Autoimmunity is one of the fastest growing fields in medicine. During the last two decades it has turned into a vast forest of new highlights in which one can easily get lost. Planning to enter this forest, one should choose a specific direction to explore. This review focuses on innate immunity and autoimmunity, pregnancy and autoimmunity, Th17 and autoimmunity, and new therapeutic approaches in autoimmune diseases.

The innate immune system is highly involved in the induction of adaptive immune responses against self and non-self-antigens. Toll-like receptors (TLRs) play a leading role in the activation of innate immune cells, thus priming auto-reactive T cells. Th17 cells and related cytokines are widely involved in many immune-mediated diseases such as rheumatoid arthritis. Thus, the recent introduction of anti-IL-17 therapies should be further evaluated. Janus kinase inhibitors and Fc receptor-targeting drugs are some of the new therapeutic strategies that are being implemented when old classical therapies lack sufficient beneficial outcomes.

**ABSTRACT**

Innate and adaptive immune response dysregulations are equally involved in the induction of autoimmunity. Toll-like receptors play a leading role in the activation of innate immune cells, thus priming auto-reactive T cells. Th17 cells and related cytokines are widely involved in many immune-mediated diseases such as rheumatoid arthritis. Thus, the recent introduction of anti-IL-17 therapies should be further evaluated. Janus kinase inhibitors and Fc receptor-targeting drugs are some of the new therapeutic strategies that are being implemented when old classical therapies lack sufficient beneficial outcomes.

**KEY WORDS:** autoimmunity, innate immunity, Th17, pregnancy

**INNATE IMMUNITY AND AUTOIMMUNITY**

The innate immune system is highly involved in the induction of adaptive immune responses against self and non-self-antigens. Toll-like receptors (TLRs) play a leading role in the activation of innate immune cells such as dendritic cells (DCs), thus inducing autoimmune responses by priming autoreactive T cells [1]. The B cell compartment is complex and comprises B cell subsets with innate-like functions, including innate response activator B cells, T-bet positive B cells, natural killer-like B cells, and human self-reactive Vh4-34-expressing B cells.

The issue of the cross talk between innate-like B cells and other adaptive and innate branches is crucial for the development of autoimmune diseases and could become a therapeutic target in down-regulating immune-mediated inflammation [2]. The continuous trigger of DCs by self-antigens enhances B cell activity and autoreactive B cells to increase the production of autoantibodies and pro-inflammatory cytokines. The innate immune system is a complex network such as antigen-presenting cells, the complement cascade, C-reactive protein (CRP), C1q, and Toll-like receptors (TLRs). Among these entire molecules, there is a high expression of TLR-7 and TLR-9 in autoreactive B cells contributing to their expansion, mainly, in systemic lupus erythematosus (SLE). A subset of DCs is identified by tolerogenic properties, thus playing role in maintaining self-tolerance [3].

Toll-like receptors are upstream pattern recognition receptors on both innate and adaptive immune cells. By detecting pathogen associated molecular patterns, they initiate signal transduction, by which the interleukin-1 receptor-associated kinase (IRAK) family mediates activating signals from TLRs. The family includes four members, all of which have a role in either positive or negative regulation of the innate immunity and are implicated in the development of autoimmune diseases. IRAK inhibition has potential therapeutic effects [4]. Natural killer (NK) cell activity is linked to inflammasome activation, having the potential to act in driving inflammation and autoimmunity. In this case, memory-like or adaptive NK cells drive NK cell-mediated autoreactive diseases. However, NK cells, namely, CD56+ are considered important players in suppressing autoimmunity thus considered immune regulators in maintaining peripheral tolerance [5]. The over-activity of the innate immune responses is highly responsible for the evolvement of many autoimmune diseases such as rheumatoid arthritis (RA), SLE, and multiple sclerosis. This response results in damage via the production of pro-inflammatory cytokines, amplifying local inflammation and further activation of additional immune or parenchymal cells the generation of matrix degrading and proteolytic enzymes or reactive oxygen species [6]. Pro-inflammatory cytokines contributing to the development of immune-mediated inflammatory diseases, such as inflammatory bowel diseases (IBD), include interleukin-3 (IL-13). IL-13 is produced by Th2 cells, NK cells, and innate lymphoid cells. In several experimental models, IL-13 was shown to play either pathogenic orprotective role in relation to the different inflammatory status. This finding suggests that targeting IL-13 should be assessed in IBD [7]. Gut microbiota appeared to affect local mucosal homeostasis contributing to the balance between the over activity of immune responses and immune tolerance. Recent evidence pointed to the relationship between gut microbiota and innate immunity, namely the role of gut microbiota, on the function of gut-associated lymphoid tissue, innate lymphoid cells, and phagocytosis. Thus a crosstalk between gut microbiota and innate immunity may contribute to the development of autoimmune diseases [8].

**Natural killer cells are important players in suppressing autoimmunity**
Rheumatic and autoimmune diseases frequently flare during pregnancy and the postpartum period. In addition, active maternal disease prior to conception increases the incidence of exacerbation during pregnancy, such as with SLE, anti-phospholipid syndrome (APS), and RA. As a result, disease activity during pregnancy negatively affects the outcome of pregnancy, including fetal complications [9,10]. Until 4 or 5 decades ago, pregnancy was almost forbidden in young women presenting with autoimmune diseases, mainly SLE. The better understanding of how to approach clinical aspects, such as the anti-phospholipid syndrome, advanced laboratory methods for follow-up, and introduction of new therapeutic approaches such as the safety of not stopping azathioprine (AZA) or hydroxychloroquine (HCQ) during pregnancy, changed the approach of not allowing pregnancy in young SLE women [11]. However, it is still highly advisable to keep SLE patients in maximal remission before conception and to avoid conception in patients with active lupus nephritis. AZA and HCQ are safe therapies during pregnancy and the risk of congenital anomalies in offspring, as well as the infertility risk, is similar to those found in general population. Yet, few studies still show higher incidence of prematurity and lower weight at birth, thus suggesting that large-scale population studies with long-term follow-up are required [12].

Standard laboratory measures of SLE disease activity can be biased during pregnancy. Hormonal changes related to pregnancy may alter laboratory parameters, such as serum complement levels, CRP, and protein electrophoresis. Poor pregnancy outcome is associated with triple or double anti-phospholipid antibodies (aPL) and hypocomplementemia. Triple aPL positivity is defined as the most significant risk factor. Thus, a better understanding of the methods used to assess disease activity during pregnancy may improve clinical follow-up and predict a better outcome. In this respect, optimal combination therapy at preconception or at the beginning of pregnancy, such as low-dose aspirin, folic acid, and vitamin D supplementation, could be beneficial for the management and treatment of obstetrical complications mainly the prevention of thrombosis [13,14]. In women presenting with SLE but without APS, the presence of proteinuria, hypertension, and thrombocytopenia was associated with unfavorable outcome. When these factors were absent, the risk of a poor outcome was very low [15].

In a recent study, type 1 interferon signature (IFN1) signature was found to be significantly higher in patients with primary APS compared to healthy individuals. This signature was associated with the occurrence of thrombosis in a younger age and the development of preeclampsia [16].

**Th17 AND AUTOIMMUNITY**

Th17 cells and their related cytokines (a big family of six related cytokines: IL-A to IL-F) are well known for their pivotal physiological role in host defense against extra-cellular pathogens, injury, and physiological stress. Being pro-inflammatory T-cells, they impact several autoimmune diseases, including RA, psoriatic arthropathy, IBD, and SLE [17]. Results from animal models and SLE patients clearly demonstrate that Th17 and IL-17 are involved in the pathogenesis of SLE. Increased serum levels and tissue expression of IL-17 in involved organs are reported to be associated with increased disease activity, autoantibody production, and immune complex deposition. The disappointing results of many clinical trials and continuous unmet needs suggests that in a subset of SLE patients with an IL-17 driven disease, anti-IL-17 therapy may be a drug of choice [18]. In IBD, both intestinal layers, surface epithelium, and lamina propria are excessively infiltrated with CD4+ T cells. Classically, IBD was considered to be mainly mediated by Th1 and Th2 cells in Crohn’s disease and ulcerative colitis, respectively. However, increased expression of Th17 was also observed in both layers in parallel with increased expression of pro-inflammatory cytokines such as IFN-γ and TNF-α. Th17 cells demonstrate functional plasticity and can be converted into either IFN- producing Th1 cells or regulatory T cells. Insights into their plasticity in inflammatory conditions will allow a better understanding of the pathogenesis of IBD [19,20].

Th17 cells and IL-17 are involved in the pathogenesis of liver diseases by inducing immune cell infiltration and liver damage. This result is followed by hepatic inflammation and fibrosis both of which are classical parameters of autoimmune liver disease. In this case, circulating levels of IL-17 and the number of IL-17 producing cells were increased in chronic immune-mediated liver diseases. This result encourages clinical studies were neutralization of IL-17 may prevent activity and progression of these diseases [21].

**Enhanced IL-17 activity in the kidney drives renal inflammation in many autoimmune diseases. This finding was reported in anti-neutrophil-cytoplasmic antibody (ANCA)-related vasculitis and SLE. Increased peripheral and local IL-17 expression**
was found to be a leading factor in the development of renal damage. Thus, the introduction of anti-IL-17 therapies in these diseases should be further evaluated [22,23].

Increased release of IL-23 and IL-17 was recently shown to be highly relevant for their systemic and local effect on bone tissue in patients with spondyloarthritis. IL-17 has a regulatory role on fibroblasts, osteoblasts, and chondrocytes, thus, contributing to both synovial inflammation and joint destruction [24]. Bollous pemphigoid and pemphigus are two autoimmune blistering diseases involving many pro-inflammatory cells and cytokines. Cytokine alterations include increased serum levels of IL-6 and IL-17 but also in blister fluids [25].

NEW THERAPEUTIC APPROACHES IN AUTOIMMUNE DISEASES

Dozens of on-going treatments for many autoimmune diseases such as SLE, RA, IBD are present in our daily practice. However, many of these treatments lack sufficient therapeutic outcomes and unmet needs are still a challenge [26]. Many new drugs are introduced that aim to achieve better clinical outcomes. Janus kinase inhibitors (JAK inhibitors) are widely used in suppressing autoimmune inflammation in SLE and RA. Currently most of these are pan-JAK inhibitors. However, selective small molecules are being tested in various rheumatic diseases, thus, becoming a relevant therapeutic target [27]. New-generation of Fc receptor-targeting drugs are developed as novel molecules and potential therapeutic alternatives to existing traditional treatments. Of these, recombinant fragment crystallisable multimers targeting Fcγ receptors (FcγRs) are in phase III clinical studies. Neonatal Fc receptor (FcRn)-targeting therapies such as efgartigimod and rozanolixizumab are also being evaluated in on-going clinical studies. In addition, Fc and FcR-targeting therapeutic include medications that target Fc of IgG such as recombinant soluble FcγIb receptor [28]. Stem cell transplantation is continuously assessed as a treatment for severe and end-stage autoimmune diseases such as SLE and systemic sclerosis [29].

CONCLUSIONS

Many other innovative aspects of autoimmunity, such as the role of neutrophils and regulatory cells and molecules, are candidate subjects to be reviewed, thus highlighting the issue of this ever-developing field.

References: