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The role of cytokines in juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory joint disease. It is the most frequent connective tissue disease in children and is a cause of various (local and systemic) complications such as limitation of movement ability, chronic uveitis, growth disturbance, anemia etc. (1). JIA is a heterogeneous disease that comprises several characteristic subtypes which differ in clinical course, severity and outcome (1, 2). JIA is an autoimmune disease, but its etiology and pathogenesis are not clearly established. Both environmental factors and genetic predisposition are suggested to contribute to the JIA pathogenesis/appearance.

Cytokines are considered to be the cause in the immunoregulatory disbalance in JIA pathogenesis. Concentrations of IL-1α (Interleukin 1α), IL-6 (Interleukin 6), TNF (Tumor Necrosis Factor) were shown to be elevated in JIA at the systemic level, in addition to their increased concentrations at the local level (3–6). Moreover, blood levels of IL-1β, IL-6, TNF correlated with various (one or more) laboratory and clinical parameters: CRP (C reactive protein), ESR (erythrocyte sedimentation rate), disease activity scores, degree of soft tissue vascularity in oligoarthritis and/or polyarthritis or in systemic arthritis (4, 5, 7, 8). Nevertheless, some authors did not observe increased concentrations of IL-1 (Interleukin 1) and/or TNF, in JIA blood or in synovial fluid (SF) and their correlations with different laboratory parameters (3, 4, 6, 8–10). Th1 cytokine profile was shown at the protein level in SF (11) and in culture supernatants from SF-derived T cell clones (12) as well as at the mRNA level in synovial tissue (13) from JIA patients. In contrast, Murray et al. found Th1, Th2 or mixed profiles in mRNA expression in synovial tissue and SF samples of JIA patients (14).

As compared to JIA, cytokines were more extensively studied in rheumatoid arthritis (RA) of adults and on arthritis mice model. The findings in RA may be helpful to a certain extent to understand the role of different cytokines in arthritis inflammation. Nevertheless, JIA is a distinctively different disease from RA in many respects, which was confirmed by comparative studies on SF and synovial tissue cytokine levels (6, 11, 14). Moreover, JIA subtypes are distinct entities (1), which also were shown to differ at both local (6, 11, 14) and systemic cytokine levels (5, 8).

GM-CSF

Data on GM-CSF (granulocyte-macrophage colony-stimulating factor) in serum of JIA patients are scarce. Yetgin et al. reported no difference in the group of patients with oligo- and polyarthritis (15). Proinflammatory role of GM-CSF was detected in rheumatoid arthritis (RA) of

adults. Atzeni et al. described detectable levels of GM-CSF in SF from RA patients (16). Experiments on methylated bovine serum albumin (mBSA)-induced murine arthritis model demonstrated that systemic administration of GM-CSF resulted in exacerbation of arthritis which included synovial hyperplasia, joint inflammation, appearance of erosive pannus tissue (17). Yetgin et al. found no difference in GM-CSF level between SF of oligo- and polyarthritis patients and serum of JIA patients or healthy children and additionally no relationship between GM-CSF levels and abnormalities in hematopoietic system (15).

Study of SF T cell clones from oligoarthritis patients demonstrated that the most of the clones tested expressed GM-CSF mRNA (12). These data indicate that expression of GM-CSF gene in JIA joint most likely is not down-regulated. Observations of Berckmans et al. (18) suggest that joint microenvironment could be the factor which influence GM-CSF production.

IFN-α and IFN-γ

The study by Gattorno et al. reveals that most SF T cell clones from oligoarthritis released large amount of IFN-γ (interferon-γ) (12, 19). Other authors compared IFN-γ expression in synovial fluid and tissue samples between JIA and RA patients and found no difference in the frequency of IFN-γ mRNA detection [14]. RA patients showed higher IFN-γ mRNA levels (20) and scores for infiltration by IFN-positive cells (21) levels in synovial tissue as compared to patients with other inflammatory arthropathies.

Increased levels of IFN-γ in joint microenvironment may maintain inflammation by activation of tissue macrophages to release inflammatory cytokines, enhancing antigen-presenting capabilities of various cell types, promoting/favouring differentiation of Th1-type cells (12). In addition, IFN-γ overexpression aggravates cartilage destruction and chondrocyte death (22). On the other hand, IFN-γ may inhibit osteoclast formation and bone resorption by influencing osteoclast inhibitory peptide-1 (23). Bakri et al. found correlation of serum IFN-γ with CRP in RA patients (24). Studies of Noda et al. and Aihara et al. showed that treatment with recombinant IFN-γ stimulated production of ANA and increased their titers in serum (25, 26).

IL-1α and IL-1β

Madson et al. reported elevated IL-1α levels in serum from oligo- and polyarticular arthritis (3), while Havemose-Poulsen et al. did not detect differences in IL-1α between healthy control and group of patients with oligo- and polyarthritis (9). In contrast, Rooney et al. reported higher IL-1β (Interleukin 1β) levels in serum from polyarthritis than in systemic arthritis (8).

Yilmaz et al. reported that serum IL-1β levels correlated with CRP and ESR in patients with systemic JIA (7), while other authors did not find such correlation in JIA patients (8). Comparing IL-1α and IL-1β levels in SF from oligoarticular, systemic JIA and RA, de Benedetti et al. detected no differences in IL-1β levels between these groups. SF from oligoarticular, systemic JIA and RA. IL-1α was detectable in 50% of the samples from oligoarticular JIA which significantly differed from systemic JIA (0%) and RA (9%) (6). Kutukculer et al. found higher IL-1α concentrations in children with polyarthritis than in controls (4).

A number of studies showed higher levels of both IL-1α and IL-1β in SF from RA than with other arthropathies (20, 27, 28). De Benedetti et al. found positive correlation of SF IL-1β levels with ESR. There was no correlation of SF IL-1α with ESR in oligoarthritis patients, excluding patients with systemic JIA (6). Immunostaining analysis showed correlation of IL-1β in RA synovium with CRP (29).

This cytokine is involved in synovial inflammation and pannus formation. In addition, IL-1 stimulate production of matrix metalloproteinasis and suppress proteoglican and type II collagen synthesis in synovial cells and chodrocytes resulting in degradation and impaired repair of cartilage. IL-1 stimulate osteoclast activation and differentiation that resulted in bone resorption (30, 31).

IL-2

The data concerning IL-2 (Interleukin 2) in patients with JIA are contradictory. Lepore et al. found IL-2 to be undetectable in serum from patients with JIA (32), while other authors demonstrated elevated serum IL-2 level in oligoarthritis and polyarthritis in comparison to healthy controls (3). Kutukculer et al. found serum IL-2 levels not to be elevated in mixed group from oligo- and polyarthritis patients, both in active and inactive period, as compared with the control group (4). There was no difference in IL-2 production from culture of peripheral blood mononuclear cells (PBMC) between JIA patients and normal controls, and no significant difference between patients with different subtypes [33].

Other authors reported undetectable levels of IL-2 in SF from JIA patients with different subtypes (3, 4). Murray et al. found detectable levels of IL-2 mRNA in mononuclear cells from SF and synovial tissue of JIA patients, with similar frequency in oligo-, polyarticular and systemic subtypes (14). Study of SF T cell clones raised from *in vivo* activated mononuclear cells of oligoarthritis patients showed that most clones tested expressed IL-2 mRNA, but only half of them produced IL-2 in variable amounts (12).

IL-4

Kutukculer et al. reported low concentrations in JIA patients and undetectable levels in controls (4). Percentage of IL-4-producing CD4+ T-cells (intracellular staining) turned out to be lower in JIA patients in comparison to healthy children, but there was no difference between oligo-, polyarticular and systemic arthritis (33). Other authors revealed undetectable IL-4 (Interleukin 4) levels in SF samples from oligoarticular JIA (4), enthesitis-related arthritis and polyarthicular RF-negative JIA (11) and in supernatants from unstimulated SF cell cultures from oligo-JIA (34). Gattorno et al. demonstrated that half of the tested synovial T cell clones from oligoarthritis produced IL-4 in variable amounts (12).

Murray et al. compared the frequency of mRNA expression in synovial tissues and SF samples from children with different JIA subtypes and RA patients and found that IL-4 mRNA was detected more often in oligoarthritis than in polyarthritis or RA, and more often in persistent oligoarthritis than in the extended one (14).

Protective and disease restricting role of IL-4 in RA was shown in studies *in vitr* (35) and on murine models (36). In addition, IL-4 was protective against bone resorption via inhibition IL-11 production by rheumatoid synovial cells (35). Jorgensen et al. showed that IL-4 also reduced rheumatoid cartilage erosion (36). Murray et al. did not confirm the presence of IL-4 mRNA from SF and synovial samples of JIA and RA patients to be predictive for non-erosive disease. However, more frequent co-occurrence of IL-4 and IL-10 mRNA was found in samples from patients with non-erosive disease than in patients with bone erosion or joint space narrowing (14).

IL-10

Havemose-Poulsen et al. reported no difference in IL-10 (Interleukin 10) levels between JIA and healthy individuals (9), while Shahin et al. found serum IL-10 levels to be elevated in JIA patients

(5). Results from studies on stimulated whole blood cultures revealed lowered IL-10 production in cultures from systemic patients (37) and not altered – from a mixed group of oligo- and polyarthritis (9). Moreover, there were elevated IL-10 levels in unstimulated cultures from group of patients with oligo- and polyarthritis (9). Serum of RA patients showed a negative correlation between IL-10 and CRP levels (38).

Scola et al. found unaltered mRNA levels of IL-10 in JIA synovial tissue (13). In the study by Murray et al. the frequency of mRNA expression in SF and synovial tissue samples in patients with different JIA subtype did not differ (14). Expression of IL-10 mRNA by all tested SF T cell clones from oligoarthritis patients was also shown (12). Investigations of RA patients revealed elevated SF IL-10 levels and elevated percentages of IFN-γ and IL-10 expressing CD4+ and CD8+ T cells (39). In contrast, Yudoh et al. found lower frequency of the regulatory CD4+ T cells producing IL-10 (40).

Lowered expression of IL-10 mRNA in synovial membrane in patients with different arthropathies was shown to be associated with joint destruction (41). Finnegan et al. observed development of severe collagen-induced arthritis in IL-10-deficient mice (4). Jorgensen et al. showed that IL-10 inhibited recruitment of mononuclear cells towards synovial tissue (36). In addition, IL-10 was shown to be chondroprotective, as this cytokine inhibited prostaglandin H synthase-2-dependent production of metalloproteinases in macrophages and direct stimulated proteoglican synthesis (42).

IL-12

Gattorno et al. explored IL-12 (Interleukin 12) in serum of JIA patients using two different immunoassays: for IL-12 p70 heterodimer and for total IL-12 (p40 subunit and p70 heterodimer) and serum levels of p40 subunit (calculated as the difference between total IL12 and IL12p70) were higher in patients with oligo-, polyarticular and systemic JIA compared with controls (43).

Scola et al. studied mRNA expression of IL-12p35 in synovial tissue samples from JIA patients and found it to be higher in JIA than non-autoimmune arthropathies (13). Elevated SF IL-12p70 levels were detected in patients with RA [44]. As IL-12 is primarily secreted by antigen-presenting cells including dendritic cells, elevated concentrations of IL-12 in synovial fluids from JIA children could be related to high amounts of dendritic cells in SF of these patients (48, 49).

IL-15

The observations concerning IL-15 (Interleukin 15) levels in systemic arthritis revealed increased serum IL-15 levels in systemic arthritis in comparison with healthy children, but did not detect any difference in IL-15 levels between polyarthritis patients and controls (47, 58). Smolewska et al. found decreased IL-15 levels in patients with oligoarthritis JIA (48), while Cao et al. reported no differences in oligoarthritis patients as compared to controls (47). Smolewska et al. also demonstrated higher IL-15 levels in systemic JIA as compared with oligo- and polyarthritis and also reported correlation of serum IL-15 levels with CRP in JIA patients (48) Elevated levels of IL-15 were reported to be higher also in RA patients (49).

Ruprecht et al. compared SF IL-15 levels between oligoarthritis and poliarthritis patients and found no differences between these groups (50). Scola et al. revealed raised mRNA levels of IL-15 in synovial tissue from JIA patients as compared to non-autoimmune arthropathies and found IL-15-positive cells located largely within perivascular aggregates (13). Studies on IL -15 in RA demonstrated stronger expression of IL-15 mRNA in synovial tissue cells (51) and elevated levels of this cytokine in SF as compared with osteoarthritis (52). In addition, fibroblast-like synoviocytes and synovial macrophages were found to produce IL-15 in culture (51).

Experiments on murine model demonstrated that administration of IL-15Rα (53) or antagonistic protein CRB-15 [54] suppressed the development of collagen-induced arthritis. IL-15 stimulated the proliferation of synovial tissue (51) and SF (55) T cells from RA patients. Mottonen et al. showed that IL-15, but not IL-2, significantly up-regulated expression of CD154, molecule necessary for the activation of T cells and their signal transmitting, on SF and peripheral blood T cells (55). Moreover, Ruprecht et al. demonstrated that *in vitro* IL-15 reduced the suppressive activity of (PB CD4+CD25+) regulatory T cells of JIA patients (50). In addition, IL-15 enhanced proliferation and resistance to apoptosis of cultured fibroblast-like synoviocytes from RA (56). Yang et al. showed that IL-15 may be related to the stabilization of newly formed vascular structures in JIA synovium, since this cytokine stimulates the survival of synovial vascular endothelial cells (57).

TNF

Findings concerning TNF levels are contradictory. Many authors reported elevated levels of TNF in JIA patients (in serum or in PBMC cultures) (4, 5, 9) as compared to healthy children, while others did not (3, 9, 58). De Benedetti et al. reported higher levels in serum from polyarthritis and systemic JIA. They also found TNF levels to be elevated in oligo-JIA, which is in contrast to our results (6).

No differences between these oligo-and polyarthritis groups were reported (4, 60). Yilmaz et al. found no difference between systemic and other JIA subtypes (7), but it is in contrast to the findings of De Benedetti et al., Rooney et al., and Shahin (5) who found higher TNF levels in patients with systemic JIA than in oligo- (6) and polyarthritis (5, 6, 8).

Kutukculer et al. found correlation of serum TNF levels with CRP, but not ESR in patients with oligo- and polyarthritis (4). Other authors did not detect any relationship between serum TNF levels and ESR or CRP values in children with polyarthritis (8) or systemic JIA (6, 8).

TNF is though to be one of the key proinflammatory cytokine in JIA pathogenesis and many authors found higher SF TNF levels in oligo- (4, 60) and polyarthritis (60). Moreover, anti-TNF therapy was shown to be effective in children with JIA (61).

Madson et. al found no increase of TNF in SF in comparison with serum (3). Moreover, some studies on RA are also in agreement with our findings. Canete et al. demonstrated considerable higher levels of IL-1β, but not of TNF (19). Ulfgren et al. detected more cells with IL-1α and IL-1β expression as compared with number of cells with TNF expression from RA synovial membrane (62).

IFN-γ/IL-4 RATIO

Using flow cytometry intracellular staining analysis of cytokine production, Huang et al. found higher ratio of Th1 (IFN-γ producing CD4+)/Th2(IL-4 producing CD4+) cells in peripheral blood of JIA patients than in healthy controls. Authors observed lower percentage of Th2 cells in JIA patients (33). Huang et al. observed no difference in IFN-γ/IL-4 ratio between all three JIA subtypes (33).

Scola et al. observed higher IFN-γ/IL-4 ratio at mRNA level in synovial tissue of JIA patients as compared with non-autoimmune arthropathies (13). Gattorno et al. demonstrated that most of the tested SF T cell clones from oligoarthritis displayed a Th1 profile of cytokine production (ratio IFN-γ/IL4 >10) (12). Higher Th1/Th2 cytokine ratio in synovial tissue was also shown in RA patients (20).

Some authors revealed higher Th1(IFN-γ-producing)/Th2(IL-4-producing) cell ratio in SF from JIA and RA (64) patients as compared to peripheral blood. These data suggest not only local, but also systemic Th1/Th2-type cytokine imbalance toward Th1-type in children with JIA.

CONCLUSIONS

To note, the analysis of literature data shows that findings concerning cytokines in JIA are very often contradictory. The reasons of these disagreements may be following:

1. As internationally recognised ILAR classification was accepted not so long ago, a number of studies on cytokines (4, 6, 15, 33, 43, 60) used other classifications, different in respect to the presence of spondyloarthropathies or rheumatoid factor.

2. Many studies did not define the course of oligoarthritis (persistent or extended) or the presence of RF in polyarthritis (48) or used mixed groups of patients with different JIA subtypes (4).

3. Studies also differed in respect to the treatment applied to patients with JIA at the beginning of the investigation: only NSAID (4, 33, 48); NSAID and/or MTX (50); NSAID and/or MTX or none (48); none or NSAID or DMARD or corticosteroids (11, 60).

4. While in studies on peripheral blood healthy children usually served as controls (6, 46, 48), there were various reference groups in investigations of synovial fluid or tissue from JIA patients: children with fractures (4), RA adult (11), patients with non-autoimmune arthropathies (13), children with spondyloarthropathy (60).

5. There were various experimental procedures (use of serum or plasma, different assays including different detection limits etc.).

6. Polymorphism of some cytokines, e.g. TNF and IL-10, is responsible for wide ranges of concentrations, making the comparison rather complicated.

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SUMMARY

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory joint disease. It is the most frequent connective tissue disease in children and is a cause of various (local and systemic) complications. Differences in the cytokines secretion is considered to be the couse of the immunoregulatory disbalance in JIA pathogenesis. In this review article we focused on the several cytokines (GM-CSF, IFN-α, IFN-γ, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-10, IL-12, IL-15, and TNF) and their role in the pathogenesis, course of disease and treatment of JIA.

Rola cytokin w młodzieńczym idiomatycznym zapaleniu stawów

Młodzieńcze idiopatyczne zapalenie stawów jest przewlekłą chorobą zapalną. Jest to najczęściej spotykana choroba tkanki łącznej u dzieci, przebiegającą z wieloma objawami lokalnymi i ogólnoustrojowymi. Uważa się, iż u podłoża tej choroby leży zaburzenie równowagi immunologicznej, do którego mogą doprowadzać zmiany w wydzielaniu cytokin. W prezentowanym artykule przedstawiano najnowsze wiadomości dotyczące roli cytokin (GM-CSF, IFN-α, IFN-γ, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-10, IL-12, IL-15, and TNF) w patogenezie, rozwoju i leczeniu młodzieńczego idiomatycznego zapalenia stawów.