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New Therapeutics Approaches in the Autoimmune Field

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ABSTRACT

The immune system is critical in defending the body against pathogens and foreign substances through innate and adaptive responses. However, dysregulation of these immune reactions can result in autoimmune diseases, where the immune system erroneously targets self-tissues. Autoimmunity is influenced by multiple factors, with specific susceptibility genes and environmental triggers contributing to disease onset and progression. Traditional treatments for autoimmune diseases, such as immunosuppressants and biologic agents, aim to manage symptoms but often fail to address the root cause of immune tolerance breakdown, leading to limited efficacy and adverse effects. In recent years, nanoparticles have emerged as potential immunomodulatory agents, offering novel therapeutic strategies targeting key immune components. Cationic nanoparticles, particularly poly(amidoamine) (PAMAM) dendrimers, can interact with extracellular nucleic acids, modulate macrophage polarization, and induce immune tolerance, thereby reducing inflammation and autoimmune activity. These nanoparticles hold promise in diseases such as rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes. Despite their potential, challenges remain in optimizing nanoparticle formulations, understanding their long-term effects, and ensuring clinical safety. Future research focusing on improving targeting efficiency, reducing toxicity, and validating clinical outcomes will translate these innovative therapies into effective treatments for autoimmune diseases.

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Introduction

Understanding Immunity: The Body's Defense System

The immune system comprises a series of cells and molecules that collectively contribute to protection against foreign elements by a coordinated reaction known as the immune response [1]. The primary physiological role of the immune system is to defend against infectious microorganisms. Nevertheless, the immune response can also be triggered by non-infectious foreign substances and byproducts of damaged cells [2]. Immune responses are finely modulated by a network of positive feedback loops that enhance the reaction and mechanisms of control that curtail inappropriate or pathological responses [3]. Indeed, failure in the regulation of immune response can lead to tissue damage and diseases, such as severe infections, tumors, allergies, and autoimmune diseases [4].

Innate vs. Adaptive Immunity: The Two Lines of Defense

The immune response consists of a series of sequential and coordinated reactions. Based on the response's speed and specificity, it is categorized into innate (natural) and adaptive (acquired) immunity [5].

Innate immunity includes physical and anatomical barriers (e.g. skin, mucosa) as well as effector cells (e.g. monocytes/macrophages, neutrophils, eosinophils, basophils, mast cells, natural killer cells, dendritic cells), antimicrobial peptides, soluble mediators (e.g. cytokines, acute phase proteins, complement system), and cell receptors (e.g. Toll-Like Receptors - TLR) [5,6]. Natural immunity is a highly conserved nonspecific response that plays a critical role in safeguarding against microbes during the initial hours or days following infection, serving as a precursor to the development of adaptive immune responses [7]. Molecules produced during innate immune reactions serve as second signals for lymphocyte activation, proliferation, and differentiation. Moreover, some innate effector cells (e.g. monocytes/macrophages, dendritic cells) collaborate with antigen presentation to stimulate antigen-specific T and B lymphocyte responses [8]. This two-signal mechanism ensures a well-coordinated and selective immune response [9].

The adaptive immunity is mediated by cells called lymphocytes and their products. There are two major populations of lymphocytes, called B and T lymphocytes, which mediate different types of adaptive immune responses [10]. Lymphocytes express highly diverse membrane receptors that are capable of identifying and responding to a wide array of substances, both microbial and non-microbial, referred to as antigens. The specific regions of complex antigens recognized by lymphocytes are referred to as determinants or epitopes [11]. The adaptive immune response is highly specific and it usually takes several weeks or days to start, progressing through a series of stages [10]. The inception of adaptive immune responses hinges on the capture and presentation

of antigens to specific naïve lymphocytes. Cells designated as antigen-presenting cells (APCs) fulfill this pivotal role [12].

Subsequently, a process called clonal expansion ensues. Within this process, numerous distinct clones of lymphocytes come into play, each equipped with a unique antigen receptor, resulting in singular antigen specificity for each clone. Following clonal expansion, activated lymphocytes undergo differentiation. These activated lymphocytes, known as effector cells, play a central role in executing the ultimate effect of the immune response [13,14]. Throughout the initiation and execution phases of both innate and adaptive immune responses, immune system cells engage in interactions with one another and with other cells within the host [15]. These interactions are often mediated by molecules known as cytokines. Virtually all immune system cells release certain cytokines and possess specific signaling receptors for several cytokines [16].

In addition to effector cells, memory cells are generated, persisting over extended periods and mounting more robust and swifter responses upon encountering the same antigen anew [17]. Once the adaptive immune response has effectively eradicated the infection, the stimuli driving lymphocyte activation wane. Consequently, a majority of effector cells die out, resulting in the decline of the immune response [18]. Memory cells remain, ready to respond vigorously if the same infection recurs in the so-called secondary immune response [19,20]. Adaptive immunity is further divided into two distinct categories: humoral immunity and cell-mediated immunity. These forms of immunity are initiated by distinct classes of lymphocytes and function to counteract various types of microbes and insults [21,22]. Humoral immunity hinges on molecules present in the blood and mucosal secretions, known as antibodies. These antibodies are generated by plasma cells originating from B lymphocytes. Their role involves recognizing microbial antigens, thereby neutralizing the infectious capabilities of the microbes. Additionally, antibodies facilitate the elimination of microbes by tagging them for destruction through phagocytosis by specialized cells and by triggering the activity of the complement system [23]. Cell-mediated immunity, also known as cellular immunity, is orchestrated by T lymphocytes (T-cells). T-cells identify and react to antigens bound to host proteins localized on the surfaces of various cells and known as major histocompatibility complex (MHC) molecules [24]. Within the realm of T lymphocytes, distinct functional subsets exist, with helper T-cells and cytotoxic T lymphocytes (CTLs) being the most well-defined. Helper T-cells primarily exert their functions through the secretion of cytokines, whereas CTLs produce molecules that facilitate the destruction of other cells. An additional subset, known as regulatory T-cells (Tregs), mainly functions to suppress immune responses [25]. Distinguishing between different types of lymphocytes is possible through the expression of unique cell surface proteins, often designated by specific Cluster of Differentiation (CD) numbers, such as CD4 or CD8. These markers serve as identifiers for the different classes of lymphocytes [26].

The primary subsets of effector T-cells include CD8+ cytotoxic T lymphocytes and CD4+ helper T-cells. Additionally, among helper T-cells, there are other different subsets of cells such as Th1, Th2, and Th17, each characterized by the expression of specific cytokines and offering protection against different types of microbes and tumors(27). Th1 and Th2 cells play a pivotal role in immunity [28]. For example, Th1 cells promote cellular immune responses, by participating in the inhibition of macrophage activation, and by stimulating B-cells to produce immunoglobulins (Ig) M and IgG1. On the other hand, Th2 cells stimulate humoral immune responses, facilitating B-cell proliferation, and inducing antibody production [29].

An essential balance exists in terms of this T-cell polarization. Research has indicated that directing the polarization towards Th1 is crucial for effectively combating cancerous cells, whereas a polarization towards Th2 may aid cancer in evading the immune system [30,31]. CD4+ helper T-cells also offer activating signals to B-cells in response to protein antigens. However, B-cells can react to numerous non-protein antigens independently of helper T-cells [32,33]. After activation, each plasma cell, a specialized type of B-cell, starts to release antibodies that possess identical antigen-binding sites as the antigen receptors initially engaged on the cell surface [34]. More in detail, polysaccharides and lipids predominantly trigger the secretion of antibodies belonging to the immunoglobulin class IgM, while protein antigens prompt the generation of antibodies from a single B-cell clone in different classes, such as IgG, IgA, and IgE to fulfill specific functions [e.g. immune function in mucous membranes (IgA), protection against parasites (IgE), etc [35]. Finally, helper T-cells also stimulate the production of antibodies with heightened affinity for the antigen, enhancing the quality of the humoral immune response, in the so-called affinity maturation process [36]. A clearer picture of the immune system is displayed in Figure 1.

Understanding and manipulating these complex mechanisms is of primary importance to shape the immune response and optimize therapeutic strategies in immune-related disorders.

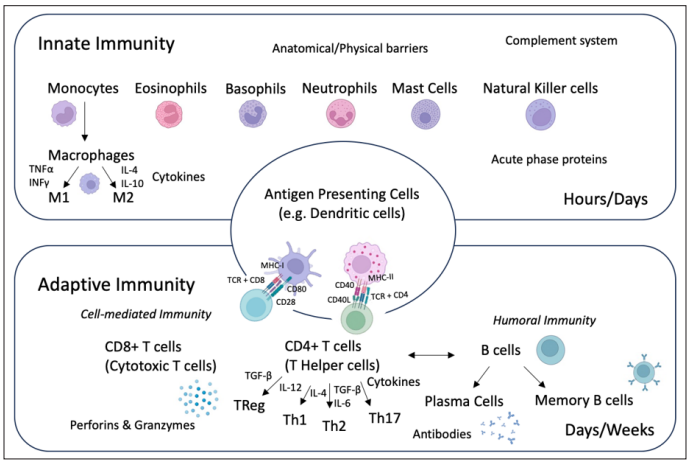

Figure 1: Immune System Landscape

Autoimmunity: When the Immune System Turns Against Itself

The process of recognition between self and non-self mediated by the immune system is not absolute. In certain circumstances, the immune system can mistakenly direct itself against itself, generating aberrant responses implicated in inflammatory disorders, collectively defined as autoimmune diseases [37]. Although the mechanisms underlying autoimmunity and autoimmune diseases are not yet fully understood, growing evidence demonstrates the influence of genetic and environmental interactions. It is currently believed that for the rise of an autoimmune disease, there is a period in which there might be an interaction between the genetic and environmental factors, followed by the autoimmune activation that leads to diagnostic clinical symptoms [38]. In normal physiological conditions, the immune system takes care of eliminating pathogens after their identification. However, there are two main cases in which the immune system functions defectively: through autoimmune diseases and in immunodeficiency disorders. The main cause of autoimmune diseases therefore lies in the failure

of recognizing the self. This phenomenon is often described as a breakdown of immunological tolerance [39]. Immune tolerance is divided into central and peripheral, and a deficiency can cause autoimmunity. Central tolerance aims to eliminate reactive B or T cells, promoting self-tolerance. This process occurs mainly in the bone marrow for B-cells and in the thymus for T-cells. Cells that bind to autoantigens thus undergo apoptosis [40]. Peripheral tolerance, in contrast to central tolerance, aims to control the excessive reactivity of B and T cells [41].

In central tolerance, T-cells that are responsible for recognizing self-antigens with a very high affinity will be eliminated in the thymus through the process of negative selection, to prevent autoimmune processes. Tregs instead will aim to suppress the activity of self-reactive T-cells, thus preventing autoimmunity [42]. Despite the thymus-mediated control mechanism, numerous autoreactive T-cells may elude thymic selection, triggering the risk of an autoimmune response. A peripheral mechanism is therefore needed to maintain self-tolerance. Subsequently, the peripheral tolerance starts its action, mediated by multiple cell classes belonging to the innate and adaptive response [43,44].

Hyperactive innate immune cells are responsible for responding to microbial triggers or high-danger signals, generating and modifying autoantigens, neoantigens, and Damage Associated Molecular Patterns (DAMPs). This modification can, in turn, be triggered by different mechanisms such as increased oxidative stress, causing damage to nucleic acids, proteins, lipids, and carbohydrates. In predisposed subjects, neoantigens can generate a cascade of inflammatory mechanisms. When cellular debris and dead cells are not properly eliminated by innate immune cells, mitochondrial and nuclear DNA and RNA are exposed to possible modifications. This entire process has a proinflammatory effect, activating TLR [45,46].

Autoimmune diseases can target different organs varying their clinical manifestations. Some are limited to specific tissues, while others have systemic characteristics. Regardless of these variations, all autoimmune diseases are believed to develop through phases. These are represented by an initial phase in which a genetic predisposition is influenced by environmental triggers. This phase is usually characterized by subclinical symptoms, in which patients are generally unaware. This is followed by a propagation phase, characterized by autoinflammatory processes and tissue damage, related to the production of cytokines and disruption of the balance between effector and regulatory T-cells. This is followed by a final resolution phase, in which there is a partial and usually short-term ability, in which the body attempts to restore the balance between effector and regulatory T-cells. This last phase is usually characterized by the relapsing of the disease [47]. In most cases, the genetic component of autoimmunity derives from changes found in class II molecules of the major histocompatibility complex (MHC II), which are essentially responsible for modulating the efficiency of antigen presentation. The remaining part of the genetic component derives from additive effects in which the cooperation of multiple genetic loci is recorded [48].

Genetic studies have shown that the same genes can increase the risk of different autoimmune diseases. Many genes contribute to autoimmune predisposition. For diseases such as Systemic Lupus Erythematosus (SLE) and rheumatoid arthritis (RA), for example, more than 100 different loci have been identified, responsible for an increased risk. The number of genes identified also suggests that pathological susceptibility is multigenic. An example is the PTPN22 gene, whose contribution has been demonstrated in several diseases including RA, SLE, and autoimmune (Type 1) diabetes mellitus. It represents one of the main susceptibility genes in addition to those of the MHC region [49-51].

RA is an organ-specific autoimmune disease caused by the presence of autoantibodies such as Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA). This disease has been identified as having a familial clustering with more than 100 loci. Several environmental factors contribute to the risk, including cigarette smoking, lack of physical exercise, stress, and diet [52].

SLE is a multiorgan systemic autoimmune disease related to a dysregulated tolerance in B cells and increased synthesis of autoantibodies. Several susceptibility loci have been highlighted, such as the Human Leukocyte Antigen (HLA) and non-HLA genes. Smoking is associated with increased production of anti-double-stranded DNA (anti-dsDNA) antibodies [52,53].

In Type 1 diabetes mellitus (T1D), autoimmunity affects pancreatic beta cells and the genetic component plays a significant role. It has been observed that familial risk is mainly related to HLA genes [54]. Low physical activity, stress, infections, diet, and psychological trauma are associated with a higher risk of incidence [55].

The standard treatment for autoimmune diseases has been based for a long time on immunosuppressants. Subsequently, there was the advent of biological immunomodulatory drugs, which targeted inflammatory mediators including cytokines. An example of this class is TNF-α inhibitors that inhibit the proinflammatory activity of this mediator, for RA. This therapy has thus represented the reference treatment for a long time, allowing disease control and reduced adverse effects compared to broad-spectrum immunosuppressants. However, anti-TNF-α therapies have also shown limitations, such as the loss of efficacy due to the triggering of resistance mechanisms as in multiple sclerosis [56].

Currently approved immunomodulatory therapies aim to treat symptoms, but they do not eradicate the underlying problem, namely the loss of immune tolerance. Refractory autoimmune diseases are not susceptible to these treatments, which, while aiming to reduce systemic inflammation, can subject the patient to opportunistic infections and harmful side effects [58-62].

B-cells and plasma cells contribute to the pathogenesis of autoimmune diseases by stimulating the production of autoantibodies. Therefore, therapeutic strategies have been designed to eliminate these cell classes. Monoclonal antibodies (mAb) interrupt B-cell and plasma cell-mediated signaling and trigger complement-dependent cytotoxicity and antibody-dependent cytotoxicity. Another strategy has been the creation of engineered T-cells via Chimeric Antigen Receptors (CAR-T therapy). Nevertheless, even these therapies have important limitations, such as the need for repeated administrations in the first case, and difficulties in the administration and the exact control of the dosage in the second case [57]. Therefore, although B-cell depletion strategies have been shown to be useful in the treatment of autoimmune diseases such as RA, SLE, multiple sclerosis, and many other immune-mediated inflammatory diseases, not all patients respond to these treatments or achieve drug-free remission [58].

Given the increasing number of autoimmune diseases in the last decades, there has been an urge to renovate therapies to reduce the side effects of classical treatments.

Nanomedicine in Action: Current Research on Nanoparticles for Autoimmune Diseases

In recent years, nanoparticles have emerged as powerful immunomodulators in treating autoimmune diseases due to their ability to interact with key immune components. Engineered nanomaterials can modulate immune recognition, either enhancing or suppressing immune responses and may alter how the immune system perceives and detects foreign substances [59]. These tiny particles, typically less than 100 nanometers in size, can be engineered to interact specifically with the components of the immune system, offering targeted therapeutic strategies, as displayed in Figure 2.

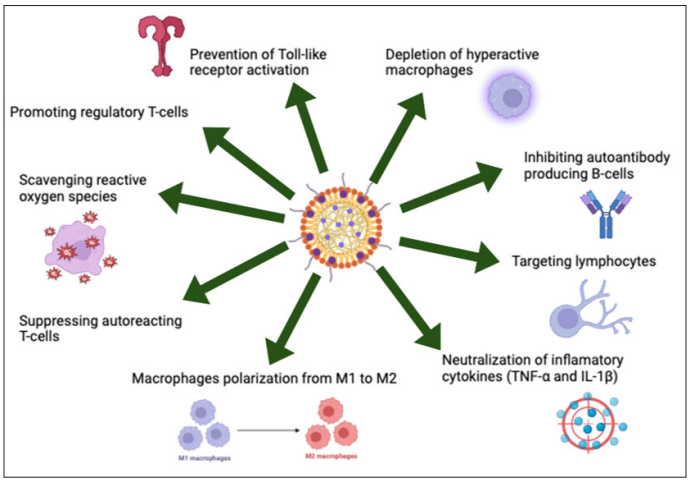

Figure 2: Schematic of Nanoparticles Employed in Autoimmune Diseases

Cationic nanoparticles can scavenge extracellular nucleic acids, such as cell-free DNA, thereby preventing Toll-like receptor activation and reducing inflammation in conditions like SLE and RA(60–67). Additionally, nanoparticle-based strategies can regulate macrophage polarization, shifting pro-inflammatory M1 macrophages to the anti-inflammatory M2 phenotype, while also depleting hyperactive macrophages involved in chronic inflammation [68-72]. Targeting lymphocytes, nanoparticles can induce immune tolerance by promoting regulatory T-cells, suppressing autoreactive T-cells(76), and inhibiting antibody-producing B-cells, showing potential in diseases such as multiple sclerosis and Type 1 diabetes(64,67,73–80). Furthermore, nanoparticles can neutralize inflammatory cytokines like TNF-α and IL-1β or scavenge reactive oxygen species, offering a comprehensive strategy for autoimmune therapy [63,81-88].

One of the most studied cationic nanoparticles is poly(amidoamine) (PAMAM) dendrimers, which are extensively studied for their ability to bind nucleic acids, making them valuable for gene delivery and as nucleic acid scavengers [89]. Their effectiveness is influenced by surface charge density, with higher-generation dendrimers (G3-G10) displaying enhanced nucleic acid binding and transfection efficiency [90,91]. Notably, PAMAM-G3 has been explored for its ability to mitigate inflammation and thrombosis by neutralizing nucleic acids that activate TLRs, a key mechanism in immune system dysregulation [92-94].

Circulating cell-free DNA (cfDNA), first identified by Mandel and Metais (1948), has been linked to autoimmune disorders, with increased levels observed in conditions such as SLE and RA [95-97]. cfDNA originates from various sources, including apoptotic cells and neutrophil extracellular traps (NETs), and can trigger inflammatory pathways through endosomal TLRs such as TLR7, TLR8, and TLR9 [98,99]. Given the role of nucleic acids in autoimmune activation, cationic nanoparticles have been explored as potential therapeutic agents to prevent excessive immune stimulation.

Cationic nanomaterials, widely used for non-viral nucleic acid delivery, have recently been investigated for their ability to suppress immune activation by scavenging extracellular nucleic acids [100]. Some of these materials, including PAMAM-G3, have been shown to reduce TLR activation by binding inflammatory nucleic acids and altering their intracellular trafficking [101]. Additionally, they can interfere with lupus-associated immune complexes by displacing autoantibodies from DNA, thereby mitigating disease progression without inducing general immunosuppression [102,103]. Beyond autoimmune diseases, cationic nanoparticles have also effectively reduced inflammatory responses in sepsis models [104,105].

Conclusions and Future Perspectives

Nanoparticles have demonstrated significant potential as immunomodulators in treating autoimmune diseases by targeting key immune components, scavenging inflammatory nucleic acids, and modulating immune cell activity. Advances in nanotechnology have enabled the design of nanoparticles with enhanced specificity, reduced toxicity, and improved therapeutic efficacy, offering promising alternatives to conventional immunosuppressive therapies. Despite these advances, challenges remain in understanding their long-term effects, immune interactions, and clinical safety.

Future research should focus on optimizing nanoparticle formulations to improve targeting efficiency, reduce off-target effects, and ensure biocompatibility. Large-scale clinical studies are needed to validate preclinical findings and assess the long-term safety of these innovative therapies. Furthermore, interdisciplinary collaborations between immunologists, materials scientists, and clinicians will be essential to drive the development of next-generation nanoparticle-based treatments. Expanding our understanding of nanoparticle-immune interactions could unlock new therapeutic possibilities and pave the way for more effective and personalized therapies for autoimmune diseases. Further research in this rapidly evolving field will be crucial to translating these promising nanotechnologies into clinical applications.

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Authors' contributions

GR, SF, and GI conceptualized the review. GR contributed to the study by creating a figure, collecting data from the literature, and editing the text. SF contributed to the study by collecting data from the literature and structuring and editing the manuscript.

GI contributed to the study by creating a figure, collecting data from the literature, editing the text, and finalizing the manuscript.

Competing interests

The authors declare that they have no competing interests.

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