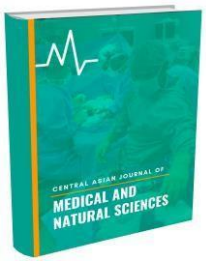

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The Role of Cytokines in Autoimmune Diseases: Pathogenesis and Therapeutic Implications

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Abstract: Autoimmune diseases are characterized by the immune system's aberrant response against the body's own tissues, leading to chronic inflammation and tissue damage. Cytokines, as critical mediators of immune responses, play a pivotal role in the development and progression of autoimmune disorders. These small signaling proteins regulate the activation, differentiation, and proliferation of immune cells, and their dysregulation can trigger or exacerbate autoimmunity. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, IL-17, and interferon-gamma (IFN-γ) have been found to be highly expressed in several autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease. Conversely, anti-inflammatory cytokines like IL-10 and transforming growth factor-beta (TGF-β) attempt to counterbalance this response but are often insufficient to control disease progression. Understanding the specific cytokine profiles and their interactions provides valuable insight into the pathogenesis of these diseases. Moreover, targeting cytokines has become a promising therapeutic approach. Biologic agents such as monoclonal antibodies and receptor antagonists have been developed to inhibit specific cytokines, significantly improving clinical outcomes in many patients. However, challenges remain, including the risk of immunosuppression and variability in patient response. Future research is focused on identifying more precise cytokine targets and developing personalized cytokine-based therapies. In conclusion, cytokines play a central role in the pathogenesis of autoimmune diseases, and modulating their activity holds great potential for innovative and effective treatments.

Keywords: Cytokines, Autoimmune Diseases, Inflammation, Pathogenesis, Immunotherapy, Biologic Agents

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1. Introduction

Autoimmune diseases are a group of diseases characterized by the abnormal activation of the immune system against self-antigens, leading to inflammation and tissue damage. More than 100 autoimmune diseases have been identified. Some of the most prevalent among the general population include rheumatoid arthritis, multiple sclerosis, and type 1 diabetes mellitus, while others such as Goodpasture syndrome, systemic lupus erythematosus, some subsets of autoimmune hepatitis, and primary biliary cirrhosis are less common [1]. Besides genetic predisposition, environmental factors play an important role in the onset of autoimmune diseases. Infections, vitamin D deficiency, hormonal factors, drug delivery, and exposure to certain chemicals such as oil pollutants are suspected factors of autoimmune diseases. Any disruption in the immune system leading to the activation of innate and adaptive immune responses results in the onset and

development of autoimmunity [2]. Cytokines are key regulators of the immune system able to activate safe immune responses against a broad spectrum of antigens and at the same time to maintain immune homeostasis; however, they can also play a crucial pathological role [3].

Autoimmune diseases are increasingly recognized as discrete disease entities in incomplete homeostasis in which dysregulated cytokines contribute to tissue-specific inflammation. In organ-specific and multiorgan autoimmune diseases, the cytokine profiles show some similarities, with elevated serum levels of some cytokines such as IL-6, IL-12, IL-17, IFNγ, or TNFα observed in at least two diseases. Despite these similarities, it has been shown that the above cytokines have, to some extent, different roles in the pathogenesis of diseases affected in tissues of distinct embryonic origin [4]. Multiple sclerosis is a centrally-acting organ-specific autoimmune disease resulting from the immune cell attack by microbiota infiltrating the brain and spinal cord. Theoretically, the inflammatory process in the brain can be resolved uniformly, resulting in a loss of motor, sensory, and cognitive function, fatigue, visual dysfunction, mood swings, sleep disturbances, and longevity issues. In systemic lupus erythematosus, it is a polygenic disorder in which the immune responses directed against self-antigens lead to the production of autoantibodies and the immune complex deposition in tissues [5].

2. Materials and Methods

This study employed a qualitative analytical approach grounded in a comprehensive literature review to investigate the role of cytokines in the pathogenesis and treatment of autoimmune diseases. A critical examination of primary and secondary scholarly sources, including peer-reviewed articles, clinical trial reports, and immunological reviews, was conducted to understand the complex interaction of cytokines within autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes. The methodology focused on synthesizing current findings related to cytokine classification, signaling pathways, and their dual role as pro-inflammatory and anti-inflammatory mediators. Special emphasis was placed on the Janus kinase/signal transducer and activator of transcription (JAK/STAT), NF-κB, and Smad signaling cascades to delineate the molecular mechanisms underlying cytokine-mediated immune dysregulation. In addition, data on biologic agents and small molecule inhibitors were critically assessed to explore therapeutic strategies targeting cytokine pathways. Sources were selected based on their relevance, recency (within the last five years), and scientific credibility from platforms like PubMed, ScienceDirect, and Google Scholar. This method allowed for the identification of key cytokines implicated in tissue-specific inflammation and the examination of the clinical efficacy and limitations of current cytokine-modulating therapies. While the study does not involve empirical experimentation, it provides a rigorous theoretical framework supported by translational insights, aiming to highlight both the pathogenic and therapeutic significance of cytokines in autoimmune diseases. The findings inform future research directions and the development of personalized, cytokine-targeted treatments.

3. Results and Discussion

3.1 Overview of Cytokines

Cytokines are a large group of low-molecular-weight peptides secreted by various cells, primarily leukocytes. The term “cytokine” encompasses numerous structurally diverse mediators such as chemokines, interferons, interleukins, and tumor necrosis factors, which have important roles in cellular growth, pathogenesis, and activation. During autoimmune reactions, cytokines mediate cell-mediated and antibody-dependent destruction of tissues by modulating the immune function and biological responses of cells. Aberrant production of cytokines, particularly inflammatory cytokines, has been associated with the development of a variety of autoimmune diseases, leading to interest in blocking cytokine pathways to find an effective treatment

[6]. Receiving only modest FDA approval, however, suggests that facultatively blocking one specific inflammatory cytokine is a rather inefficient method [7], [8].

The complexity of the dysregulation of cytokine networks during autoimmunity likely explains the heterogeneous progress of the disease and responses to therapy. The targeting of grievances with an antibody against a certain cytokine is sometimes met with partial success due to the compensatory effects of other cytokines, hence the emergence of new treatments focusing on signaling pathways that inhibit downstream cascades of multiple cytokines. The effect of these treatments is broader and more unspecific, and therefore not many argue for their use in chronic, long-term autoimmune conditions that tax each patient with a unique cytokine railopathy. Multiple sclerosis is an often seen autoimmune disease first described by Charcot [9], [10]; it involves inflammation, demyelination and axonal preservation in the CNS and leukocyte infiltration into the brain and spinal cord. Binominal disease old-age peaks have been reported [11], [12]: RR MS sitting at 30–35 years and PP MS at 50–60 years. It is more prevalent in women (M:F ~ 1:3). Grading is based on the expanded disability status scale (EDSS), an instrument scoring the physical disabilities of a patient [13].

3.2 Definition and Classification

Autoimmune diseases are recurring or persistent diffusely spread lesions of organs and tissues mediated by the immune system that selectively recognize and attack self-antigens. The mediators of such diseases can be cytokines, abzymes, agents of the complement system. Cytokines play a critical role in regulating lymphoid cell responses to antigenic stimuli and, thus, affect the pathogenesis of autoimmune diseases. Investigations of the role of cytokines in these diseases have received prominent attention for many years [14], [15]. However, during the earlier years findings of such studies were often conflicting and, as a consequence, the interpretation of reports could be subjective. More recently, investigators have taken advantage of gene knockout technology, which is on the path that offers more rigorous studies of the role of individual cytokines in such complex diseases. Also, clinical studies helped to establish more direct relationship between certain diseases and the expression of specific cytokine genes [16], [17].

Current knowledge highlights the complexities of the cytokine network and upholds the validity of a view emerging from earlier studies that the development and the progression of autoimmune diseases involve a delicate balance of cytokine mediators. Nevertheless, the contribution that altered cytokine synthesis plays in the processes leading to autoimmunity cannot be overstated. This synthesis represents a state of immunodysregulation already long before the onset of clinical stage [18]. From current data, it is difficult to predict whether defects in the synthesis of a particular hypo- or hyperactive cytokine in an individual patient, will lead to exacerbated or ameliorated disease. But it seems plausible that the sustained imbalance of cytokine mediators at either the systemic or local level promotes and sustains the autoimmune response. However, productive research in this or other direction should include a comprehensive array of cytokines and employ flexible study designs, as their results are bound to be affected by patient- and disease-specific circumstances [19], [20].

3.3 Mechanisms of Action

The molecular mechanisms orchestrating the interaction of the immune and nervous system produce a specialized form of neuroinflammation. There is now a common agreement that neuroinflammation is a critical player in the pathophysiology of several brain disorders, including major depressive disorder. Bone is an enigmatic and innately regenerative organ for which the nature of therapeutic procedures is not trivial. Drugs comparable to PTH may be suitable in postmenopausal women [21], [22].

The cytokine network decides the immune system triggering reactions of the crucial recipients for viral and bacterial infections [23]. The assembling of the immune profile against pathogens moreover circumstantiates in a cytokine tissue more interested in

inflammatory responses rather than untouched operation. This may explain infection-vexed reactions diverse from acute, such as septic shock, to indurated settings of continuing trauma [24]. All the reviews and the understanding of the neuro-inflammatory cytokines have been confined to methodical logic, always promoting healing strategies in the situation of neuroinflammation [25], [26].

4. Cytokines in Disease Pathogenesis

Autoimmune diseases are chronic and may involve multiple organ systems. The pathogenesis of autoimmune disease is not fully understood, but unbalanced immune responses activated in genetically pre-disposed individuals are important. Cytokines are small molecular weight proteins secreted by a variety of cells that either enhance or inhibit the function of other cells. Therefore, they regulate innate and adaptive immune. Cytokines produced within the context of dysregulated immune activation can be pathogenic [27]. The pleiotropic cytokine interleukin-6 (IL-6) is produced by various cell types in response to different stimuli and activates multiple intracellular signaling pathways. Janus kinases (JAKs) transduce signals from IL-6 receptors inducing the intracellular activation of the transcription factors of the Signal Transducer and Activator of Transcription (STAT) factor family (pSTATs) [7]. In addition to these events, STAT activation induces the expression of suppressor proteins, including the protein inhibitors of activated STAT (PIAS) that limit further activation of the JAK/STAT signaling cascade [28], [29]. In mice, IL-6 contributes to the development and differentiation of both T follicular helper (Tfh) cells and B cells within germinal centers (GCs). Both pathogenic autoantibodies and T-dependent immune responses in systemic lupus erythematosus (SLE) involve B cells and GCs, and aberrant GC reactions appear to be an important contributor to the development and progression of this disease [30]. Chronic activation of the IL-6/STAT3 signaling by concurrent systemic manifestations in chronically inflamed organs will promote the differentiation of autoreactive T and B cells, enhance the GC response, and accelerate extrafollicular autoantibody-producing bone-marrow plasma cell development. Thus, one general mechanism by which IL-6 may exacerbate the pathology of SLE is to promote spurious and self-reinforcing immune reactions. These findings suggest, however, that therapy aimed at inhibiting IL-6/STAT3 signaling is likely to be contraindicated in many SLE patients. Multiple sclerosis (MS) is a typical demyelinating and neurodegenerative disease of the central nervous system (CNS), while ulcerative colitis (UC) is a chronic, relapsing inflammatory disease specific to the colon and rectum [31], [32]. Despite hosting fundamentally different antigens and being anatomically separated by the blood-brain barrier, the CNS and colon share similar effector immune responses as dominated by interleukin-17 (IL-17)-producing T cells therein. In label-free single-cell mass cytometry experiments with in-depth data analysis, profound alterations in the numbers, phenotypes, functions, and cytokine-expression profiles in peripheral blood immune cells in MS and UC were detected. Furthermore, for the first time, the similarity in immune-cell alterations between diseases, including an increased cell-to-cell interaction, was revealed. By computational modeling, a biospatial focus on peripheral blood immune cells in MS and UC was dissected, disentangling disease-specific cell alterations from adaptive immune responses. The latter determined the reduced lifestyle of UC immune cells, leading, in part, to therapeutic implications [33], [34]. Conversely, potential adverse systemic effects of current MS treatments were highlighted. The findings are crucial for a systemic understanding of comorbidities and drug effects for autoimmune diseases of diverse etiologies [35].

4.1 Cytokine Networks

Changes in the cytokine profile and cytokine networks are an integral part of autoimmune diseases and contribute to the tissue-specific inflammation of the affected organ. In this review, changes in cytokine levels are systematically presented in serum or plasma from patients with SLE and with MS [36]. The role of cytokines in progression of SLE and MS is significant because changes in the levels of these autocrine and

paracrine messengers disrupt intercellular interactions within the immune system [37]. Selected studies using methods that can detect immunoregulatory polypeptides in the serum/plasma of SLE or MS patients were analyzed in the context of the cytokine network in the course of these diseases. Unlike a study focused on the individual role of cytokines in SLE or MS, a systematic review of altered cytokine networks from the point of view of a wide range of agonistic and antagonistic cytokines will contribute to a deeper understanding of cytokine disturbances in the course of these diseases [38]. It will also help in the search for new and optimization of existing therapy methods based on immunomodulators. One of the mechanisms for the formation of new therapeutic strategies will be modulation of the functions of hyperactivated or pro-inflammatory cytokines showing pathogenic action in SLE or MS [39]. Improved cytokine therapies can target transduction pathways activated by cytokines and used by many of them. This approach will accelerate the development of new anti-cytokine therapy methods and optimize the design of clinical trials [40], [41].

4.2 Role in Inflammation

Autoimmune diseases are characterized by immune reactions against self-components. Since the early 1980s, they have been recognized as conditions where dysregulated cytokines critically contribute to tissue-specific inflammation. Nevertheless, wide inter- and intragroup variations make it difficult to proceed with a straightforward analysis of cytokines in autoimmune diseases. Many features of cytokines in autoimmune diseases and explanatory comments comprise case reports and examinations of biopsied samples that cannot represent the entire pathophysiological process [42], [43].

Cytokine profiling of chronic inflammatory diseases is very complicated because dysregulation of at least a few dozen of them are involved. For systemic diseases, combined cytokine/chemokine/extracellular matrix metalloproteinase profiling would be clinically very difficult. As a result, the profile of only some representative cytokines and chemokines in some quite different autoimmune diseases have been compared, involving a protozoal infection, an organ-specific, and a systemic disease [44], [45]. Complications are added by the fact that all of these diseases are herb-induced, but their onset requires contact with bacterial and viral infections.

The aim is not to consider all complicated aspects of cytokine profiles in different autoimmune diseases but to scrutinize structural, chronological, diagnostic, and pathophysiological aspects of cytokines in the context of inflammatory changes in certain chronic immune diseases [46], [47]. Nevertheless, a short analysis of representative, well-studied cytokines associated with selected immune diseases is presented, focusing mainly on interleukins, interferons, or tumor necrosis factors and on JAK-STAT, TGF-β, and NF-κB signaling pathways [48].

4.3 Cytokines and Immune Regulation

Small numbers of potentially self-reacting lymphocytes can still leak out into the periphery due to the stochastic nature of VDJ recombination. Moreover, beneficial as it may be in order to maintain a diverse and adaptable immune repertoire, this phenomenon does not necessarily lead to pathology, because additional mechanisms of peripheral tolerance, such as anergy, apoptosis, suppression or active inhibition, restrain the activation of these cells. Nevertheless, in genetically susceptible individuals, or following specific antigen insults such as infections or tumors, systemic activation of the immune system can override the tolerogenic mechanisms and break immune homeostasis [49], [50]. Any defect concerning the differentiation or function of these pathways can lead to the development of autoimmunity. Autoimmune diseases are defined as a group of pathological immune responses against autologous tissues. Although they may have multiple etiologies, in all of these cases the breakdown of tolerance to self-antigens is mainly mediated by T cells through the modulation of B cells [51], [52]. Effector T cells killing of target cells is facilitated by an inflammatory reaction,

suggested by the finding of inflammatory infiltrates in the tissue lesions. The autoimmune etiology is mostly secondary to the recognition of self or foreign molecules acting as antigens by innate sensors, which trigger sterile inflammation and the engagement of autoreactive T and B cells. Initial discoveries of mutations in different genes encoding for negative regulators of immune recognition transduction suggested that this was the principal cause of the disease [53]. However, autoimmune responses would be secondary to chronic inflammation and cytokine snowballing, directly causing tissue damage and the disarrangement of the tissue architecture. Early studies in animal models showed that the transfer of chronic proinflammatory signals, such as IFNs, or the protracted activation of physiological ligands of these innate immune molecules, would lead to a plethora of autoimmune symptoms and anomalies. Subsequent genetic approaches, genome-wide association studies, and auto-antibody titers in ICI-treated patients have shown that cancer immunotherapy could kick-start the development of de novo autoimmunity, disclosing a previously unappreciated immunodysregulation occurring in these life-saving therapies [54].

Cytokines are crucial immune mediators that activate and polarize the immune response. To grant a meaningful host defense, the immune system must detect and effectively respond to invading pathogens through coordinated intercellular signals. Cytokines are low-weight secreted proteins that mediate signals over a small distance or within the producing cell itself [55]. These pleiotropic molecules can act on immune, endothelial, epithelial, and stromal cells, effecting a multitude of activities, such activation, chemotaxis, phagocytosis or the release of antigens, or the killing of infected or cancerous cells. Upon the delivery of the antigen from activated antigen presenting cells, the T cell receptor reshuffles the membrane leading to the activation of transcription factors. This gene program will dictate the differentiation of antigen-specific nai◎ve T cells into effector T cells, helping other immune cells to eliminate the pathogen. Different combinations of paracrine signals, such as cytokines, determine the T cell subset outcome [56]. Type 1 helper cells (Th1) engage the T-bet transcription factor and secrete IFN-γ; they are primarily involved in responses to intracellular pathogens and parasites. In contrast, type 2 helper cells (Th2) express GATA3 and produce IL-4, IL-5, and IL-13, key drivers of humoral and extracellular responses to helminths. Full commitment for either Th1 or Th2 polarization involves reciprocal positive reinforcement mechanisms, such that IFN-γ suppresses GATA3, and IL-4 does the same on T-bet [57].

5. Specific Autoimmune Diseases

Autoimmune diseases are defined as inflammatory diseases which can involve different types of tissues. Nowadays, they are recognized as diseases in which the proinflammatory cytokines contribute to tissue-specific inflammation, fibrosis or altered function. The JAK/STAT, Smad2/3, and NF-κB pathways, as well as the crosstalk between these pathways, are involved in the pathogenesis of two autoimmune diseases, multiple sclerosis and systemic lupus erythematosus. These pathways are mainly activated by cytokines in an autocrine or paracrine manner [58], [59].

Autoimmune diseases are organ-specific and affect the central nervous system or they can affect many organs and organ systems. Despite these differences, both diseases share disease entities, which suggests that certain common pathways are involved in their pathogenesis [60], [61], [62]. The central role in the crosstalk between the earlier mentioned signaling pathways is assigned to T cells. It was shown in the model that Treg cells directly inhibit Th1 and Th17 cells, and in consequence, a decreased population of CNS infiltrating Teff cells is noted [63]. The clinical phase of the experimentally induced disease is directly associated with a decreased number of Treg cells in the CNS at disease onset and during the early remission phase. It is in line with observations suggesting defects in the Treg cell population in MS patients, due to a reduced population of Th1, but not Th2 cells. A significant reduction in Treg cells can be found in a group of MS patients in comparison to healthy individuals or patients affected with other

autoimmune and neurological diseases. Such a defect is directly associated with the disease activity and the progression of the relapsing-remitting form of MS [63].

5.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune, inflammatory, systemic chronic disease which typically affects the synovial joints. The pathogenesis of RA is determined by the activation of auto-antigen-specific T lymphocytes and B lymphocytes. Activated T cells subsequently activate macrophages and synovial fibroblasts; triggering the production of pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin-1ß (IL-1ß), interleukin-6 (IL-6)), which in turn sustain the inflammation by increasing leukocyte recruitment and cellular proliferation, induce T and B lymphocyte differentiation and immunoglobulin production and increase the expression of matrix metalloproteinases and osteoclasts leading to the degradation of cartilage and bones. Another family of cytokines consists of anti-inflammatory cytokines (interleukin-1 receptor antagonist (IL-1ra), IL-4, IL-10, IL-13, IL-37) blocking the effects of their pro-inflammatory analogs [64]. Currently, the inflammatory process is considered to begin in the lung where citrullinated proteins are generated. Cytokines also exert their pathogenic action not only on the synovial cells, but also on the extra-articular ones thus promoting the systemic manifestations and co-morbidities of the disease [65]. All these considerations are pivotal for the present pharmacological approach to RA. In this context, drugs targeting cytokines and their receptors represent the modern pharmacological approach to RA. Therapeutic antibodies blocking TNF-α represent the first example of anti-cytokine therapy for RA and are still the most commonly used among biologic agents [66], [67]. Currently, anti-TNF-α mAbs, namely adalimumab, infliximab, golimumab, certolizumab-pegol and the decoy receptor etanercept, are the most common biologic drugs used in RA. Anti-TNF drugs clearly decrease the synovial inflammation, slow down the erosive process and prevent long-term disabilities. The disabling effects of chronic inflammation on morbidity and mortality account for the health care cost of RA, which is about twofold higher than for the general population [68]. Rapamycin, commercially named Sirolimus, represents a mTOR inhibitor possessing anti-proliferative and anti-inflammatory actions. It is used to prevent rejection of solid organ transplants and to release coronary artery stents. A possible beneficial effect of Sirolimus in RA is based on the evidence that mTOR-p70S6K is hyper-activated in RA and promotes high cell turn-over of synovial fibroblasts which is responsible of chronic inflammation and joint destruction [69], [70]. Both mTOR and p70S6K inhibitors, including rapamycin, decrease the hyperplasia of the synovial lining in RA. DMARDs are traditionally used to manage RA patients and include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine A, D-penicillamine [71]. Methotrexate is the most widely used DMARDs and it is generally well tolerated. Unfortunately, more active and toxic therapy is needed when the disease is not controlled and progresses toward refractoriness and chronicity [72], [73].

5.2 Systemic Lupus Erythematosus

Therapy focusing on single cytokine or immunocompetent cell is difficult. Lupus is a hyperergic and disseminated autoimmune disease, involving the interaction of many kinds of autoimmune cells and cytokines. Instead of a single mediator, a mediator network forms, and acts on several kinds of cells. Immune regulation through the formation of cytokine network is complex. The regulation of the networks is not fully understood. Therapy using cytokines and cells as a one-way signal is inefficient [74], [75]. More efforts to understand the complex interaction between cytokines and cells might bring good results in other inflammatory diseases, such as rheumatoid arthritis. Agents, like neutralizing fusion proteins, or cytokine receptor fragments, small peptides, as well as low molecular weight compounds are excellent alternative tools for the immune intervention [76].

Beside genetic factors, SLE is thought to result from complex interactions between numerous environmental factors, particularly viruses and oestrogens, and other factors, such as cytokines and growth factors. A number of organs and systems may become involved, as the kidney, lung, joints, central, and peripheral nervous system, haematopoietic system, endocrine system, alimentary system, serous membranes, dermal tissues, lymphatic systems, and so on. In addition to these organs and tissues, SLE patients are often accompanied by secondary SS and rheumatoid arthritis [77], [78]. In SLE patients, each organ is involved in different ways, so that pathogenesis is quite different. For example, in the case of the kidney, either a direct complement-unrelated humoral immunity may play a role in capillary damages in filter units, or cellular immunity may play a key role, especially T-cell immunity, in the interstitium, giving rise to interstitial nephritis [79], [80], [81].

5.3 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disorder affecting the central nervous system (CNS), primarily within the brain and spinal cord [82], [83]. The pathogenesis of MS is complex and involves autoimmune responses mediated by immune cells and soluble mediators such as cytokines. CD4+ T cells are believed to be major effectors that initiate and propagate the autoimmune response leading to CNS damage. The migration of activated immune cells across the blood–brain barrier is critical for the initiation of MS that underlies an inflammatory phase in the CNS, the primary component of the acute focal demyelinated plaques. As described elsewhere, this is triggered by the activation and infiltration of myelin-specific Th1, Th17, and ThGM-CSF+ CD4+ T cells [84], [85]. Once the acute response subsides, disease progression is driven to some extent by chronic inflammation with the continuous migration of broader populations of immune cells into the CNS. As the disease progresses, however, the autoimmune response appears to be somewhat compartmentalized within the subarachnoid space hence the formation of GC-like immune aggregates, enriched for T, B, antigen presenting cells, and complement activation [86], [87]. More importantly, focal inflammatory lesions within the BGM largely shielded from natural clearance mechanisms may prolong or even perpetuate the propagation of CD4+ mediated immune injury [88], [89], [90].

5.4 Type 1 Diabetes

Loss of tolerance to insulin-producing pancreatic beta cells in the Type 1 Diabetes of the Non Obese Diabetic (NOD) mouse results from an interaction that involves many cell types, including the beta cell. Agents that inhibit the signal transduction of Type 1 Interferons have the potential to both prevent and reverse diabetes in this model [91], [92]. The nano-dispersion of AG490 particles in an oil-in-water stabilizer emulsion was now demonstrated to prevent and also to be efficacious in recently diagnosed (new onset) diabetic NOD mice. Prompted by suggestions that chronic early use of rapamycin might preserve beta cell function in new onset NOD mice, the non-obese diabetic (NOD) mouse model of type 1 diabetes (T1D) was employed to ask if the tyrphostin agent AG490, a JAK-2 tyrosine kinase inhibitor that prevents signal transduction in a highly purified type 1 interferon receptor preparation, might inhibit T1D induction by non-related antigens (cross T1D) [91]. T1IFN are a large family of cytokines that interact with the same shared receptor [93], [94]. The instruments of signal transduction are the JAK-1 and JAK-2 tyrosine kinases. The tyrphostin AG490 inhibits autophosphorylation of these kinases and prevents signal transduction. As a result, AG490 prevents the chain of gene and protein production, which link cytokine binding to cytoplasmic membrane receptors to receptor endocytosis, nuclear translocation, and the initiation of DNA transcription [95], [96]. Agents that prevent signal transduction by T1IFN have the potential (as demonstrated for the NOD mouse) to prevent both the induction of T1D by antigens or infection that induce the secretion of T1IFN as well as the chronically established T1D that results from the network of glands and cytokine signals in the draining T1D

pancreatic lymph nodes [97], [98]. T1IFN significantly favored the amplification and expansion of this network [99], [100].

6. Therapeutic Implications of Targeting Cytokines

IL-10 is an anti-inflammatory cytokine, produced by a plethora of myeloid and lymphoid cells, as well as tubular cells [101]. It plays a crucial role in terminating excessive T-cell responses, in order to prevent chronic inflammation; this is particularly important at the mucosal level, where the barrier needs to be restored and inflammatory stimuli cleared. Intriguingly, an IL-10 deficiency in mice affects the lamina propria, which becomes predominantly IFN-γ producing and mice develop spontaneous enterocolitis [102], [103], as well as fibrosis at the lung level; moreover, such animals present symptoms similar to those of patients with Crohn's disease. Mechanistically, IL-10 displays multiple effects, such as a competition with IL-12 for the same receptor, an oscillation in SOCS3 and Stat3 expression, and an induction of the IL-10R blocking interleukin-1α gene, to create repressive conditions to prevent further transcription at the level of strong inflammatory gene promoters. Furthermore, the role of miR-10a and miR-10b, regulating the synthesis of two transcription factors implicated in its production: CREB and ATF5, respectively, has been thoroughly investigated. In the context of autoimmunity, data of miRNA-dependent regulation of IL-10 came from the adoptive transfer of Treg cells in EAE [104], [105].

EAE was not induced by Treg cells, if they were pre-treated with let-7e, a miR upregulated in this disease, that impairs the level of IL-10 in these cells due to targeting the 3′UTR of the Mrna [106], [107]. Further data linking miRNA up- or down-regulation to the modification of the levels of IL-10 in autoimmune diseases relates to RA, psoriasis vulgaris, and SLE. In the context of RA, a substantial effort was put into the identification of various miRs deregulated upon FLS exposure to IL-17 (alone or in combination with TNF-α) or TNF-α. No data were obtained about miRs up-regulated upon challenge, whereas it was found that miR-223 was down-regulated in any condition tested. miR-223 expression is inversely correlated to those of STAT3, and SOCS3 and its over-expression reduces the synthesis of IL-10, a positive STAT3 target [108], [109].

6.1 Biologics and Monoclonal Antibodies

In the last two decades, the use of biologics and monoclonal antibodies modulating the interaction among immune cells has become a staple of targeted medical therapies. The pool of medications used to treat autoimmune diseases has rapidly expanded to include many antagonists of certain cytokines, in particular monoclonal antibodies. The treatment targets not only cytokines but also the receptors via the signaling cascade, for example targeted inhibitors of IL-6R or JAK kinases [110], [111]. In the family of JAK kinases, JAK1 and TyK2 facilitate signal transduction via IL-12, IL-23, interferons α and β, and IL-10 family interleukins. The anti-TNF-α class of therapeutic agents has revolutionized the treatment and management of inflammatory disorders, effectively curing rheumatoid arthritis and several other diseases known to be caused by excess TNF-α. The first biologics essentially reduced the immune response and consequently increased risks posed by infections and the development of neoplasia; however, lots of fresh research has focused on bringing forth the selective and effective ways to fight autoimmune diseases with many more medications [112], [113]. One of the still insufficiently researched molecules is IL-15 which can be considered as a possible target for autoimmune or inflammatory diseases. Combinatorial signals from IL-15 and TGF-β direct the differentiation of RORγT+CD4+ cells into IL-17A and GM-CSF coproducing T cells (Th-17 GM-CSF). Recent studies showed an essential onymy between GM-CSF and IL-23 signaling in maintaining stable and pathogenic Th-17 [114], [115]. Cytokine IL-23 synergizes with IL-6 to directly induce the formation of pathogenic Th-17 GM-CSF or when there is excess of T-bet and high production of IL-2 in the environment of Th-17 polarization of pathogenic Th-1 GM-CSF. The activation of Th-17 GM-CSF cells occurs after interaction of GM-CSF with cells CNS that further activate other T cells. Moreover,

IL-15 stimulates the production of GM-CSF by Th17 cells, and IL-23R expression correlates with the expression of GM-CSF. Another interesting thing is that IL-15 is a common γ-chain receptor derivative and is a part of the heterodimeric receptor that assembles the signaling machinery [7]. According to the new publication rats that have overexpression of IL-15 in the central nervous system develop cumulative and late onset experimental autoimmune encephalomyelitis. The work of Dumas et al. shows that CK15 regulates energy metabolism and maintains the phenotype of SMC-like cells in VSMC in vitro and in vivo. In addition, in mice with atherosclerosis, the deletion of Il15b in macrophages reduces atherogenesis in the genes dependent on the atherogenic phenotype, and the deletion of IL-15 in vivo reduces inflammation in adipose tissue in obese mice. The professional scholar writer thinks that the publication about Il-15 opens a new field of its application in autoimmune diseases [116], [117].

6.2 Small Molecule Inhibitors

New small molecule inhibitors will enable therapeutic intervention at the level of specific tyrosine kinases (i.e., JAK, SYK, Btk) differentially regulated by cytokines. Furthermore, a disruption of immune cell signaling required for cytokine action may also result with small molecule intervention [118], [119]. The improved understanding of cytokine function and signaling will contribute to the rational selection or design of small molecule inhibitors for therapeutic applications. Recently, positive clinical data with IRAK4 inhibitors have been reported, as well as in lupus which suggest that both p38MAPK and JNK may not be good examples considering the failure of a number of inhibitors in the respective pathways also in clinical trials [120], [121]. Besides the therapeutic potential of new small molecule compounds, novel inhibitory approaches besides RNA interference are also emerging. Due to its central role in the signaling networks triggered by a variety of cytokines in different cell types, kinase inhibition is a particularly interesting therapeutic approach in autoimmunity as well as in diseases where inflammation is a key driver of pathology. Synovial inflammation due to infiltration of a variety of immune cells results from the action of pro-inflammatory cytokines, chemokines and metalloproteinases [122], [123]. These proteins activate and recruit synovial fibroblasts that in turn produced additional cytokines. These signaling networks are interconnected by crosstalk pathways by sharing a number of components including kinases [124]. With progresses in the understanding of cytokine function and cytokine-inspired signaling pathways, new ideas for intervention at the level of enzyme targets have been developed. Major possibilities include specific kinase inhibitors as well as small modulator compounds targeting protein interactions [125], [126].

6.3 Cytokine Blockade Strategies

Cytokines mediate a wide variety of immunologic actions, including cellular activation, differentiation, and proliferation, mediator production, antibody synthesis, migration, and proliferation of inflammatory cells, haematopoiesis, angiogenesis, fibroblast and osteoclast activation. These autocrine and paracrine function biological activity proteins are key effectors in the pathogenesis of many human autoimmune and inflammatory diseases [127], [128]. RA, the seronegative spondyloarthropathies PsA and AS, CRST, IBD, and Behçet's disease characterize systemic inflammatory conditions in which cytokine networks exert a pervasive influence. Symptomatic therapeutics for chronic inflammatory diseases such as RA have evolved considerably over the course of the past two and a half centuries [129], [130]. However, no curative therapy has yet been devised, and RA still leads to progressive disability and premature death. Modern-day awareness of the disease began with the seminal 1800 publications by Landré-Beauvais and Haygarth. Targeting of cytokines using secreted or cell surface receptor-specific monoclonal antibodies has proven a powerful strategy for the management of certain chronic immune-mediated diseases, such as asthma and the autoimmune rheumatic diseases. These proteins mediate fundamental immunoregulatory roles and their pleiotropic functions, as well as a propensity for synergy, meaning that even subtle

alterations in production or function can lead to profound biologic effects [131], [132]. This wide array of biological activities render cytokines a tantalizing target for the manipulation of aberrant immune function in inflammatory diseases [6]. Strong corroborative evidence from both preclinical and clinical evaluations has well established tumour necrosis factor α (TNF-α), interleukin (IL)-1, and IL-6 as critical mediators of pathologic inflammation in joint tissue. Also, clearly, they are important in the nodules, and the sickness and the fatigue, and in the muscle weakness. The most significant improvements are seen in swollen joint counts, tender joint counts, patient assessments, pain measurements, and morning stiffness duration. The goal because any new therapy might have an irreversible final effect. Malaysia because different racial groups suffer from white. The only thing that makes the side effect from the growth of one's merits of this crippling and debilitating disease [133].

7. Challenges in Cytokine Targeting

Autoimmune diseases are largely heterogeneous and exist in almost all medical fields. Some, such as rheumatoid arthritis, are broadly characterized by inflammation of the joints. This literature will focus on the roles of cytokines in the pathogenesis of autoimmune diseases and introduce partners that have potential as targets for pharmaceutical intervention. Among potential targets for therapeutic prevention, current studies have highlighted extreme roles of cytokines and an improvement in understanding their system. During the progression of the diseases, they acted as not only risk parts but also as brokers of cell signals that are important as biomarkers. Efforts to expand new drug targets have drawn attention to 40 cytokines like tumor necrosis factor (TNF), a lot of interleukin (IL), and appealing targets have more recently been figured out. However, there has been some difficulty developing effective drugs, and certain concerns have been raised for the use of antibodies [134]. There are two essential troubles in attempting to discover new drugs that target cytokines. One of them is the complex nature of cytokines. Cytokines are influential peptides existing in very tenuous levels. Chronic exposure leads to remotion from the plasma by cis binding cytokine receptors or by cytokine-neutralizing antibodies. The body has advanced to defend itself from numerous multiple infections that involve pathogenic conditions that cause a lot of cytokines to be released all together, so the very potent and interactive character of cytokines could have initiated this system. Experimentally that has been observed in mice with overexpression of individual cytokines, It has been difficult to replicate the phenotype induced by the natural inflammatory location of the concerned cytokines [135]. If two cytokines are restricted to collaborate with each other, this develops a contradictory phenotype juxtaposed with that observed with overexpression of a single cytokine. However, the pathogenesis of many autoimmune diseases is complex and involves various cytokine networks. Thus, targeting more than one cytokine might be required for a valid therapeutic strategy. There are numerous limitations in manipulating a further advanced cytokine network, for which two can be addressed. At first, the pharmacokinetic features of the all-protein are not very simulative [136].

7.1 Side Effects and Safety

Biologics are biological products derived or manufactured from living entities and are increasingly used as immunomodulation agents to treat various chronic inflammatory diseases. As of 2012, the global market for immunomodulatory biologics was worth more than 110 billion US dollars, and these biologics play a vital role in treatment regimens for many diseases, such as cancer, autoimmune diseases, and inflammatory conditions. By targeting neural regulation of inflammation, as opposed to blocking the activity of proinflammatory cytokines, side effects could be kept to a minimum and broader dosage targets might be achievable [137], [138].

Several immunomodulatory biologics have been approved for the last 20 years and have significantly benefited patients with autoimmune disorders. However, biologics carry a higher cost of adverse events than traditional therapies [139]. In addition, higher

rates of infections and malignancies have been observed. In the past decade, therapies targeting proinflammatory molecules including interferon-γ, TNF-α, IL-1, IL-6, and granulocyte-macrophage colony-stimulating factor have been developed and are increasingly being adopted in the clinic to treat patients. Effectiveness in the clinic stands in stark contrast to the diseases themselves, as an estimated timescale for the onset of many autoimmune diseases is on the order of weeks to months, and in the case of sepsis, mere hours. For other inflammatory states in which therapies targeting proinflammatory cytokines are often employed—such as Crohn's disease its effectiveness can take weeks or months to become clinically clear. Than for the proinflammatory cytokines of interest from the end of life stimulus to the approval of the last of the therapies targeting it, on average 6 years had passed [140]. There are many diseases for which a better understanding of their molecular underpinnings of the endogenous proinflammatory circulating milieu has failed to translate into dramatically improved therapies, despite transpires that there are no effective pharmacological means of inhibiting to date [141]. On the other hand, anti-bacterial interferon-γ—primarily in the context of vaccination—remains in early-stage development despite the established and intuitive link between interferon-γ and the immune response to intracellular pathogens [142]. Thus, given both the complexity and urgency of immune responses and the myriad reasons for the failures of therapy—aging, lack of increased new molecular entities (NMEs) and an incomplete understanding of the immune response—it is paramount to consider alternatives to inhibiting proinflammatory cytokines as therapies for many diseases [143,144].

7.2 Resistance Mechanisms

Resistance mechanisms in autoimmune diseases often involve complex interactions between cytokines, immune cells, and various signaling pathways that contribute to disease progression and therapeutic challenges. These mechanisms can lead to the evasion of immune surveillance, allowing the persistence of autoreactive cells and exacerbating tissue damage. Understanding the interplay between these factors is crucial for developing targeted therapies. This understanding will enable researchers to identify specific cytokine signaling pathways that can be modulated to enhance therapeutic efficacy and overcome resistance mechanisms that often hinder treatment outcomes [145]. By targeting these pathways, novel therapeutic strategies can be developed that not only address the underlying immune dysregulation but also provide a means to circumvent the adaptive resistance that frequently emerges during treatment. These strategies could enhance the efficacy of existing treatments and reduce the likelihood of relapse, ultimately leading to improved patient outcomes and a better understanding of the complex interplay between cytokines and the immune system in autoimmune diseases [146]. Furthermore, addressing resistance mechanisms can lead to the development of novel therapeutic approaches that target specific cytokine pathways. Such advancements may enable clinicians to tailor treatments more effectively, considering individual patient responses and the unique cytokine profiles associated with different autoimmune diseases. This approach not only enhances the understanding of disease mechanisms but also paves the way for innovative therapeutic strategies that can overcome resistance mechanisms employed by the immune system. Understanding these mechanisms can lead to the development of targeted therapies that specifically inhibit the pathways through which cytokines promote inflammatory responses in autoimmune diseases [147].

8. Future Directions in Research

Cytokines are a group of proteins that are released by specific cells of the immune system and have a specific effect on the interactions and communication between cells. It is believed that cytokines are involved in the cause of many systemic autoimmune disease, especially the long-standing autoimmune diseases. Cytokines play an important role in the pathogenesis of rheumatic diseases through joint destruction. The effects of cytokines on cells and balance play an essential role in vascularization of the synovium.

In this relationship, it is thought that the production of metalloproteinase in the process of activated fibroblastic cells is caused by the increase of economics [127]. Because fibroblastic cells as an activation of metalloproteinase are governed by economics. The removal of cytokines that play a role in this destruction of balance can be provided by releasing a metalloproteinase inhibitor or reducing the release rate of metalloproteinase by the intervention of fibroblastic activation. This inhibitor is mainly secreted by mesenchymal cells and cells that provide support. It contains glycosaminoglycan and protein structure and is leaked in the region of anatomic leakage. Due to its molecular size, chondroitin sulfate is membranous and heals cartilage and in the shape of proteoglycan. Fourteen different glycoproteins, which accumulate and decrease respectively during decay, are determined. Proteoglycan synovial liquid turns into foam-like physical properties. Therefore, it maintains the gas movement and normal distribution of the load in the cartilage. Cytokines disturb these structures and functions and lead to the difficulty of synoviummus glucose movement and decrease in asset synthesis [147], [148].

Several strategies for interleukin (IL)-1 mediated disease modulation have been explored. IL-1 receptor antagonist (IL-1Ra) may act as a physiological brake upon IL-1 by occupying its receptor without up-regulating demonstrable biological consequences. Even in patients with a high IL-1/IL-1Ra glass, durable inhibition of IL-1 by exogenously administered IL-1Ra can transiently improve some downstream inflammatory variables. Anecdotal cases suggest considerable promise in at least one hereditary autoinflammatory syndrome [148]. Anti-hY18 is an anti-IL-1 monoclonal antibody that specifically targets ILp. However, in two small clinical trials, a trend in reduction of disease activity was observed without statistical significance. The absence of a more robust response might relate to sub-optimal dosing or the study of very refractory patient populations. Action upon the IL-1 signaling pathway downstream of the cognate receptor has been complex. Efforts to prohibit the activation of cytoplasmic factors necessary for the processing and nuclear transcriptional activities of IL-1 have not yet acquired meaningful clinical efficacy [149].

8.1 Novel Cytokine Targets

Cytokines mediate a wide variety of immunologic actions and are key effectors in the pathogenesis of several human autoimmune diseases. Their pleiotropic functions and propensity for synergistic interactions render them intriguing therapeutic targets . The notable clinical success that has accompanied the advent of 'targeted biologics' has somewhat tempered predictions that these agents will be displaced by more 'innovative' small molecules. 30 years after its identification, the continued centrality of cytokines to diverse immune-mediated processes is assured. The dizzying array of functions mediated by cytokines ensures that both traditional and 'new generation' cytokines will remain at the fore of translational rheumatology [147], [149].

Dendritic cells, T cells, and B cells can all be considered pivotal actors in early human autoimmune arthritis. Macrophages are arguably the most polyfunctional cell lineage present in the joint. In the context of both rodent and human synovitis, macrophages appear to not only perpetuate inflammation, but also drive disease chronicity. Their longevities, ability to recruit non-activated leukocytes from the bloodstream, and efficacy in presenting antigens and activating T cells all serve to render them key regulators of the progression to maladaptive autoimmunity and bone/cartilage damage [145], [150]. Macrophages are instrumental in determining the topography of cytokine expression in inflamed sites. Prospective analysis of cytokine and transcription factor expression in defined joint regions aides macromolecular definition of the pro-inflammatory milieu's pinpoint location. Far from simply an inactive mechanical scaffold, the joint has, of late, been ascribed a more dynamic role in murine studies. Fibroblast-produced chemo- and lymphokines, when delivered to otherwise unaffected joint cavities, promote chronic synovitis. Fibroblasts have been isolated from human arthritic tissue, which are

competent APCs. Fibroblast lines derived from synovium overlying rheumatoid synovitis express a similar molecular 'trait' in a keratin and macrophage cytologic context. Fibroblasts may themselves act as important immuno-modulators, possibly contributing to synovial lymphoid neogenesis.

8.2 Personalized Medicine Approaches

Cytokines are low molecular weight proteins acting as molecular effectors in the immune system. They regulate the development, maturation, and responses of effector cells. In some cases, ongoing investigations are working to elucidate the functions and therapeutic implications of cytokine-like micro proteins. The identification of novel cytokines, micro proteins, and their immunological functions sheds new light on the mitigating or aggravating role of such cytokines and micro proteins in immunoregulation. In particular, emerging evidence indicates that vitamin D may exert an immunomodulatory effect on autoimmune diseases, particularly for multiple sclerosis, type 1 diabetes, and rheumatoid arthritis [151]. Efforts to develop new agents, which either selectively increase the effects of protective cytokines or micro proteins or, specifically, inhibit pathogenic cytokines may provide potential therapeutic benefits against autoimmune diseases. However, understanding the functions and signaling of cytokines/micro proteins in the immune system is still in its early stage. Substantial efforts in terms of comprehensive investigations are needed before new biological agents for clinical application can be purified. A miRNA negatively regulates the expression of multiple proteins in a modest way, and miRNAs regulate gene expression at the post-transcriptional level [152], [153].

The unique ability of miRNAs to modulate genes translation/mRNA stability and the involvement of miRNAs in the regulation of immune homeostasis, immune tolerance, and immune activation suggest that novel strategies for targeting miRNAs may be useful for potently targeting cytokines as well as for identifying markers with potential prognostic or therapeutic value. For example, the downregulation of some protective miRNAs could lead a cell's hyper-sensitivity to pathogenic stimuli. miRNAs over-expressed in immune cells could contribute to the exaggerated inflammatory response characteristic of autoimmune diseases. Time-course expression of selected miRNA/-146a, -181c, and -155 in LPS-stimulated DCs in the presence or absence of drugs. PTGS and steric blocking are the two mechanisms adopted by the available anti-miRNA drugs to interfere with mature miRNAs [154]. PTGS drugs are short, chemically unmodified oligoribonucleotides designed to perfectly hybridize the mature miRNA. This interaction leads to the formation of an RNA-induced silencing complex, responsible for the silencing of miRNA acting as a guide strand in miRNA-RISC formation. The currently available anti-miRNA drugs are not efficient in exploiting a steric blocking mechanism to sequester miRNAs. It is expected that there will be an increasingly widespread use of these new drugs with relevant therapeutic implications [155].

4. Conclusion

In order to increase the knowledge about the role of miRNAs and RNA binding proteins in the post-transcriptional regulation of cytokines in human macrophages, an unbiased high throughput approach was developed, leveraging on all the flexibility and specificity of the different cell systems and conditions, and increasing the translational relevance using human primary cells. Macrophages can be plastic cells with respect to activation, tuning both effector functions and cytokine profile to modulate the immune response. Indeed, the recent focus of anti-inflammatory strategies is on reprogramming, rather than suppression of activated macrophages. Many examples of targeting cytokine production by manipulating miRNAs have been reported [6]. Post-transcriptional regulation of cytokine expression can occur at many different levels and types of RNA based mechanisms have been described. Despite the recent progress, much is still unknown about the involvement of miRNAs in the cross-talk between TLRs and RNA

binding proteins in up-regulating the expression of cytokines in tolerized macrophages, as well as of the cooperation of RBPs with other RNA based mechanisms of post-transcriptional regulation. Early detection and treatment before the progression to more severe joint damage and physical impairment is a primary goal in RA. The identification and monitoring of serological biomarkers to allow an early diagnosis, a correct patient classification, and to predict the occurrence of a disease, enable also a proper follow-up of the response to therapy. Microribonucleic acids (miRNAs) are a class of small non-coding RNA molecules of about 19-25 nucleotides in length that negatively regulate gene expression at the post-trascriptional level by translational repression, mRNA degradation, or cleavage. miRNAs are present in serum, plasma, and most body fluids, both in free form and enclosed in microvesicles, exosomes, or high density lipoproteins, giving them remarkable stability in comparison with other RNA molecules, and are deregulated in several diseases, in particular in cancer and autoimmune diseases. MiRNAs regulate the expression of many genes. Their tissue specific and temporal action, as well as the ability of the same miRNA to target many different mRNAs lead to an extreme complex pattern of regulation in the context of inflammation. miRNAs target transcripts related to TLRs signaling, cytokine and chemokine production, immune cell maturation, and many other inflammatory processes. In inflammation miRNAs can act both as mediators and effectors, being induced by pro-inflammatory factors and modulating the expression of several inflammatory genes. Deregulation in the expression of miRNAs has been described in several diseases, in particular in cancers and autoimmune diseases. Alterations in the expression of circulating miRNAs occur in patient affected by RA or OA with respect to healthy control or patients affected by different rheumatic diseases and many miRNA have been associated to the pathogenesis or hallmark of inflammation, i.e. miRNA-146, miRNA-155, the let-7, miRNA-16, the miR-17-92, the miR-17-92 cluster, miRNA-203, miRNA-221, the miRNA-223 cluster that is called miR-223 family, and the miRNA-335. Importantly, when RNA analysis isn't feasible due to the sample size limitations, the miRNA-based BMDs could allow estimation of the inflammation involvement in joint disease through the singular analysis of these miRNAs.

Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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