reduce side effects and toxicity associated with the drug.

Overcoming biological barriers. NPs can be designed to overcome biological barriers that normally limit drug efficacy, such as the blood-brain barrier. This is useful for the treatment of central nervous system diseases, where drug delivery is a significant challenge.

Potential in cancer therapy. NPs can be targeted to tumors, where they can release chemotherapeutic drugs directly into the tumor microenvironment. This not only enhances cancer cell death but can also modify the tumor microenvironment to make it less conducive to cancer development and metastasis.

Treatment of autoinflammatory diseases. Since several cells of the immune system play a crucial role in inflammation, including monocytes and dendritic cells, targeting these cells to inflamed areas with NPs containing anti-inflammatory or immunomodulatory agents may be an effective strategy for treating inflammatory and autoimmune diseases.

Vaccine and drug delivery. NPs play a dual role as vehicles for vaccines to enhance immunogenicity and as drug carriers to improve targeting and bioavailability, directly addressing challenges in the treatment of autoimmune diseases by ensuring that drugs reach their intended targets effectively (Huang et al., 2024).

Combating pathogens and managing inflammation. Beyond delivery, NP actively combats pathogens and inflammation, contributing to the development of advanced biosensors for pathogen detection and imaging techniques, crucial for the diagnosis and treatment of inflammatory diseases (Huang et al., 2024).

CONCLUSION

As we delve deeper into the complexities of autoimmune diseases, the potential of NPs emerges as a ray of hope, offering pathways to treatments that are both targeted and potentially less onerous than current standards. By improving drug delivery, modulating the immune response and even directly mitigating disease symptoms, NPs are at the forefront of a new era in the treatment of diseases such as lupus, rheumatoid arthritis and multiple sclerosis. This revolution in treatment strategy not only promises improved quality of life for millions of people, but also opens the prospect of therapies that could more precisely combat the underlying causes of these debilitating diseases without the often-severe side effects associated with broad-spectrum drugs.

The ongoing research and case studies elucidated here underscore both the challenges and bright future of NP application in the treatment of autoimmune diseases. While obstacles such as scalability, cost and safety persist, the advances highlight a clear and potent potential for NPs to alter the landscape of autoimmune disease management fundamentally. As researchers continue to explore and refine these nanotechnologies, the promise of more effective, personalized and less invasive treatment modalities looms on the horizon, offering a glimmer of hope for millions of people struggling with these chronic diseases.

FREQUENT QUESTIONS

What is the role of nanoparticles in disease management?

NPs are extremely small particles that can be used in the treatment of human diseases and can improve the efficacy of existing drugs. They have the ability to circumvent biological barriers and improve drug delivery to the intended site, thereby increasing drug efficacy.

How does nanotechnology relate to disease prevention and treatment?

Nanotechnology is a useful cutting-edge method to interfere with bacterial growth through various mechanisms. For example, the development of layered nanomaterials (NMs) such as graphene, MoS2 and MXenes has resulted in a new class of nanoparticles capable of interacting with microbial membranes. So compared to traditional antibiotics, antibacterial agents based on these NPs can be applied in low doses, which helps to

reduce unwanted side effects and overcome the problem of resistance (Sethulekshmi et al., 2022).

There is also evidence indicating that metallic NPs exhibit antimicrobial and regenerative properties, metal oxide NPs regulate inflammation and promote tissue regeneration, MXene NPs enhance cell adhesion and proliferation, while metalorganic NPs (MOFs) offer controlled drug delivery capabilities (Faghani & Azarniya, 2024).

When did nanotechnology first emerge?

The era of modern nanotechnology began in 1981 with the invention of the tunneling microscope, which enabled the visualization and manipulation of individual atoms. This innovative development earned International Business Machines Corporation (IBM) scientists Gerd Binnig and Heinrich Rohrer the Nobel Prize in Physics in 1986.

What is the role of nanomedicine in the treatment of diseases?

Nanomedicine is a segment of medicine that incorporates nanotechnology to prevent and treat disease that is considered one of the most powerful methods to improve the therapeutic efficacy of a drug and minimize toxicity. This is achieved by improving the bioavailability of drugs, modifying how they are distributed in the body, and controlling the timing and speed of drug release.

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CONFLICT OF INTEREST

We, the authors of this review, declare that we have no conflict of interest in relation to this manuscript.

We have participated in the bibliographic selection, data collection, drafting of the manuscript and layout of the figures and approved the final version of the manuscript. We did not receive any financial or other benefit from any entity that could be perceived as a conflict of interest in relation to the content of this manuscript.

AUTHOR CONTRIBUTION

KAD and MRL did a collective review and construction of the present manuscript, KAD did the critical review of the articles in which she had made the selection. KAD and MRL elaborated the figures, and both authors reviewed and corrected the other's contributions.

REFERENCES

Alvarez, K., Palacio, J., Agudelo, N. A., Anacona, C. A., Castano, D., Vasquez, G. & Rojas, M. (2023). B cell-targeted polylactic acid nanoparticles as platform for encapsulating jakinibs: potential therapeutic strategy for systemic lupus erythematosus. *Nanomedicine (Lond), 18*(27), 2001-2019. https://doi.org/10.2217/nnm-2023-0241

Alvarez, K. & Rojas, M. (2023). Nanoparticles targeting monocytes and macrophages as diagnostic and therapeutic tools for autoimmune diseases. *Heliyon, 9*(9), e19861. https://doi.org/10.1016/j.heliyon.2023.e19861

An, E. K., Zhang, W., Park, H. B., Kim, S. J., Eom, H. Y., Hwang, J., Kwak, M., Lee, J. Y., Lee, P. C. & Jin, J. O. (2023). Immunosuppressive nanoparticles containing recombinant PD-L1 and methotrexate alleviate multi-organ inflammation. *Biomaterials, 301*, 122233. https://doi.org/10.1016/j.biomaterials.2023.122233

Brzezicka, K. A., Arlian, B. M., Wang, S., Olmer, M., Lotz, M. & Paulson, J. C. (2022). Suppression of autoimmune rheumatoid arthritis with hybrid nanoparticles that induce B and T cell tolerance to self-antigen. *ACS Nano, 16*(12), 20206-20221. https://doi.org/10.1021/acsnano.2c05643

Burbano, C., Vasquez, G. & Rojas, M. (2014). Modulatory effects of CD14+CD16++ monocytes on CD14++CD16- monocytes: a possible explanation of monocyte alterations in systemic lupus erythematosus. *Arthritis Rheumatology, 66*(12), 3371-3381. https://doi.org/10.1002/art.38860

Chandrashekara, S. (2012). The treatment strategies of autoimmune disease may need a different approach from conventional protocol: a review. *Indian*

Journal Pharmacology, 44(6), 665-671. https://doi.org/10.4103/0253-7613.103235

Comi, G., Bar-Or, A., Lassmann, H., Uccelli, A., Hartung, H. P., Montalban, X., Sorensen, P. S., Hohlfeld, R., Hauser, S. L. & Expert Panel of the 27th Annual Meeting of the European Charcot, F. (2021). Role of B cells in multiple sclerosis and related disorders. *Annals of Neurology, 89*(1), 13-23. https://doi.org/10.1002/ana.25927

Faghani, G. & Azarniya, A. (2024). Emerging nanomaterials for novel wound dressings: From metallic nanoparticles and MXene nanosheets to metal-organic frameworks. *Heliyon, 10*(21), e39611. https://doi.org/10.1016/j.heliyon.2024.e39611

Funauchi, M., Ohno, M., Minoda, M. & Horiuchi, A. (1993). Abnormal expression of intercellular adhesion molecule-1 on peripheral blood mononuclear cells from patients with systemic lupus erythematosus. *Journal of clinical & laboratory immunology, 40*(3), 115-124. https://www.ncbi.nlm.nih.gov/pubmed/7877151

Gad, S. S., Fayez, A. M., Abdelaziz, M. & Abou El-Ezz, D. (2021). Amelioration of autoimmunity and inflammation by zinc oxide nanoparticles in experimental rheumatoid arthritis. *Naunyn-Schmiedeberg's Archives of Pharmacology, 394*(9), 1975-1981. https://doi.org/10.1007/s00210-021-02105-2

Galea, R., Nel, H. J., Talekar, M., Liu, X., Ooi, J. D., Huynh, M., Hadjigol, S., Robson, K. J., Ting, Y. T., Cole, S., Cochlin, K., Hitchcock, S., Zeng, B., Yekollu, S., Boks, M., Goh, N., Roberts, H., Rossjohn, J., Reid, H. H.,Thomas, R. (2019). PD-L1- and calcitriol-dependent liposomal antigen-specific regulation of systemic inflammatory autoimmune disease. *JCI Insight, 4*(18), e126025. https://doi.org/10.1172/jci.insight.126025

Ganguly, D., Haak, S., Sisirak, V. & Reizis, B. (2013). The role of dendritic cells in autoimmunity. *Nature Review Immunology, 13*(8), 566-577. https://doi.org/10.1038/nri3477

Garg, V. & Jusko, W. J. (1994). Bioavailability and reversible metabolism of prednisone and prednisolone in man. *Biopharmaceutics and Drug Dispositio, 15*(2), 163-172. https://doi.org/10.1002/bdd.2510150208

Ginhoux, F., Mildner, A., Gautier, E. L., Schlitzer, A., Jakubzick, C., Varol, C., Bain, C. & Guermonprez, P. (2020). Editorial: Monocyte Heterogeneity and Function. *Frontiers in Immunology, 11*, 626725. https://doi.org/10.3389/fimmu.2020.626725

Hampe, C. S. (2012). B Cell in autoimmune diseases. *Scientifica (Cairo), 2012*. https://doi.org/10.6064/2012/215308

Horwitz, D. A., Bickerton, S., Koss, M., Fahmy, T. M. & La Cava, A. (2019). Suppression of murine lupus by CD4+ and CD8+ Treg cells induced by T cell-targeted nanoparticles loaded with Interleukin-2 and transforming growth factor beta. *Arthritis and Rheumatoly, 71*(4), 632-640. https://doi.org/10.1002/art.40773

Huang, Y., Guo, X., Wu, Y., Chen, X., Feng, L., Xie, N. & Shen, G. (2024). Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. *Signal Transduction and Targeted Therapy, 9*(1), 34. https://doi.org/10.1038/s41392-024-01745-z

Joseph, A., Baslet, G., O'Neal, M. A., Polich, G., Gonsalvez, I., Christoforou, A. N., Dworetzky, B. A. & Spagnolo, P. A. (2024). Prevalence of autoimmune diseases in functional neurological disorder: influence of psychiatric comorbidities and biological sex. *Journal of Neurology, Neurosurgery and Psychiatry, 95*, 865-869. https://doi.org/10.1136/jnnp-2023-332825

Kumar, P., Saini, S., Khan, S., Surendra Lele, S. & Prabhakar, B. S. (2019). Restoring self-tolerance in autoimmune diseases by enhancing regulatory T-cells. *Cellular Immunology, 339*, 41-49. https://doi.org/10.1016/j.cellimm.2018.09.008

Lee, N. K., Kim, S. N. & Park, C. G. (2021). Immune cell targeting nanoparticles: a review. *Biomaterials Reserach, 25*(1), 44. https://doi.org/10.1186/s40824-021-00246-2

Lemos, H., Huang, L., McGaha, T. & Mellor, A. L. (2015). STING, nanoparticles, autoimmune disease and cancer: a novel paradigm for immunotherapy? *Expert Review of Clinical Immunology, 11*(1), 155-165. https://doi.org/10.1586/1744666X.2015.995097

Li, H., Yang, Y. G. & Sun, T. (2022). Nanoparticle-based drug delivery systems for induction of tolerance and teatment of autoimmune diseases. *Frontiers of Bioengineering and Biotechnology, 10*, 889291. https://doi.org/10.3389/fbioe.2022.889291

Londoño, J., Peláez Ballestas, I., Cuervo, F., Angarita, I., Giraldo, R., Rueda, J. C., Ballesteros, J. G., Baquero, R., Forero, E., Cardiel, M., Saldarriaga, E., Vásquez, A., Arias, S., Valero, L., González, C., Ramírez, J., Toro, C. & Santos, A. M. (2018). Prevalencia de la enfermedad reumática en Colombia, según estrategia COPCORD-Asociación Colombiana de Reumatología. Estudio de prevalencia de enfermedad reumática en población colombiana mayor de 18 años. *Revista Colombiana de Reumatología, 25*(4), 245-256. https://doi.org/10.1016/j.rcreu.2018.08.003

Marco-Dufort, B., Willi, J., Vielba-Gomez, F., Gatti, F. & Tibbitt, M. W. (2021). Environment controls biomolecule release from dynamic covalent hydrogels. *Biomacromolecules, 22*(1), 146-157. https://doi.org/10.1021/acs.biomac.0c00895

Medina-Ramirez, S. A., Soriano-Moreno, D. R., Tuco, K. G., Castro-Diaz, S. D., Alvarado-Villacorta, R., Pacheco-Mendoza, J. & Yovera-Aldana, M. (2024). Prevalence and incidence of diabetic retinopathy in patients with diabetes of Latin America and the Caribbean:

A systematic review and meta-analysis. *PLoS One, 19*(4), e0296998. https://doi.org/10.1371/journal.pone.0296998

Merad, M., Sathe, P., Helft, J., Miller, J. & Mortha, A. (2013). The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. *Annual Review of Immunology, 31*, 563-604. https://doi.org/10.1146/annurev-immunol-020711-074950

Mitarotonda, R., Giorgi, E., Eufrasio-da-Silva, T., Dolatshahi-Pirouz, A., Mishra, Y. K., Khademhosseini, A., Desimone, M. F., De Marzi, M. & Orive, G. (2022). Immunotherapeutic nanoparticles: From autoimmune disease control to the development of vaccines. *Biomaterials Advances, 135*, 212726. https://doi.org/10.1016/j.bioadv.2022.212726

Nashi, E., Wang, Y. & Diamond, B. (2010). The role of B cells in lupus pathogenesis. *The International Journal of Biochemistry & Cell Biology, 42*(4), 543-550. https://doi.org/10.1016/j.biocel.2009.10.011

Quintana, F. J. (2013). Nanoparticles for the induction of antigen-specific Tregs. *Immunotherapy, 5*(5), 437-440. https://doi.org/10.2217/imt.13.25

Sethulekshmi, A. S., Saritha, A., Joseph, K., Aprem, A. S. & Sisupal, S. B. (2022). MoS(2) based nanomaterials: Advanced antibacterial agents for future. *Journal of Controlled Release, 348*, 158-185. https://doi.org/10.1016/j.jconrel.2022.05.047

Silverman, G. J. & Carson, D. A. (2003). Roles of B cells in rheumatoid arthritis. *Arthritis Research & Therapy, 5*(Suppl 4), S1-6. https://doi.org/10.1186/ar1010

Sivamaruthi, Bhagavathi & Nallasamy, Prakash & Sivakumar, Suganthy & Kesika, Periyanaina & Chaiyasut, Chaiyavat. (2022). Pharmaceutical and biomedical applications of starch-based drug delivery system: A review. *Journal of Drug Delivery Science and Technology, 77*, 103890-103899. https://doi.org/10.1016/j.jddst.2022.103890

Smiljanovic, B., Radzikowska, A., Kuca-Warnawin, E., Kurowska, W., Grun, J. R., Stuhlmuller, B., Bonin, M., Schulte-Wrede, U., Sorensen, T., Kyogoku, C., Bruns, A., Hermann, S., Ohrndorf, S., Aupperle, K., Backhaus, M., Burmester, G. R., Radbruch, A., Grutzkau, A., Maslinski, W. & Haupl, T. (2018). Monocyte alterations in rheumatoid arthritis are dominated by preterm release from bone marrow and prominent triggering in the joint. *Annals of the Rheumatic Diseases, 77*(2), 300-308. https://doi.org/10.1136/annrheumdis-2017-211649

Smolensky, M. H. & Peppas, N. A. (2007). Chronobiology, drug delivery, and chronotherapeutics. *Advanced Drug Delivery Reviews, 59*(9-10), 828-851. https://doi.org/10.1016/j.addr.2007.07.001

Tsai, S., Shameli, A., Yamanouchi, J., Clemente-Casares, X., Wang, J., Serra, P., Yang, Y., Medarova, Z., Moore, A. & Santamaria, P. (2010). Reversal of autoimmunity by boosting memory-like autoregulatory T cells. *Immunity, 32*(4), 568-580. https://doi.org/10.1016/j.immuni.2010.03.015

Wang, H. F., Wang, Y. Y., Li, Z. Y., He, P. J., Liu, S. & Li, Q. S. (2024). The prevalence and risk factors of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. *Annals of Medicine, 56*(1), 2332406. https://doi.org/10.1080/07853890.2024.2332406

Wang, J., Yang, J. & Kopecek, J. (2022). Nanomedicines in B cell-targeting therapies. *Acta Biomaterialia, 137*, 1-19. https://doi.org/10.1016/j.actbio.2021.10.024

Wu, Z., Zhang, S., Zhao, L., Fei, Y., Wang, L., Li, J., Wen, X., Zeng, X., Zhang, F. & Li, Y. (2017). Upregulation of CD16- monocyte subsets in systemic lupus erythematous patients. *Clinical Rheumatoly, 36*(10), 2281-2287. https://doi.org/10.1007/s10067-017-3787-2

Yang, Y. & Santamaria, P. (2021). Evolution of nanomedicines for the treatment of autoimmune disease: From vehicles for drug delivery to inducers of bystander immunoregulation. *Advanced Drug Delivery Reviews, 176*, 113898. https://doi.org/10.1016/j.addr.2021.113898

Yap, D. Y. H. & Chan, T. M. (2019). B Cell Abnormalities in Systemic Lupus Erythematosus and Lupus Nephritis-Role in Pathogenesis and Effect of Immunosuppressive Treatments. *International Journal of molecular science, 20*(24), 6231-6249. https://doi.org/10.3390/ijms20246231

Zhu, J., Chen, W., Sun, Y., Huang, X., Chu, R., Wang, R., Zhou, D. & Ye, S. (2022). Recent advances on drug delivery nanoplatforms for the treatment of autoimmune inflammatory diseases. *Materials Advances, 3*(21), 7687-7708. https://doi.org/10.1039/d2ma00814a

Zolnik, B. S., Gonzalez-Fernandez, A., Sadrieh, N. & Dobrovolskaia, M. A. (2010). Nanoparticles and the immune system. *Endocrinology, 151*(2), 458-465. https://doi.org/10.1210/en.2009-1082