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Mini review

Cytokine balance and cytokine-driven natural killer cell dysfunction in systemic juvenile idiopathic arthritis

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ABSTRACT

Systemic juvenile idiopathic arthritis (sJIA) is a severe inflammatory childhood disorder, characterized by a specific pattern of systemic features and a typical cytokine profile. Patients are at risk to develop macrophage activation syndrome (MAS), an acute life-threatening condition defined by excessive proliferation and activation of macrophages and T cells. Defects of unknown cause in the natural killer (NK) cell cytotoxic capacity are presumed to underlie the pathogenesis of MAS and have been detected in sJIA patients. Here, we provide an overview of the cytokine profiles in sJIA and related mouse models. We discuss the influence of cytokines on NK cell function, and hypothesize that NK cell dysfunction in sJIA is caused by altered cytokine profiles.

1. Introduction

Juvenile idiopathic arthritis (JIA) denotes a heterogeneous group of arthritic diseases of unknown origin that start before the age of 16 and persist for at least 6 weeks. Together, they represent the most common chronic rheumatic syndrome in childhood. On the basis of number of joints involved and accompanying extra-articular symptoms, 7 different subtypes of JIA are distinguished (for an overview and international classification criteria, see [1]). One of these subtypes is systemic (s)JIA, formerly known as Still's disease. sJIA is one of the most perplexing childhood disorders, exhibiting distinct disease symptoms compared to other forms of JIA. Its distinctive character is expressed by the manifestation of systemic symptoms in combination with chronic arthritis and by the absence of associations with MHC class II alleles. Extra-articular symptoms of sJIA are spiking fever, lymphadenopathy, rash, neutrophilia and thrombocytosis [2,3]. Over the past decades, the knowledge of the pathogenesis of sJIA has profoundly expanded, leading to a better understanding and eventually to better treatment strategies. A striking feature of sJIA is its association with macrophage activation syndrome (MAS). MAS is a severe, potentially life-threatening complication of several systemic inflammatory disorders, but it is most frequently observed in association with sJIA. The disease is characterized by pancytopenia, hepatosplenomegaly, coagulopathy and neurologic involvement [4,5]. The presence of hemophagocytic macrophages in bone marrow aspirates of patients and the close resemblance to a group of histiocytic disorders, collectively known as hemophagocytic lymphohistiocytosis (HLH), has led to the hypothesis of MAS being an HLH variant. HLH comprises two different conditions with comparable clinical presentation: primary or familial HLH (FHL) and secondary or acquired HLH. FHL represents a group of rare, autosomal recessive immune disorders. Secondary or acquired HLH, among which MAS is reckoned, occurs without clear genetic background, in association with any of a range of infectious agents, malignancies or autoimmune diseases [6,7]. An overview of the clinical and laboratory features of sJIA, MAS and FHL is given in Table 1.

Defects in the cytotoxic machinery of lymphocytes and natural killer (NK) cells underlie the symptoms in FHL [6]. The occurrence of comparable defects is well-documented in MAS and has also been reported in sJIA patients [8–10]. Cytotoxic cells are essential to kill infected cells. Defective cytotoxic machinery thus results in prolonged delivery of antigens, leading to excessive proliferation of T cells and macrophages and to escalating production of cytokines. In FHL, the decreased killing capacity originates from mutations in cytotoxicity-related genes. In MAS and sJIA, the decreased NK cell cytotoxicity is rather an acquired defect, presumably resulting from a disrupted cytokine environment [4,11]. In this review, we

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Table 1
Symptoms of sJIA, MAS and FHL.

	sJIA	MAS	FHL
References	[1–3,9,12,100,101]	[4,6,7,9,12,100,102–104]	[6,7,9,104–111]
Incidence	~1/100,000	Unknown	~0.12/100,000
Clinical features			
Fever	Quotidian	Persistent	Persistent
Rash	Evanescent	Petechial/macular	Maculopapular
Mucosal bleeding	–	+	+
Hepatomegaly	+	+	+
Splenomegaly	+	+	+
Lymphadenopathy	+	+	+
Arthritis	+	–	–
Serositis	+	–	–
CNS dysfunction	±	+	+
Laboratory features			
Neutrophil count	↑↑	↓	↓
Platelet count	↑↑	↓	↓
Anemia	+	+	+
ESR	↑↑	Normal or sudden ↓	Normal or ↓
CRP	↑	↑	↑
Bilirubin	Normal	Normal or ↑	↑
ALT/AST	Normal or ↑	↑↑	↑↑
PT	Normal	↑	↑
PTT	Normal	↑	↑
Fibrinogen	↑	↓	↓
Ferritin	Normal or ↑	↑↑	↑↑
D-dimers	↑	↑↑	↑↑
sCD25	Normal or ↑	↑↑	↑↑
Hypoalbuminemia	–	+	+
Hyponatremia	–	+	+
Hypertriglyceridemia	–	+	+
sCD163	Normal or ↑	↑↑	↑↑
NK cell dysfunction	Possible	Frequent	Common
Hemophagocytic macrophages	Possible	Frequent	Very frequent

+, often diagnosed; –, not diagnosed/described; ↑↑, strong increase; ↑, increase; ↓, decrease. Abbreviations: ALT/AST, alanine aminotransferase/aspartate aminotransferase; CNS, central nervous system; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FHL, familial hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; NK, natural killer; PT, prothrombin time; PTT, partial thromboplastin time; sCD, soluble cluster of differentiation; sJIA, systemic juvenile idiopathic arthritis.

provide an overview of cytokines that are differentially expressed in sJIA when compared to healthy controls; we summarize the relation between cytokines and NK cell activity and propose a hypothesis about the influence of the cytokine environment on NK cells in sJIA.

2. Distinct cytokine profile in sJIA patients

The distinct clinical presentation and immunologic abnormalities in sJIA have prompted investigators to consider it as an autoinflammatory rather than an autoimmune disease [2,11]. The absence of HLA associations, the marked neutrophilia and the upregulation of innate immune pathways in gene expression profiles of sJIA patients account for this classification. Moreover, genetic polymorphisms specifically affecting innate immune gene expression have been linked to the disease, and might explain the predisposition of specific children to develop excessive inflammation to certain infectious triggers [2,12]. Classically, autoinflammatory syndromes are characterized by fever and a systemic inflammation, induced by excessive activation of the innate immune system and inappropriately high levels of inflammatory cytokines [13]. Several research groups have demonstrated a characteristic cytokine profile in sJIA, which will be discussed below. Furthermore, mouse models for sJIA (and MAS) emphasize the importance of cytokines with harmful pro-inflammatory potential.

2.1. Cytokine analysis in sJIA patients

Gene expression clusters in leukocytes or peripheral blood mononuclear cells (PBMCs) are indicative of a typical expression profile in sJIA, distinct from that in healthy controls and other subtypes of JIA. This was confirmed at the protein level by analysis of cytokines in the plasma or serum of patients or after *in vitro* stimulation of blood cells. Table 2 summarizes inflammatory cytokines of which the expression has been explored in sJIA. Results concerning the most extensively studied cytokines, *i.e.* interleukin (IL)-1β, IL-6, IL-10, IL-17, IL-18, tumor necrosis factor (TNF)-α and interferon (IFN)-γ, are described in detail.

2.1.1. Interleukin-1β

IL-1β is reputed for driving inflammation in many pathological instances and for mediating bone erosion in rheumatic diseases [13,14]. In sJIA, multiple symptoms can be explained by overexpression of IL-1β, including fever, neutrophilia, thrombocytosis and arthritis [13]. Polymorphisms in genes of the IL-1 family associated with sJIA have been shown for the IL-1 ligand as well as for the IL-1 receptor cluster region [15]. Although some studies demonstrated increased serum levels of IL-1 in patients with sJIA [16–18], most researchers observed an absence of a prominent IL-1 gene expression signature or significant protein levels, which led to controversy about its relevance in the disease [19–26]. Importantly, excessive production of the receptor antagonist of IL-1β was demonstrated in the serum of sJIA patients [16,23,24,27,28]. Nonetheless, a strong indication of the importance of IL-1β in sJIA came from the successful treatment of patients with the IL-1 receptor antagonist anakinra, which resolved clinical symptoms and laboratory abnormalities [26,29,30]. Likewise, clinical trials proved the effectiveness of another IL-1 inhibitor, canakinumab, in a substantial percentage of patients [31]. The over-representation of toll-like receptor (TLR)/IL1R pathway genes in gene expression profiles of sJIA patients further indicated indirectly an important