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Investigations of cellular immunity in juvenile idiopathic arthritis

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Abstract

The following was emphasised in an informative, educational issued on the American College of Rheumatology website in April 2017: "About one child in every 1000 develops some type of chronic arthritis. These disorders can affect children at any age, although rarely in the first six months of life. It is estimated that around 300,000 children in the United States have been diagnosed with the condition". Therefore, knowledge of immunological investigations in patients with juvenile idiopathic arthritis is important for finding new treatment pathways. Our aim was to assess the immunological investigations and immune system implications in juvenile idiopathic arthritis. We will discuss: a) the specifically targeted proteins – the citrullinated peptide antibodies; b) non-specifically targeted proteins – heat-shock proteins (anti-HSP60, -65, and -70 antibodies), CLEC16A, inflammasomes, and phagocyte-derived S100; c) interleukins – IL-1, IL-6, IL-10, IL-17, and IL-18; d) innate immunity – macrophage activation syndrome, natural killer cells, complement activity, and immune complexes; and e) therapeutic targets – monoclonal antibodies, JAK inhibitors, and intravenous immune globulin.

Key words: *juvenile idiopathic arthritis, immunopathology, immunological targets.*

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Introduction

The pathological mechanism of autoinflammatory diseases includes the activation of the innate immune system associated with the lack of autoantibody synthesis [1]. The connections between autoinflammation and autoimmunity favour medical means of treating autoinflammatory diseases [2, 3]. Juvenile idiopathic arthritis (JIA) represents the "classic" autoinflammatory disorder [4]. Therefore, an immunological approach of the pathological mechanism in JIA is necessary.

Specifically targeted proteins

Citrullinated peptides (CCP) were specifically targeted in JIA. Hromadnikova *et al*. analysed the presence of IgG anti-CCP antibodies and IgG anti-keratin antibodies in sera of JIA patients at more than one year after diagnosis. Thus, a rare occurrence of anti-CCP was found [5]. Later, Wu *et al*. concluded that the clinical specificity of anti-CCP3 (third generation) was lower than that of the anti-CCP2 assay in JIA diagnosis, due to the cross-reaction in patients with telangiectasia syndrome [6]. Habib *et al*. found that anti-CCP antibodies are correlated with joint erosions in JIA patients ($p = 0.004$) [7]. Anti-CCP antibodies, as non-systemically reacting antibodies, were intensively studied in JIA [8]. Wang *et al*. found a high specificity of 99.0% (95% CI: 98.0-100.0%) of anti-CCP antibody for the diagnosis of JIA [9]. Therefore, CCP are specifically targeted by autoantibodies [10].

Non-specifically targeted proteins

Heat stock proteins

The relationship between bacterial heat shock proteins (HSP) and autoimmunity was first disclosed in the *Mycobacterium bovis* (MB)-induced model of adjuvant arthritis [11]. Zlacka *et al*. studied the frequency of anti-HSP60, -65, and -70 antibodies in the sera of JIA patients. They found that the number of JIA patients (16/209, 7.6%) with elevated anti-HSP65 antibodies was equal to that of the healthy controls (4/50, 8%) [12]. Nguyen *et al*. found that the sera of JIA patients reacted with individual MB-HSP65 fragments P1-163 and P290-534. The levels of these fragments were increased in JIA patients compared to

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the healthy controls [13]. The immune response against self hsp65 in autoimmune arthritis was found to be protective rather than pathogenic [14]. On the other hand, the inhibition of regulatory T (Treg) cells, such as natural Foxp3(+) Treg and self HSP-induced Treg cells, along with a decreased amount of anti-inflammatory cytokine IL-10, results in the loss of immune tolerance [15]. These insights into HSP65 immunity would not only advance our understanding of the disease process in JIA, but also lead to the development of novel therapeutic approaches for autoimmune arthritis [16].

CLEC16A

CLEC16A was not associated with the susceptibility to anti-CCP-positive rheumatoid arthritis (RA) [17]. However, we found a functional link between human CLEC16A variation and the risk of autoimmunity [18].

Inflammasomes

Inflammasomes are multi-protein complexes composed of a NOD-like receptor (NLR)/an AIM-like receptor (ALR), and the adapter molecule apoptosis-associated speck-like protein, which contains a CARD (ASC), and caspase-1. The NOD-like receptor family, pyrin domain containing 1 (NLRP1) haplotypes, contributes to the susceptibility of developing vitiligo. There are other single nucleotide polymorphisms (SNPs) that alter the susceptibility and severity of JIA [19]. Recent studies conclude that inappropriate recognition of cytoplasmic self-DNA by AIM2 contributes to the development of psoriasis, dermatitis, arthritis, and other autoimmune and inflammatory diseases [20].

Phagocyte-derived S100

Phagocyte-derived S100 proteins are valid tools in the diagnosis of autoinflammatory diseases. In addition, these proteins may help to gain a better understanding of the pathophysiology of autoinflammatory disorders such as systemic juvenile idiopathic arthritis (sJIA) [21]. sJIA can be distinguished from other forms of JIA that usually manifest as a milder phenotype. S100 protein complexes enhance the pro-inflammatory phenotype [22].

Interleukins

The efficacy of the interleukin (IL)-1 and IL-6 as inhibiting agents in sJIA was debated [23]. IL-6 plays a significant role in many rheumatological diseases and has been described as both a pro- and anti-inflammatory cytokine [24]. IL-6 is thus crucially involved in the regulation of immune responses, haematopoiesis, and inflammation. When infections and tissue injuries occur, IL-6 is promptly synthesised in order to perform a protective role in the host's defence against stress or trauma. A humanised anti-IL-6 receptor monoclonal antibody has been proven to be outstandingly efficacious against JIA [25]. IL-1 and IL-6 play a major role in the pathogenesis of sJIA, thus the treatment using IL-1 and IL-6 inhibitors has been shown to be highly effective [26]. Tocilizumab (TCZ), a humanised anti-IL-6 receptor antibody, was developed [27]. IL-6 blockers were used in systemic onset JIA. TCZ, the first humanised anti-human IL-6 receptor antibody, inhibits the activity of IL-6 [28]. IL-10 gene polymorphism was associated with susceptibility to JIA. Harsini *et al*. observed no differences in the frequency of alleles, genotypes, and haplotypes of the IL-10 gene between groups of patients and controls [29]. However, Fathy *et al*. found a significant positive association between the IL-10 –1082 AA gene variant and susceptibility to polyarticular juvenile idiopathic arthritis (pJIA) [30]. A statistically significant increase in TNF-α, IFN-γ, IL-10, and IL-17 levels was found in children with JIA [31]. IL-17A was also prevalent in sera from patients with active sJIA, but the pathophysiological role of IL-17 is still unknown [32]. Another interleukin studied in sJIA was IL-18 [33]. Patients with sJIA shared a similar cytokine profile pattern characterised by a significant increase in IL-18 [33]. Myeloid-related protein (MRP) 8, MRP14, S100A12, and IL-18 are already being used as markers for active sJIA. Furthermore, in the case of non-sJIA subtypes, different markers such as HLA-B27, antinuclear-antibodies, RF, erythrocyte sedimentation rate, and C-reactive protein represent a resource for disease classification, prognosis, and activity. Ongoing studies are assessing the clinical role of MRP8, MRP14, and S100A12 [34]. Shimizu *et al*. observed that IL-18 might play a key role in the pathogenesis of macrophage activation syndrome (MAS). A serum IL-18 level greater than 47750 pg/ml might be a useful marker for predicting MAS development [35].

Innate immunity

MAS and natural killer cells

MAS, known as secondary haemophagocytic lymphohistiocytosis, is a complication of many rheumatic diseases, most commonly sJIA [36] – 10% of children with sJIA develop MAS. However, MAS occurs subclinically in another 30-40% [37]. Natural killer (NK) cells are activated early during inflammatory events in order to help shape the ensuing adaptive immune response. De Matos *et al*. concluded that CD94/NKG2A represents a key regulator in the synovial NK-cell cytokine synthesis, resulting in an activated phenotype of synovial NK-cell cytokine [38]. Defects of an unknown cause in the NK cell's cytotoxic capacity are presumed to underlie the pathogenesis of MAS, and they have been detected in sJIA patients [39]. Patients with JIA-ERA (enthesitis related arthritis) have an increased frequency of NK cells (12.89% ±5.65%) compared to healthy controls (9.34% ±3.06%; $p = 0.019$)

and diseased controls (8.81% ±4.73%; $p = 0.01$) [40]. The pathogenesis of MAS may be related to the decrease in NK cell activity. The most consistent immunological abnormality reported in these patients is the impairment of cytotoxic functions. However, the detailed mechanism of this condition, including a clear role of NK cell dysfunction, is still being studied [41].

Complement activity and immune complexes

Complement activity was related to thymocytotoxic activity. The presence of thymocytotoxic activity was tested in synovial fluid obtained from JIA patients [42]. The rheumatoid factor cross-reactive idiotype (RF-CRI) was expressed in high concentrations in the sera of some patients with JIA. However, Bonagura *et al.* found an increased expression of RF-CRI in systemic lupus erythematosus (SLE) patients, which correlated inversely with C3 serum levels ($r = 0.3925$, $p < 0.05$) [43]. Jarvis *et al*. used two methods of sequential column chromatography to purify immune complexes from the synovial fluids of children with JIA. They demonstrated that high molecular weight complexes, containing IgM-RF, have not bound C4 *in vivo*, but activate the classical pathway *in vitro*. In contrast, complexes that have bound C3 *in vivo* do not contain IgM-RF and are weak complement activators *in vitro* [44]. JIA patients have been shown to have high levels of circulating immune complexes (CICs), which are correlated with disease activity. Low *et al*. concluded that JIA CICs might be used as a marker for increased B-cell activity [45]. Data from JIA patients suggested a scenario where different external antigens incite multiple antigen-specific pathways, cytotoxic T-cell responses, activation of the classic complement cascade, and production of pro-inflammatory cytokines [46]. Recent studies have demonstrated that complement activation and the overall levels of immune complexes are correlated with disease activity in JIA, thus indicating their role in the pathophysiology of the disease [47].

Immunological targets

Monoclonal antibodies are (largely) used in the treatment of neoplastic, autoimmune, and inflammatory diseases. Therefore, the clinical applications of monoclonal antibodies have become broader. Monoclonal antibody targets include, among others, CD20, HER-2, EGFR, IL-6 receptor, TNF-α, CD30, VEGF-A, IgE. Examples of immune-mediated and inflammatory diseases that respond to the monoclonal antibody treatment include RA, Crohn's disease, ulcerative colitis, JIA, psoriasis and psoriatic arthritis, Wegener's granulomatosis, microscopic polyangiitis, ankylosing spondylitis (AS), plaque psoriasis, and asthma [48]. Adalimumab, a human monoclonal antibody to tumour necrosis factor alpha (TNF-α), demonstrated efficacy and tolerability in patients suffering from many inflammatory conditions such as RA, psoriatic arthritis, plaque psoriasis, inflammatory bowel diseases, ulcerative colitis, paediatric Crohn's disease, intestinal Behçet's disease, AS, axial spondyloarthritis, and JIA [49]. Adalimumab was initially approved (in 2002) for the treatment of moderate to severe RA. In the following years, its anti-inflammatory properties were applied to the pJIA treatment [50]. CT-P13 became the first monoclonal antibody biosimilar approved by the European Medicines Agency [51]. However, countless medical authorities disagree with the extrapolation of its prescription for JIA, due to its biosimilarity. It has only been tested in two disease models: AS and RA [52]. We have searched for recent/novel monoclonal Ab treatment for JIA in the 2017 literature and found the following: Braun-Moscovici *et al*. evaluated the serum infliximab (IFX) levels and levels of IFX-Ab in the management of rheumatic diseases. The most useful information for therapy was obtained in patients with low IFX levels and low levels of IFX-Ab [53]. Machado *et al*. evaluated the safety of TCZ in the treatment of JIA and found that TCZ was the best therapy for patients with severe forms of sJIA and pJIA, but further laboratory assessments of these patients were needed [54].

The enzymes in the Janus kinase (JAK) family are signalling molecules. JAK inhibitors are novel targets in sJIA [55]. Tofacitinib response, a JAK inhibitor, was studied in JIA [56] and was found to be safe in RA treatment, but it interferes with signal transduction via cytokine receptors using the common γ-chain [57], and clinical trials remain in an early phase [58].

Intravenous immune globulin (IVIG) infusions were effective in alleviating the systemic manifestations of sJIA but were less effective in controlling long-lasting arthritis for more than one year [59]. IVIG is a biologic immune-modulatory agent that operates through various mechanisms. Therefore, IVIG may be considered a potential tool for the treatment of juvenile chronic arthritis [60].

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