The State of the Immune Status in Rheumatoid Artritis.

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ABSTRACT

A review of the literature on the prognosis of rheumatoid arthtitis, its inflammatory autoimmune disease with articular and systemic effects. Its exact cause is unknown, but genetic and environmental factors are contributory. T cells, B cells. Joint damage begins at the synovial membrane, where the influx and/or local activation of mononuclear cells and the formation of new blood vessels cause synovitis. Antigen-activated CD4(+) T cells amplify the immune response by stimulating other mononuclear cells, synovial fibroblasts, chondrocytes and osteoclasts. Several types of immunomodulatory molecules, mainly cytokines secreted by immune cells, mediate the pathogenesis of RA. Sensitive biomarkers are critical for early detection of disease, as well as for monitoring disease activity and progression. This review aims to discuss the pathogenic role of various immune cells and immunological molecules in RA.

Keywords: Rheumatoid arthritis, autoimmune disease, genetic and environmental factors, biomarker, immune cells, B-cells, T-cells.

Introduction.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that arises more frequently in females than males, being predominantly observed in the elderly. The prevalence rate reported in 2002 ranged from 0.5% to 1% of the population and had regional variation. Clinical manifestations of rheumatoid arthritis appear between the ages of 20 and 40 years, more often in women than in men, with a ratio of 2–3:1 [1] According to the World Health Organization (WHO), within 10 years after the onset of the disease, at least 50% of patients in developed countries cannot work full-time, presumably due to the resulting disability [1]. The annual incidence of RA in Northern Europe and the United States is 0.15–0.6 per 1000, while 0.5–1.0% of the population is affected worldwide [2]. Identified risk factors for the disease are female gender, age, tobacco use, silica exposure, and obesity [2]. The involvement of RA in joints usually has a characteristic presentation with synovitis occurring in symmetrical small joints. Joint swelling is the external reflection of synovial membrane inflammation following immune activation. The normal synovial compartment is infiltrated by leukocytes and the synovial fluid is inundated with pro-inflammatory mediators that interact to produce an inflammatory cascade, which is characterized by the interactions of fibroblast-like synoviocytes (FLSs) with the cells of the innate immune system, including monocytes, macrophages, mast cells, DCs, and so on, as well as cells of adaptive immune system such as T lymphocytes (cell-mediated immunity) and B cells (humoral immunity). The two immune systems and their

interactions are intimately involved in the development of ACPA-positive RA, which results in the failed resolution of inflammation (chronic synovitis). Monocytes/macrophages have been found to massively infiltrate synovial membranes[51] and be central to the pathophysiology of inflammation. Most interest in the contribution of T cells has focused on their antigen-driven role and cytokine release of specific T cell subsets. CD4 effector T cells are major drivers of abnormal immunity in RA by sustaining chronic synovitis and supporting autoantibody production and a lack of reactive oxygen species could boost pro-inflammatory T cells, which shed light on the importance of energy metabolism in RA. As for B cells, the research focuses on their antigen presentation, antibody formation and release, and cytokine release into the milieu. Therefore, better understanding of the mechanisms of disordered innate immunity, including immune complex-mediated complement activation, adaptive immune responses against self-antigens, and abnormal cytokine networks may open up new avenues to restore immunologic homeostasis.

Pathogenic role of immune cells in rheumatoid arthritis.

It is well known that B cells are an important component of human adaptive immunity, but in the case of RA, they also function as one of the main factors in the onset of RA [3]. Autoreactive B cells are B cells that identify host antigens and follow the destruction of such cells or tissues [3]. Autoreactive B cells are usually eliminated by repair mechanisms either during the transition from early immature to immature B lymphocytes in the bone marrow or before B cells become mature naive B cells [4]. Both of these processes are tightly regulated by two immune checkpoints: the central and peripheral B-cell tolerance checkpoints [4]. The central checkpoint of B-cell tolerance is controlled by B-cell growth factors, which regulate B-cell receptor (BCR) and toll-like receptor (TLR) signaling [5]. Peripheral B-cell tolerance involves extrinsic B-cell factors such as regulatory T cells. In RA patients, both checkpoints are usually defective, resulting in a large production of autoreactive mature naive B cells. Mainly B cells, T cells and macrophages play a critical role in the pathogenesis of RA. These cells can either reside in the synovium or circulate in the peripheral blood. T- and B-cell activated macrophages produce various cytokines and chemokines to support joint inflammation. The cytotoxic effect modulates physiological epigenetic processes, which affects gene expression and the determination of the phenotype characteristic of various forms of pathology. IL-6 and TNF are found in the environment of CD4+ T-cells, the AHR receptor (aryl hydrocarbon receptor) is activated. Its presence specifically affects the expression of cytokines characteristic of Th17. A significant increase in the concentration of pro-inflammatory cytokines IL-1, IL-6, TNF-α, etc. in the mother's body in the prenatal period, as well as in the subsequent development of the child's body, affects the differentiation of CD4+ T cells into Th17 lymphocytes during inflammation [6].

In RA, multiple isotypes of antibodies, including IgG, IgA, and IgM, are directed against these citrullinated peptides [7]. The presence of ACPA IgA is consistent with the hypothesis that ACPA is associated with smoking or microbiome dysbiome, since IgA is associated with a mucosal origin of the immune response. The synovial fluid of inflamed RA joints contains citrullinated proteins, suggesting that ACPA may bind to these antigens in the joint and possibly increase local inflammation [8] the putative target protein of ACPA is vimentin. In collagen-induced arthritis (CIA), mouse models of passive transfer of ACPA cannot induce synovitis, although they may worsen pre-existing synovitis [8]. Therefore, it is suggested that multiple hits are necessary for the development of RA. The hypothesis is that autoantibodies may specifically lead to the non-resolution and chronicity of a normally transient immune response, such as following injury or infection.

Genetic and environmental risk factors may lead to an increased rate of post-translational modification (hypercitrullation, hypercarbamylation). Autoantibodies against these post-translational modifications are produced (ACPA), which can activate other

(immune) cells via Fc receptors and stimulate the production of cytokines. The underlying inflammatory cascade eventually leads to clinically apparent arthritis. AMPA anti-modified protein antibodiest.[9]

Conclusion.

As technologies and methodologies begin to advance, there is a rapid interest in understanding the medical treatments for RA. The therapeutic goal of RA has shifted from relieving the symptoms of the disease to stopping the disease processes. In addition to the type of RA treatment, early detection of the disease, method of measuring the disease, classification of the disease, and remission criteria play a critical role in improving patient outcomes. Immune cells, especially B and T lymphocytes, are key components involved in each of the aspects mentioned above. Current evidence suggests that these immune cells could be used as one of the therapeutic approaches for RA, such as T cell and B cell depletion.

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