Clinical Immunology 219 (2020) 108538

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

How autoinflammation may turn into autoimmune inflammation: Insights from monogenetic and complex IL-1 mediated auto-inflammatory diseases

N.M. ter Haar[a,b], M.H.A. Jansen[a], J.F. Frenkel[a], S.J. Vastert[a,b,*]

[a] Department of Pediatric Rheumatology and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Center for Translational Immunology (CTI), University Medical Center Utrecht, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Auto-inflammation
Mechanisms of disease
Auto-immune inflammation

ABSTRACT

IL-1 mediated auto-inflammatory diseases are characterised by episodes of unexplained fever, generalized and localized inflammation. The characteristic symptoms predominantly result from exaggerated activation of innate immune pathways. However, in some patients with typical IL-1 mediated diseases, chronic disease manifestations develop in the absence of acute inflammation, suggesting the involvement of adaptive immune pathways. We discuss clinical observations as well as novel insights in how chronic activation of innate immune pathways can lead to auto-immune disease features in patients with auto-inflammatory diseases and how we need to better understand these sequelae in order to improve treatment strategies.

1. Introduction

The term auto-inflammation was coined in the late nineties of the previous century by McDermott [1], to describe recurrent and seemingly unprovoked fever and inflammation lacking the typical features of classical auto-immune diseases. The first genes associated with monogenetic auto-inflammatory disorders, encoded proteins associated with innate immune cells. It transpired that in this group of inflammatory disorders, innate immune pathways were dysregulated as opposed to auto-immune disease in which adaptive immune pathways are involved. The first group to be identified as hereditary auto-inflammatory diseases were the 'periodic fever syndromes'. These have also been termed 'classical' inflammasomopathies, because overactivation of the IL-1 pathway seems to be the cardinal underlying disease mechanism. However, there is more than one innate response pattern and hence the spectrum of auto-inflammatory diseases has expanded over the past decades, to include, among others, those involving type -1 interferon signalling.

This review focusses on the 'classical' IL-1 mediated inflammasomopathies where previous reviews included type I interferonopathies and complement disorders [2] or focused on systemic Juvenile Idiopathic Arthritis (sJIA) as a specific complex inflammatory disease [3]. The characteristic features of IL-1 mediated inflammasomopathies are recurrent episodes of fever, increased levels of acute phase reactants and signs of organ involvement like lymphadenopathy, arthritis/arthralgia, serositis or mucosal/skin involvement. These clinical manifestations are supposed to result from exaggerated activation of innate immune pathways. In addition, it has become clear that patients with 'classical' auto-inflammatory diseases may develop more chronic disease manifestations that suggest involvement of adaptive immune pathways as well.

We will describe disease mechanisms in monogenetic 'auto-inflammatory diseases Familial Mediterranean Fever, CAPS, TRAPS and Mevalonate Kinase deficiency (MKD) and subsequently how these insights have also impacted recent understanding of complex a multifactorial auto-inflammatory disorders like systemic JIA. We describe the clinical signs of presumed auto-immune involvement in these diseases and discuss the existing evidence and insights of the underlying auto-immune pathways involved in order to increase our understanding how typical auto-inflammation may drive auto-immune pathways.

2. Monogenetic classical auto-inflammatory diseases: mechanisms of disease related to typical auto-inflammatory clinical symptoms

The classical monogenic auto-inflammatory diseases are mediated by exaggerated inflammasome activation and IL-1β production [4]. In short, inflammasomes are complexes of proteins that activate caspases, leading to processing and secretion of active IL-1β and IL-18. The core component of most inflammasomes are proteins of the NOD-like

* Corresponding author at: University Medical Center Utrecht, Wilhelmina Children's Hospital, Department of Pediatric Rheumatology, Lundlaan 6, 3584 EA Utrecht, the Netherlands.
E-mail address: b.vastert@umcutrecht.nl (S.J. Vastert).

https://doi.org/10.1016/j.clim.2020.108538
Received 15 December 2019; Received in revised form 14 June 2020; Accepted 8 July 2020
Available online 15 July 2020
1521-6616/ © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/BY/4.0/).

receptor (NLR) family. These either carry an N-terminal pyrin domain (NLRP) or a caspase-recruitment domain (NLRC). Inflammasomes are rapidly assembled in response to a variety of stimuli, through nucleation of an adaptor protein ASC, harbouring a PYRIN domain as well as a Caspase Activation and Recruitment Domain (CARD). ASC filaments assemble through interaction of their PYRIN domains, bringing CARD domains in close proximity to each other. These subsequently recruit the pro-enzyme pro-caspase I, which undergoes autoproteolysis to yield the active protease Caspase I [5]. Caspase I in turn, is able to cleave the inactive cytokine precursors *pro-IL-1β* and *pro-IL-18* into the active pro-inflammatory cytokines IL-1β and IL-18., Alternative infammasome activation is possible as well, for example in caspase-8 mediated NLRP3 inflammasome activation, though the exact mechanisms behind this have to be elucidated [6].

In the next section, we will summarize typical clinical findings of disease episodes in four of the classical IL-1 mediated *inflammasomopathies*: FMF, MKD, CAPS and TRAPS. Moreover, we will discuss the presumed mechanisms of inflammasome activation in these diseases. We will then discuss examples of auto-immune manifestations in classical IL-1 mediated inflammasomopathies and the presumed mechanisms involved. Conversely, we will address the involvement of innate pathways in typical auto-immune diseases.

3. Familial Mediterranean Fever (FMF): gain-of-function mutations in the pyrin inflammasome

FMF is the most common monogenic auto-inflammatory disease, mainly affecting populations around the Mediterranean sea [7]. Patients with FMF suffer from episodes of fever, serositis, arthritis and skin manifestations and are at risk for development of systemic amyloid A amyloidosis [8]. The prevalence of FMF in Turkey, Armenia and Israel is estimated to be between 1:400 and 1:1000 [7]. FMF is caused by mutations in *MEFV,* which encodes the protein pyrin [9]. The mechanism by which *MEFV*-mutations lead to disease was initially thought to involve to a loss of function of anti-inflammatory function of the pyrin protein, although this could not be supported by a variety of murine studies [4]. Recent studies indicate that FMF-associated *MEFV* mutations (predominantly in exon 10) are actually gain-of-function mutations leading to constitutive activity of the pyrin inflammasome [10,11,12]. Normally, pyrin is only activated when cellular Ras homolog family member A (RhoA) GTPases are inhibited, e.g. by bacterial toxins like the TcdA and TcdB toxin from Clostridium Difficile [12,13]. Once active, pyrin assembles with ASC and pro-caspase 1, inducing activation and secretion of IL-1β and IL-18. Most FMF patients do not have constitutively enhanced autonomous IL-1β signalling or clinical symptoms of inflammation between attacks [14]. The *MEFV* variants associated with increased IL-1β production in response to environmental triggers such as lipopolysaccharide, do not interfere with the production of the regulatory natural antagonist protein IL-1receptor antagonist (IL-1RA), which may explain the observation that the inflammatory episodes resolve spontaneously within 2-3 days [14].

4. Mevalonate Kinase Deficiency (MKD) metabolic defects resulting in pyrin inflammasome activation

The phenotypic spectrum of MKD ranges from a milder phenotype, known as hyper IgD syndrome (HIDS) to a severe form, known as mevalonic aciduria [15]. MKD is characterized by episodes of fever accompanied by gastro-intestinal symptoms, myalgia, arthralgia, skin rash and lymphadenopathy [16]. Additionally, mevalonic aciduria patients exhibit growth retardation and severe neurological and ocular involvement [17]. Albeit a rare disease with less than 500 cases reported worldwide, a disproportionate number of patients are reported from the Netherlands, probably due to a founder mutation (V377I) in the Dutch population [18]. Typically, the inflammatory episodes in MKD last around 4 days [16]. The most prevalent clinical features during a disease episode including fever are: (cervical) lymphadenopathy (~85% of patients), gastro-intestinal symptoms (> 95% of patients), mucocutaneous symptoms (~85% of patients) and musculoskeletal symptoms (~80% of patients, most prominent are arthralgia and myalgia). Most of the affected children (87%) display an episodic disease pattern, whereas a minority of MKD patients suffers from continuous disease activity. Chronic arthritis has been reported in about a quarter of patients and may become erosive [16].

MKD is caused by loss-of-function mutations in *MVK*, which encodes mevalonate kinase. Enzyme activity of mevalonate kinase is severely decreased in patients with MKD [18–20]. The mechanism linking mevalonate kinase enzyme deficiency to inflammation has remained elusive until recently [10,11]. Now it has transpired that decreased mevalonate kinase activity leads to low levels of geranylgeranyl pyrophosphate (GGPP), a downstream molecule of the mevalonate pathway. Less GGPP results in inactivation of RhoA and subsequent activation of the pyrin inflammasome and thus hypersecretion of IL-1β. This explains the therapeutic efficacy of IL-1 blockade in MKD [21–23].

5. Cryopyrin Associated Periodic Syndrome (CAPS): activation of the NLRP3-inflammasome

Gain-of-function mutations in *NLRP3* cause constitutive over-activation of the NLRP3-inflammasome [24]. The conformational changes in the NLRP3 protein of CAPS patients result in enhanced NLRP3-inflammasome assembly and increased production of (especially) IL-1β [25], and as reviewed in 2019the clinical spectrum of CAPS is wide [26], At the 'benign' end of the spectrum, familial cold auto-inflammatory syndrome (FCAS) is characterised by brief self-limiting episodes of fever, rash, and conjunctivitis when exposed to cold. At the other extreme, almost continuously increased IL-1β production within the first year of life results in neonatal onset multisystem inflammatory disorder (NOMID). The disease may be the result of germline mutations but even somatic mosaicism for *NLRP3* gene mutations in myeloid cell lineages can lead to severe disease., Expansion of mutated clones over time may result in later onset of clinical symptoms in patients [27–29].

The NLRP3-inflammasome can be activated by both pathogen-associated molecular patterns (PAMPs) and intrinsic (non-bacterial derived) danger-associated molecular patterns (DAMPs). An example of a PAMP is lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria which elicits strong immune responses via Toll-like receptor (TLR)4. Examples of DAMPs are extracellular ATP and the S100A proteins, the levels of which are strongly elevated in several auto-inflammatory disorders [30,31]. The classical activation of the NLRP3-inflammasome requires two signals [24]. First of all, TLR4-signalling by DAMPs or PAMPs causes NF-κB activation, which leads to production of NLRP3, pro-IL-1β and pro-IL18. A second danger signal, such as extracellular ATP or mitochondrial reactive oxygen species (ROS), leads to the assembly of a multimeric inflammasome complex. This complex includes NLRP3 and the adaptor protein apoptosis-associated speck-like protein containing a ASC. This protein has a CARD domain enabling recruitment of pro-caspase-1, which is subsequently cleaved into the active caspase-1. The result is the cleavage of inactive pro-IL-1β and pro-IL-18 into their active forms. Monocytes of CAPS patients seem to produce more IL-1β after TLR4 stimulation compared to healthy controls, not requiring exogenous ATP [32]. Clinically, CAPS patients display excellent responses to IL-1 signalling blockade [33–35].

6. TRAPS: Endoplasmic reticulum stress leading to auto-inflammation?

TRAPS is a dominantly inherited auto-inflammatory disease, characterized by prolonged episodes of fever (typically 7-14 days), abdominal pain, arthralgia and migratory myalgia and rash. Around 5-10% of TRAPS patients develop (chronic) arthritis as part of their disease [36].

TRAPS is caused by mutations (mostly residing in exon 2-3-4) in *TNFRSF1A*, which leads to conformational changes (misfolding) in the encoded TNF-receptor TNFR1 [1]. The mutated TNFR1 is retained in the endoplasmic reticulum, but the exact mechanism how this leads to inflammation has not completely been elucidated yet [4]. Some mechanisms have been proposed, such as the unfolded protein response and increased mitochondrial ROS production, both leading to activation of JNK and MAPK signalling and subsequent increase in production of pro-inflammatory cytokines like TNFα and IL-1β [37,38]. Furthermore, decreased surface expression of TNFR1 due to mutated TNFR1 might also result in reduced shedding of the exogenous part of the receptor, which functions as a natural antagonist for TNF-α. The observation that TRAPS patients in general have a better response to IL-1 blockade than to TNF-blockade favours a TNF-independent disease mechanism [21,39]. One example of such a mechanism has been proposed to relate to defective autophagy, a pathway involved in the elimination of insoluble intracellular aggregates, linking TRAPS with the TNF-R1-IL-1 signalling cascade [40].

7. How chronic inflammation in classical IL-1 mediated auto-inflammatory diseases may induce adaptive immune pathways

As outlined in the introduction of this review and in the description of the classical IL-1 mediated auto-inflammatory diseases, increased inflammatory responses develop in these monogenetic disorders as a result of gain-of-function mutations or loss-of-function mutations in genes involved in the build-up and activation of inflammasomes. In 2018, Achmet Gul proposed the terms autonomous versus hyperinflammatory states in auto-inflammatory disorders [41]. In the 'hyperinflammatory state' the host will develop enhanced innate immune system dominated inflammatory responses upon a defined trigger. These episodes generally last for days before returning to a normal state without inflammation in between attacks. Examples are the typical episodes of FMF or the milder episodes seen in CAPS, like episodes of familial cold associated auto-inflammatory syndrome (FCAS).Opposed to this phenotype of the 'hyperinflammatory state', is the so called 'autonomous inflammatory state', in which specific gain of function mutations result in continuous production of IL-1β and IL-18, with ongoing inflammatory activity between attacks. For example, patients with the dominantly inherited p.Ser242Arg mutation in exon 2 of *MEFV*, develop a different clinical phenotype than most FMF patients, related to constitutive pyrin-inflammasome activation and continuous IL-1β production. This phenotype has been named pyrin-associated auto-inflammation with neutrophilic dermatosis (PAAND) and is characterised by a chronic course of fever, neutrophilic dermatosis arthralgia/myalgia, pyogenic arthritis, cardiomyopathy and serositis. Phosphorylation of serine at this position is an important regulatory mechanism of pyrin activity, and a missense mutation at this site results in autonomous activation of the pyrin-inflammasome, resulting in persistent (or autonomous) inflammatory disease [13,42]. Interestingly, it has been suggested that a subgroup of FMF patients, with inadequate response to colchicine, display a more "autonomous" phenotype as well, due to (epi-) genetic and/or environmental factors inducing persistent Caspase I activity and subsequent IL-1β production [41]. In some of these patients, the 'autonomous state' may be temporary and blocking the activity of IL-1β by biologic treatment may 'reset' the autonomous production of IL-1β, sometimes resulting in restored response to colchicine [43].

Prolonged elevation of IL-1β and IL-18 in patients with autonomous auto-inflammatory states can also affect T cell differentiation [44,45]. Auto-immune animal models show that IL-1signaling in T cells, when synergizing with IL-6 and IL-23 activation, results in the induction / differentiation of Th17 cells and to Th17 mediated immunopathology [46]. Indeed, in CAPS patients, levels of IL-17 in serum and numbers of Th17 T cells in peripheral blood were increased, and both normalized after the start of IL-1β blockade with Canakinumab, accompanying clinical improvement in these patients [47]. This Th17 polarization in IL-1mediated disease has shown to occur in FMF patients as well [48]. Interestingly, in FMF, up to 3% of the patients will eventually develop often seronegative (HLAB27) spondyloarthropathy, mainly sacroiliitis [49,50].

IL-18 is known as an inducer / activator of type-1 responses in innate cells (like NK cells, macrophages and innate lymphoid cells) as well as adaptive cells (like Th1 and B cells), promoting the release of cytokines like interferon-γ [51]. Already in 2000, it was shown that in conjunction with IL-12, IL-18 is able to enhance Th1 Immune responses [52]. In 2013, Brydges et al elegantly showed a divergence between IL-1 and IL-18 in disease manifestations in murine model of CAPS [53]. By breeding NLRP3 mutations on an IL-18Receptor (IL-18R) knock-out background, they showed that IL-1 and IL-18 mediated pathology occurs at different stages of the disease process [53]. Knocking out the IL18R resulted initially in partial resolution of symptoms including skin and visceral disease in young mice and a normalization of serum cytokines in comparison with the IL-1R knock-out mice. However, aging of the IL-18R knock-out mice led to increased systemic inflammation compared to the IL-1R knock-out mice, indicating that IL-1 drives inflammation earlier in the disease course compared to IL-18. Therefore, one could hypothesize that IL-18 activity might be one of the mechanisms for late residual disease in some CAPS patients on maintenance therapy with IL-1 blockade. In agreement with this, (human) patients with a congenital deficiency of the IL-1 receptor antagonist (DIRA), resulting in life-threatening systemic inflammation with multifocal osteomyelitis, periostitis, and pustulosis, may in turn experience less residual disease as long as adequately being treated with adequate IL-1R-blockade [54].

Finally, new insights in immunological responses have revealed that the innate immune response can induce a sort of immunological memory, now called trained immunity [55], in which a second stimulus with a different pathogen after a first induction of an innate response by an infection or vaccination, can result in a stronger inflammatory response with a broader specificity [56]. This trained immunity involves epigenetic re-programming of innate immune cells by histone modification and metabolic changes in myeloid derived cells [57]. This explains for example how activation of the cholesterol pathway is involved in stimulation of trained immunity in MKD, and how mevalonate is the critical molecule of this pathway inducing epigenetic changes such as H3K4me3 histone modifications in the promoter regions of *TNFA* and *IL6* genes [58]. This environment could then contribute to increased sensitivity for the activation of adaptive immune pathways.

8. (Functional) variants of genes involved in inflammasome activation are associated with both the susceptibility to auto-immune diseases and the subsequent disease course

The interaction of inflammasome-activation and auto-immune pathways is further reflected by the recent findings that multiple functional variants / polymorphisms in inflammasome-related genes have been shown to be associated with disease susceptibility, severity and disease course in multiple diseases that are regarded as typically auto-immune disorders. For example, genetic polymorphisms and functional variants in genes involved in priming of the inflammasome, like P2X(7) and *NLRP1*, seem to be associated with the development of vitiligo [59,60], systemic lupus erythematosus (SLE) [61], rheumatoid arthritis (RA) [62,63] and systemic sclerosis [64,65]. These variants in *NLRP1* have been shown to result in exaggerated IL-1β excretion under resting and activating (LPS stimulation) conditions in cultured monocytes [60].

Moreover, the disease course and response to treatment of complex auto-immune disorders can be linked to specific polymorphisms and/or functional variants in genes for inflammasome components. In RA for example, increased levels in Caspase-I and IL-18 were observed in

patients with active arthritis, prior to the start of anti TNF-treatment (infliximab) [63]. NLRP3-inflammasome-related gene expression (*NLRP3-FL CASP 1, MEFV, ASC*) was upregulated, suggesting increased activity of the NLRP3 inflammasome. Interestingly, the response to anti-TNF treatment (infliximab) was associated as well with a specific SNP in *CARD8* in this study [63].

Altogether, these findings seem to point to a contribution of inflammasome activation in the chronic inflammatory cascades in autoimmune disease.

9. Disease mechanisms in a complex auto-inflammatory diseases: systemic Juvenile Idiopathic Arthritis

Although auto-inflammatory disorders clinically, genetically and immunologically clearly differ from classical auto-immune disorders, the difference is not black and white as many diseases display features of both disorders. To explain this, McGonagle proposed the *immunological disease continuum* in 2009 [66]. Therein, the monogenetic auto-inflammatory disorders are at one end of the spectrum and the classic autoimmune diseases at the other. Intermediate in this continuum are polygenic diseases with prominent auto-inflammatory and/or auto-immune components. SJIA is such a multifactorial auto-inflammatory disease. The disease manifestations and clinical features in sJIA clearly differ from the other subtypes of JIA. Especially early in the disease course, auto-inflammatory pathways seem to underly the clinical characteristics. SJIA is characterized by the presence of prominent systemic inflammatory features, which (may) includes arthritis. There is a typical spiking fever pattern for more than 2 weeks, and at least 1 of the following symptoms: a skin rash, generalised lymphadenopathy, hepatosplenomegaly or serositis [67]. Routine laboratory parameters reflect marked inflammation with increased levels of CRP and ferritin, a raised ESR, thrombocytosis and leucocytosis with neutrophilia. In analogy to how rheumatologists have defined classification criteria for adult onset Still's disease, recently Martini et al have proposed new classification criteria for sJIA, in which now arthritis is not a prerequisite reflecting the notion that systemic inflammation (and not arthritis) is really the cardinal feature of this disease [68].

On a genetic level, polymorphisms in the putative promoter regions of several cytokines have been associated with sJIA [69–74]. In the past decade, the National Institute of Health (NIH) performed a genome-wide association study (GWAS) in a cohort of 770 systemic JIA patients and 6947 healthy controls patients from 9 national patrient cohorts and identifiedgenetic risk loci for sJIA [75]. The consortium investigated 26 single nucleotide polymorphisms (SNPs) in 11 loci that had been previously implicated in sJIA [76]. These loci included plausible contributors to disease biology, including *IL1A/B*, *IL1R2*, *IL10/20*, *IL6*, and *MVK*. However, none of these 26 SNPs were found to be associated with sJIA in the larger cohort. Extending the analysis to other SNPs within these 11 regions, only one locus emerged as significantly associated with systemic JIA risk – *IL1RN*, encoding the IL-1 receptor antagonist (IL-1ra). Intriguingly, the complexity of this disease is underscored by another key observation in this GWAS study: a significant association to HLA-DRB1*11 haplotypes in patients with sJIA [77]. Although this haplotype differs from HLA haplotypes associated with non-systemic JIA, this finding does suggest involvement of adaptive immune pathways in sJIA as well.

The importance of aberrant innate immune responses in the pathophysiology of sJIA is further supported by critical observations in over a decade of translational research as reviewed in 2014 and 2015 [78,79]. Especially in the early phases of sJIA there is prominent innate immune activity and a limited role for adaptive immunity. Specifically the IL-1 pathway and the IL-6 pathway appear to be central in the pathophysiology of sJIA. The strong IL-1 signature in sJIA was first shown by Virginia Pascual in 2005 and since then evidence has amplified that many features of sJIA are IL-1 mediated [30,80–84]. As a translation of these observations, blocking the IL-1 route via recombinant IL-1RA (rIL-1RA, Anakinra) or long acting IL-1 blocking agents (Canakinumab) showed beneficial effects of IL-1 blockade in sJIA even in patients with longstanding steroid resistant disease [85–87].

Especially in the early phase of sJIA, innate immune cells, such as monocytes and neutrophils, are clearly increased in peripheral blood and seem to play a cardinal role in the evolving systemic inflammation [88,89]. These neutrophils display an activated and primed phenotype, resembling neutrophils in the early phase of sepsis [90,91]. Interestingly, natural killer (NK) cells are deficient in both numbers and function, which may contribute to the high risk of developing macrophage activation syndrome (MAS), a well-known dangerous complication of sJIA [92–95]. MAS is less common in patients with classical monogenic auto-inflammatory disorders. However, a clear exception to this is the NLR-family CARD-containing protein 4 (NLCR4) inflammasomopathy, in which a gain of function mutation leads to life-threating inflammation with infantile enterocolitis and episodes of MAS [96]. Interestingly, NLRC-4 patients have levels of IL-18 that are chronically strongly elevated. As IL-18 levels are also very high in (active) sJIA at time of MAS, they seem to play an important role in the development of MAS [95,97–99].

10. Divergence in disease-course in sJIA: window of opportunity for IL-1 blockade early in the disease?

Notwithstanding the central role of the IL-1β pathway in sJIA, it has become clear that not all sJIA patients respond equally well to IL-1 blockade [32,86,100]. This suggests the involvement of more than just IL-1 mediated mechanisms in the disease pathogenesis. In fact, the IL-6 pathway is an important disease mechanisms as well, explaining a variety of clinical characteristics of sJIA and exemplified by excellent clinical responses to therapeutic blockade of IL-6 in many patients [101,102]. The picture arises of a heterogeneous disease with a subset of patients responding to IL-1 directed therapies, a subset responding to IL-6 blockade and a subset remaining unresponsive to both IL-1 and IL-6 blocking modalities

Thus, sJIA seems to be an example of a complex auto-inflammatory IL-1 mediated disease, with IL-6 and IL-18 mediated inflammatory features as well. Interestingly, observations in several case series and 1 prospective cohort study showed that most sJIA patients achieve inactive disease or disease remission when intervened early in the disease with rIL-1RA therapy [89,100,103,104]. These observations support the existence of a so-called 'window of opportunity'. Apparently, at least in a significant subset of sJIA patients, the early phase of this disease is dominated by IL-1 dependent disease mechanisms, and early intervention by (1st line) therapeutic IL-1 blockade, has resulted in excellent clinical outcomes [103–105]. The prospective Dutch cohort study using rIL-1RA therapy as 1st line therapy in a treat-to-target approach, reports excellent disease remission rates also 3-5 years after diagnosis without the need for maintenance therapy in the majority of patients. The rates for chronic arthritis after 3 and 5 years are remarkably low, when compared to pre- rIL-1RA cohorts [104,106–108].

11. Adaptive immune mechanisms in sJIA with a persistent disease course?

Historical cohort studies over the past 30 years have consistently shown that more than half of the children with SJIA have a persistent disease course [109,110]. Indeed, notwithstanding the intriguing response to IL-1 blockade early in the disease course, not all sJIA patients respond equally well to rIL-1RA therapy [86,100,111]. Apparently, the targeted blockade of IL-1 by rIL-1RA is insufficient in a subset of patients to prevent or overcome a perpetuating loop of chronic inflammation.

There are several indications for involvement of auto-immune pathways being relevant in the disease mechanisms of sJIA as well. As

stated before, the GWAS study in sJIA coordinated by NIH, found *HLA-DRB1*11* to be associated with sJIA [77]. In addition, Hugle et al showed in their single center cohort study that many sJIA patients developed positive antinuclear antibodies and rheumatoid factor over time, suggesting triggering of auto-immune pathways during the course of sJIA [112]. Later work of this group indicated involvement of the transcription factors STAT3, STAT4 and BCL6, already present quite early in the disease course [113]. These transcription factors play an important role in T- and B cell differentiation respectively.

Several translational studies have provided evidence for the involvement of the Th17 pathway in the pathophysiology of sJIA, at least in patients with a persisting disease course [114–116]. Similar to what is described in the monogenetic IL-1 mediated inflammasomopathies, several murine studies have shown that activation of the IL-1 and/or IL-18 pathway could contribute to the induction of Th17 cells [46,47,117]. In this respect, the presence of IL-6, which is over-expressed in sJIA [101,118], and IL-23 could be of importance as well [119]. Besides an effect on T cell differentiation, increased IL-1R signalling has shown to stimulate effector functions in Th1, Th2 and Th17 cells [120]. Interestingly, a recent study pointed to a potential role of IL-1 activation in stimulating production of IL-17 by γδT cells in sJIA [115]. Accordingly, another study showed that mice lacking IL-1RA expression (the natural occurring antagonist for IL-1 signalling), develop spontaneous Th17 driven arthritis [121]. Very recently, Henderson et al published data on effector and regulatory T (Treg) cell subsets in patients with different disease courses in sJIA [116]. They sjowed that in sJIA patients in the acute inflammatory course of the disease, Th17 signatures could be predominantly identified in Treg cell populations, whereas in patients with a more chronic disease course, the Th17 signature predominantly resided in effector T cell, but less in Treg populations. Moreover, data from sJIA patients in whom IL-1 blockade was used within the 1st month of the disease, seemed to abolish Th17 expression in Treg, suggesting that chronic exposure to IL-1signaling is a driving factor to Th17 polarisation in sJIA,.

Altogether, persistent activation of both IL-1 and IL-18 pathways might be involved in the perpetuation of inflammation in sJIA, shifting from a primarily innate response in the early phases of disease to a more chronic and complex immune response, including T, B and γδT cells, in (a subset of) chronically affected sJIA patients.

12. Concluding remarks

Translational research in monogenetic and complex inflammatory diseases with a clear auto-inflammatory signature has improved our insight in the disease mechanisms underlying these recurrent and/or chronic inflammatory diseases. Moreover, it has resulted in the successful employment of targeted treatments in both the mono-genetic and complex auto-inflammatory diseases, increasingly in an early phase of the disease in a treat-to-target approach. Current treatment strategies often result in high response rates, certainly when compared to the pre-biologic era. However, it also has become clear that not all patients respond equally well, some loose response over time, and some develop complications and / or a more chronic disease course in which different disease mechanisms, including more adaptive immune pathways seem to play a role. In order to benefit these complex or difficult to treat patients as well, we need to further dissect and target the relevant pathways involved.

Acknowledgements

We acknowledge the financial support of the Dutch Arthritis Society, grant number LLP-10, the Netherlands.

References

[1] M.F. McDermott, I. Aksentijevich, J. Galon, E.M. McDermott, B.W. Ogunkolade, M. Centola, E. Mansfield, M. Gadina, L. Karenko, T. Pettersson, J. McCarthy, D.M. Frucht, M. Aringer, Y. Torosyan, A.M. Teppo, M. Wilson, H.M. Karaarslan, Y. Wan, I. Todd, G. Wood, R. Schlimgen, T.R. Kumarajeewa, S.M. Cooper, J.P. Vella, C.I. Amos, J. Mulley, K.A. Quane, M.G. Molloy, A. Ranki, R.J. Powell, G.A. Hitman, J.J. O'Shea, D.L. Kastner, Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes, Cell. 97 (1999) 133–144, https://doi.org/10.1016/s0092-8674(00)80721-7.

[2] C.M. Hedrich, Shaping the spectrum – From autoinflammation to autoimmunity, Clin. Immunol. 165 (2016) 21–28, https://doi.org/10.1016/j.clim.2016.03.002.

[3] C. Kessel, C.M. Hedrich, D. Foell, Innately adaptive or truly autoimmune, Arthritis Rheumatol. (Hoboken, N.J.). (2019), https://doi.org/10.1002/art.41107.

[4] K. Manthiram, Q. Zhou, I. Aksentijevich, D.L. Kastner, The monogenic autoinflammatory diseases define new pathways in human innate immunity and inflammation, Nat. Immunol. 18 (2017) 832–842, https://doi.org/10.1038/ni.3777.

[5] N. Van Opdenbosch, P. Gurung, L. Vande Walle, A. Fossoul, T.-D. Kanneganti, M. Lamkanfi, Activation of the NLRP1b inflammasome independently of ASC-mediated caspase-1 autoproteolysis and speck formation, Nat. Commun. 5 (2014) 3209, , https://doi.org/10.1038/ncomms4209.

[6] M.M. Gaidt, T.S. Ebert, D. Chauhan, T. Schmidt, J.L. Schmid-Burgk, F. Rapino, A.A.B. Robertson, M.A. Cooper, T. Graf, V. Hornung, Human monocytes engage an alternative inflammasome pathway, Immunity 44 (2016) 833–846, https://doi.org/10.1016/j.immuni.2016.01.012.

[7] E. Ben-Chetrit, I. Touitou, Familial mediterranean fever in the world, Arthritis Rheum. 61 (2009) 1447–1453, https://doi.org/10.1002/art.24458.

[8] S. Ozen, E.D. Batu, S. Demir, Familial Mediterranean fever: recent developments in pathogenesis and new recommendations for management, Front. Immunol. 8 (2017) 253, https://doi.org/10.3389/fimmu.2017.00253.

[9] French FMF Consortium, A candidate gene for familial Mediterranean fever, Nat. Genet. 17 (1997) 25–31, https://doi.org/10.1038/ng0997-25.

[10] M.K. Akula, M. Shi, Z. Jiang, C.E. Foster, D. Miao, A.S. Li, X. Zhang, R.M. Gavin, S.D. Forde, G. Germain, S. Carpenter, C.V. Rosadini, K. Gritsman, J.J. Chae, R. Hampton, N. Silverman, E.M. Gravallese, J.C. Kagan, K.A. Fitzgerald, D.L. Kastner, D.T. Golenbock, M.O. Bergo, D. Wang, Control of the innate immune response by the mevalonate pathway, Nat. Immunol. 17 (2016) 922–929, https://doi.org/10.1038/ni.3487.

[11] Y.H. Park, G. Wood, D.L. Kastner, J.J. Chae, Pyrin inflammasome activation and Rho A signaling in the autoinflammatory diseases FMF and HIDS, Nat. Immunol. 17 (2016) 914–921, https://doi.org/10.1038/ni.3457.

[12] H. Van Gorp, P.H.V. Saavedra, N.M. de Vasconcelos, N. Van Opdenbosch, L. Vande Walle, M. Matusiak, G. Prencipe, A. Insalaco, F. Van Hauwermeiren, D. Demon, D.J. Bogaert, M. Dullaers, E. De Baere, T. Hochepied, J. Dehoorne, K.Y. Vermaelen, F. Haerynck, F. De Benedetti, M. Lamkanfi, Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in Pyrin inflammasome activation, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 14384–14389, https://doi.org/10.1073/pnas.1613156113.

[13] H. Xu, J. Yang, W. Gao, L. Li, P. Li, L. Zhang, Y.-N. Gong, X. Peng, J.J. Xi, S. Chen, F. Wang, F. Shao, Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome, Nature 513 (2014) 237–241, https://doi.org/10.1038/nature13449.

[14] A. Omenetti, S. Carta, L. Delfino, A. Martini, M. Gattorno, A. Rubartelli, Increased NLRP3-dependent interleukin 1beta secretion in patients with familial Mediterranean fever: correlation with MEFV genotype, Ann. Rheum. Dis. 73 (2014) 462–469, https://doi.org/10.1136/annrheumdis-2012-202774.

[15] A. Simon, H.P.H. Kremer, R.A. Wevers, H. Scheffer, J.G. De Jong, J.W.M. Van Der Meer, J.P.H. Drenth, Mevalonate kinase deficiency: evidence for a phenotypic continuum, Neurology. 62 (2004) 994–997, https://doi.org/10.1212/01.wnl.0000115390.33405.f7.

[16] N.M. Ter Haar, J. Jeyaratnam, H.J. Lachmann, A. Simon, P.A. Brogan, M. Doglio, M. Cattalini, J. Anton, C. Modesto, P. Quartier, E. Hoppenreijs, S. Martino, A. Insalaco, L. Cantarini, L. Lepore, M. Alessio, I. Calvo Penades, C. Boros, R. Consolini, D. Rigante, R. Russo, J. Pachlopnik Schmid, T. Lane, A. Martini, N. Ruperto, J. Frenkel, M. Gattorno, The phenotype and genotype of mevalonate kinase deficiency: a series of 114 cases from the Eurofever registry, Arthritis Rheumatol. (Hoboken, N.J.). 68 (2016) 2795–2805, https://doi.org/10.1002/art.39763.

[17] G.F. Hoffmann, C. Charpentier, E. Mayatepek, J. Mancini, M. Leichsenring, K.M. Gibson, P. Divry, M. Hrebicek, W. Lehnert, K. Sartor, Clinical and biochemical phenotype in 11 patients with mevalonic aciduria, Pediatrics 91 (1993) 915–921.

[18] S.M. Houten, C.S. van Woerden, F.A. Wijburg, R.J.A. Wanders, H.R. Waterham, Carrier frequency of the V377I (1129G > A) MVK mutation, associated with Hyper-IgD and periodic fever syndrome, in the Netherlands, Eur. J. Hum. Genet. 11 (2003) 196–200, https://doi.org/10.1038/sj.ejhg.5200933.

[19] J.P. Drenth, L. Cuisset, G. Grateau, C. Vasseur, S.D. van de Velde-Visser, J.G. de Jong, J.S. Beckmann, J.W. van der Meer, M. Delpech, Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group, Nat. Genet. 22 (1999) 178–181, https://doi.org/10.1038/9696.

[20] L. Cuisset, J.P. Drenth, A. Simon, M.F. Vincent, S. van der Velde Visser, J.W. van der Meer, G. Grateau, M. Delpech, Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome, Eur. J. Hum. Genet. 9 (2001) 260–266, https://doi.org/10.1038/sj.ejhg.5200614.

[21] F. De Benedetti, M. Gattorno, J. Anton, E. Ben-Chetrit, J. Frenkel, H.M. Hoffman, I. Kone-Paut, H.J. Lachmann, S. Ozen, A. Simon, A. Zeft, I. Calvo Penades, M. Moutschen, P. Quartier, O. Kasapcopur, A. Shcherbina, M. Hofer, P.J. Hashkes,

J. Van der Hilst, R. Hara, S. Bujan-Rivas, T. Constantin, A. Gul, A. Livneh, P. Brogan, M. Cattalini, L. Obici, K. Lheritier, A. Speziale, G. Junge, Canakinumab for the treatment of autoinflammatory recurrent fever syndromes, N. Engl. J. Med. 378 (2018) 1908–1919, https://doi.org/10.1056/NEJMoa1706314.

[22] J.I. Arostegui, J. Anton, I. Calvo, A. Robles, E. Iglesias, B. Lopez-Montesinos, R. Banchereau, S. Hong, Y. Joubert, G. Junge, V. Pascual, J. Yague, Open-label, phase II study to assess the efficacy and safety of canakinumab treatment in active hyperimmunoglobulinemia D with periodic fever syndrome, Arthritis Rheumatol. (Hoboken, N.J.). 69 (2017) 1679–1688, https://doi.org/10.1002/art.40146.

[23] E.J. Bodar, L.M. Kuijk, J.P.H. Drenth, J.W.M. van der Meer, A. Simon, J. Frenkel, On-demand anakinra treatment is effective in mevalonate kinase deficiency, Ann. Rheum. Dis. 70 (2011) 2155–2158, https://doi.org/10.1136/ard.2011.149922.

[24] M. Lamkanfi, V.M. Dixit, Mechanisms and functions of inflammasomes, Cell. 157 (2014) 1013–1022, https://doi.org/10.1016/j.cell.2014.04.007.

[25] S. Tassi, S. Carta, L. Delfino, R. Caorsi, A. Martini, M. Gattorno, A. Rubartelli, Altered redox state of monocytes from cryopyrin-associated periodic syndromes causes accelerated IL-1beta secretion, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 9789–9794, https://doi.org/10.1073/pnas.1000779107.

[26] L.M. Booshehri, H.M. Hoffman, CAPS and NLRP3, J. Clin. Immunol. 39 (2019) 277–286, https://doi.org/10.1007/s10875-019-00638-z.

[27] M. Saito, R. Nishikomori, N. Kambe, A. Fujisawa, H. Tanizaki, K. Takeichi, T. Imagawa, T. Iehara, H. Takada, T. Matsubayashi, H. Tanaka, H. Kawashima, K. Kawakami, S. Kagami, I. Okafuji, T. Yoshioka, S. Adachi, T. Heike, Y. Miyachi, T. Nakahata, Disease-associated CIAS1 mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients, Blood 111 (2008) 2132–2141, https://doi.org/10.1182/blood-2007-06-094201.

[28] N. Tanaka, K. Izawa, M.K. Saito, M. Sakuma, K. Oshima, O. Ohara, R. Nishikomori, T. Morimoto, N. Kambe, R. Goldbach-Mansky, I. Aksentijevich, G. de Saint Basile, B. Neven, M. van Gijn, J. Frenkel, J.I. Arostegui, J. Yague, R. Merino, M. Ibanez, A. Pontillo, H. Takada, T. Imagawa, T. Kawai, T. Yasumi, T. Nakahata, T. Heike, High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study, Arthritis Rheum. 63 (2011) 3625–3632, https://doi.org/10.1002/art.30512.

[29] Q. Zhou, I. Aksentijevich, G.M. Wood, A.D. Walts, P. Hoffmann, E.F. Remmers, D.L. Kastner, A.K. Ombrello, Brief report: cryopyrin-associated periodic syndrome caused by a myeloid-restricted somatic NLRP3 mutation, Arthritis Rheumatol. (Hoboken, N.J.). 67 (2015) 2482–2486, https://doi.org/10.1002/art.39190.

[30] M. Frosch, M. Ahlmann, T. Vogl, H. Wittkowski, N. Wulffraat, D. Foell, J. Roth, The myeloid-related proteins 8 and 14 complex, a novel ligand of toll-like receptor 4, and interleukin-1beta form a positive feedback mechanism in systemic-onset juvenile idiopathic arthritis, Arthritis Rheum. 60 (2009) 883–891, https://doi.org/10.1002/art.24349.

[31] H. Wittkowski, M. Frosch, N. Wulffraat, R. Goldbach-Mansky, T. Kallinich, J. Kuemmerle-Deschner, M.C. Fruhwald, S. Dassmann, T.-H. Pham, J. Roth, D. Foell, S100A12 is a novel molecular marker differentiating systemic-onset juvenile idiopathic arthritis from other causes of fever of unknown origin, Arthritis Rheum. 58 (2008) 3924–3931, https://doi.org/10.1002/art.24137.

[32] M. Gattorno, S. Tassi, S. Carta, L. Delfino, F. Ferlito, M.A. Pelagatti, A. D'Osualdo, A. Buoncompagni, M.G. Alpigiani, M. Alessio, A. Martini, A. Rubartelli, Pattern of interleukin-1beta secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with CIAS1 mutations, Arthritis Rheum. 56 (2007) 3138–3148, https://doi.org/10.1002/art.22842.

[33] R. Goldbach-Mansky, N.J. Dailey, S.W. Canna, A. Gelabert, J. Jones, B.I. Rubin, H. J. Kim, C. Brewer, C. Zalewski, E. Wiggs, S. Hill, M.L. Turner, B.I. Karp, I. Aksentijevich, F. Pucino, S.R. Penzak, M.H. Haverkamp, L. Stein, B.S. Adams, T.L. Moore, R.C. Fuhlbrigge, B. Shaham, J.N. Jarvis, K. O'Neil, R.K. Vehe, L.O. Beitz, G. Gardner, W.P. Hannan, R.W. Warren, W. Horn, J.L. Cole, S.M. Paul, P.N. Hawkins, T.H. Pham, C. Snyder, R.A. Wesley, S.C. Hoffmann, S.M. Holland, J.A. Butman, D. L. Kastner, Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition., N. Engl. J. Med. 355 (2006) 581–592. doi:https://doi.org/10.1056/NEJMoa055137.

[34] H.M. Hoffman, M.L. Throne, N.J. Amar, M. Sebai, A.J. Kivitz, A. Kavanaugh, S.P. Weinstein, P. Belomestnov, G.D. Yancopoulos, N. Stahl, S.J. Mellis, Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies, Arthritis Rheum. 58 (2008) 2443–2452, https://doi.org/10.1002/art.23687.

[35] H.J. Lachmann, I. Kone-Paut, J.B. Kuemmerle-Deschner, K.S. Leslie, E. Hachulla, P. Quartier, X. Gitton, A. Widmer, N. Patel, P.N. Hawkins, Use of canakinumab in the cryopyrin-associated periodic syndrome, N. Engl. J. Med. 360 (2009) 2416–2425, https://doi.org/10.1056/NEJMoa0810787.

[36] H.J. Lachmann, R. Papa, K. Gerhold, L. Obici, I. Touitou, L. Cantarini, J. Frenkel, J. Anton, I. Kone-Paut, M. Cattalini, B. Bader-Meunier, A. Insalaco, V. Hentgen, R. Merino, C. Modesto, N. Toplak, R. Berendes, S. Ozen, R. Cimaz, A. Jansson, P.A. Brogan, P.N. Hawkins, N. Ruperto, A. Martini, P. Woo, M. Gattorno, The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry, Ann. Rheum. Dis. 73 (2014) 2160–2167, https://doi.org/10.1136/annrheumdis-2013-204184.

[37] A.A. Lobito, F.C. Kimberley, J.R. Muppidi, H. Komarow, A.J. Jackson, K.M. Hull, D.L. Kastner, G.R. Screaton, R.M. Siegel, Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS), Blood 108 (2006) 1320–1327, https://doi.org/10.1182/blood-2005-11-006783.

[38] A.C. Bulua, A. Simon, R. Maddipati, M. Pelletier, H. Park, K.-Y. Kim, M.N. Sack, D.L. Kastner, R.M. Siegel, Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS), J. Exp. Med. 208 (2011) 519–533, https://doi.org/10.1084/jem.20102049.

[39] N. Ter Haar, H. Lachmann, S. Ozen, P. Woo, Y. Uziel, C. Modesto, I. Kone-Paut, L. Cantarini, A. Insalaco, B. Neven, M. Hofer, D. Rigante, S. Al-Mayouf, I. Touitou, R. Gallizzi, E. Papadopoulou-Alataki, S. Martino, J. Kuemmerle-Deschner, L. Obici, N. Iagaru, A. Simon, S. Nielsen, A. Martini, N. Ruperto, M. Gattorno, J. Frenkel, Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review, Ann. Rheum. Dis. 72 (2013) 678–685, https://doi.org/10.1136/annrheumdis-2011-201268.

[40] T. Bachetti, S. Chiesa, P. Castagnola, D. Bani, E. Di Zanni, A. Omenetti, A. D'Osualdo, A. Fraldi, A. Ballabio, R. Ravazzolo, A. Martini, M. Gattorno, I. Ceccherini, Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS)., Ann. Rheum. Dis. 72 (2013) 1044–1052. doi:10.1136/annrheumdis-2012-201952.

[41] A. Gül, Dynamics of inflammatory response in autoinflammatory disorders: autonomous and hyperinflammatory states, Front. Immunol. 9 (2018) 2422, https://doi.org/10.3389/fimmu.2018.02422.

[42] S.L. Masters, V. Lagou, I. Jeru, P.J. Baker, L. Van Eyck, D.A. Parry, D. Lawless, D. De Nardo, J.E. Garcia-Perez, L.F. Dagley, C.L. Holley, J. Dooley, F. Moghaddas, E. Pasciuto, P.-Y. Jeandel, R. Sciot, D. Lyras, A.I. Webb, S.E. Nicholson, L. De Somer, E. van Nieuwenhove, J. Ruuth-Praz, B. Copin, E. Cochet, M. Medlej-Hashim, A. Megarbane, K. Schroder, S. Savic, A. Goris, S. Amselem, C. Wouters, A. Liston, Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation, Sci. Transl. Med. 8 (2016) 332ra45, https://doi.org/10.1126/scitranslmed.aaf1471.

[43] A. Gul, H. Ozdogan, B. Erer, S. Ugurlu, O. Kasapcopur, N. Davis, S. Sevgi, Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever, Arthritis Res. Ther. 17 (2015) 243, , https://doi.org/10.1186/s13075-015-0765-4.

[44] G.J. Martinez, R.I. Nurieva, X.O. Yang, C. Dong, Regulation and function of proinflammatory TH17 cells, Ann. N. Y. Acad. Sci. 1143 (2008) 188–211, https://doi.org/10.1196/annals.1443.021.

[45] Y. Chung, S.H. Chang, G.J. Martinez, X.O. Yang, R. Nurieva, H.S. Kang, L. Ma, S.S. Watowich, A.M. Jetten, Q. Tian, C. Dong, Critical regulation of early Th17 cell differentiation by interleukin-1 signaling, Immunity 30 (2009) 576–587, https://doi.org/10.1016/j.immuni.2009.02.007.

[46] S. Ikeda, S. Saijo, M.A. Murayama, K. Shimizu, A. Akitsu, Y. Iwakura, Excess IL-1 signaling enhances the development of Th17 cells by downregulating TGF-beta-induced Foxp3 expression, J. Immunol. 192 (2014) 1449–1458, https://doi.org/10.4049/jimmunol.1300387.

[47] D. Lasiglie, E. Traggiai, S. Federici, M. Alessio, A. Buoncompagni, A. Accogli, S. Chiesa, F. Penco, A. Martini, M. Gattorno, Role of IL-1 beta in the development of human T(H)17 cells: lesson from NLPR3 mutated patients, PLoS One 6 (2011) e20014, , https://doi.org/10.1371/journal.pone.0020014.

[48] A. Ovadia, A. Livneh, O. Feld, I. Ben-Zvi, E. Kukuy, S. Kivity, M. Lidar, M. Barda-Saad, Y. Shinar, T helper 17 polarization in familial Mediterranean fever, Genes Immun. 14 (2013) 212–216, https://doi.org/10.1038/gene.2013.6.

[49] L. Zhong, H. Song, W. Wang, J. Li, M. Ma, MEFV M694V mutation has a role in susceptibility to ankylosing spondylitis: A meta-analysis, PLoS One. 12 (2017) e0182967, , https://doi.org/10.1371/journal.pone.0182967.

[50] F. Aydin, Z.B. Özçakar, N. Çakar, E. Çelikel, N. Uncu, B. Çelikel Acar, F. Yalçinkaya, Sacroiliitis in children with familial Mediterranean fever, J. Clin. Rheumatol. Pract. Reports Rheum. Musculoskelet. Dis. 25 (2019) 69–73, https://doi.org/10.1097/RHU.0000000000000770.

[51] A. Mantovani, C.A. Dinarello, M. Molgora, C. Garlanda, Interleukin-1 and related cytokines in the regulation of inflammation and immunity, Immunity 50 (2019) 778–795, https://doi.org/10.1016/j.immuni.2019.03.012.

[52] K. Tominaga, T. Yoshimoto, K. Torigoe, M. Kurimoto, K. Matsui, T. Hada, H. Okamura, K. Nakanishi, IL-12 synergizes with IL-18 or IL-1beta for IFN-gamma production from human T cells, Int. Immunol. 12 (2000) 151–160, https://doi.org/10.1093/intimm/12.2.151.

[53] S.D. Brydges, L. Broderick, M.D. McGeough, C.A. Pena, J.L. Mueller, H.M. Hoffman, Divergence of IL-1, IL-18, and cell death in NLRP3 inflammasomopathies, J. Clin. Invest. 123 (2013) 4695–4705, https://doi.org/10.1172/JCI71543.

[54] I. Aksentijevich, S.L. Masters, P.J. Ferguson, P. Dancey, J. Frenkel, A. van Royen-Kerkhoff, R. Laxer, U. Tedgard, E.W. Cowen, T.-H. Pham, M. Booty, J.D. Estes, N.G. Sandler, N. Plass, D.L. Stone, M.L. Turner, S. Hill, J.A. Butman, R. Schneider, P. Babyn, H.I. El-Shanti, E. Pope, K. Barron, X. Bing, A. Laurence, C.-C.R. Lee, D. Chapelle, G.I. Clarke, K. Ohson, M. Nicholson, M. Gadina, B. Yang, B.D. Korman, P.K. Gregersen, P.M. van Hagen, A.E. Hak, M. Huizing, P. Rahman, D.C. Douek, E.F. Remmers, D.L. Kastner, R. Goldbach-Mansky, An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist, N. Engl. J. Med. 360 (2009) 2426–2437, https://doi.org/10.1056/NEJMoa0807865.

[55] M.G. Netea, L.A.B. Joosten, E. Latz, K.H.G. Mills, G. Natoli, H.G. Stunnenberg, L.A. J. O'Neill, R.J. Xavier, Trained immunity: a program of innate immune memory in health and disease, Science. 352 (2016) aaf1098. doi:10.1126/science.aaf1098.

[56] M.G. Netea, J.W.M. van der Meer, Trained immunity: an ancient way of remembering, Cell Host Microbe. 21 (2017) 297–300, https://doi.org/10.1016/j.chom.2017.02.003.

[57] W.M. Song, M. Colonna, Immune training unlocks innate potential, Cell. 172 (2018) 3–5, https://doi.org/10.1016/j.cell.2017.12.034.

[58] S. Bekkering, R.J.W. Arts, B. Novakovic, I. Kourtzelis, C.D.C.C. van der Heijden, Y. Li, C.D. Popa, R. Ter Horst, J. van Tuijl, R.T. Netea-Maier, F.L. van de Veerdonk,

T. Chavakis, L.A.B. Joosten, J.W.M. van der Meer, H. Stunnenberg, N.P. Riksen, M.G. Netea, Metabolic induction of trained immunity through the mevalonate pathway, Cell. 172 (2018) 135–146.e9, https://doi.org/10.1016/j.cell.2017.11.025.

[59] Y. Jin, C.M. Mailloux, K. Gowan, S.L. Riccardi, G. LaBerge, D.C. Bennett, P.R. Fain, R.A. Spritz, NALP1 in vitiligo-associated multiple autoimmune disease, N. Engl. J. Med. 356 (2007) 1216–1225, https://doi.org/10.1056/NEJMoa061592.

[60] C.B. Levandowski, C.M. Mailloux, T.M. Ferrara, K. Gowan, S. Ben, Y. Jin, K.K. McFann, P.J. Holland, P.R. Fain, C.A. Dinarello, R.A. Spritz, NLRP1 haplotypes associated with vitiligo and autoimmunity increase interleukin-1beta processing via the NLRP1 inflammasome, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 2952–2956, https://doi.org/10.1073/pnas.1222808110.

[61] A. Pontillo, M. Girardelli, A.J. Kamada, J.A.T. Pancotto, E.A. Donadi, S. Crovella, P. Sandrin-Garcia, Polimorphisms in inflammasome genes are involved in the predisposition to systemic lupus erythematosus, Autoimmunity 45 (2012) 271–278, https://doi.org/10.3109/08916934.2011.637532.

[62] A. Kastbom, D. Verma, P. Eriksson, T. Skogh, G. Wingren, P. Soderkvist, Genetic variation in proteins of the cryopyrin inflammasome influences susceptibility and severity of rheumatoid arthritis (the Swedish TIRA project), Rheumatology (Oxford) 47 (2008) 415–417, https://doi.org/10.1093/rheumatology/kem372.

[63] R.J. Mathews, J.I. Robinson, M. Battellino, C. Wong, J.C. Taylor, S. Eyre, S.M. Churchman, A.G. Wilson, J.D. Isaacs, K. Hyrich, A. Barton, D. Plant, S. Savic, G.P. Cook, P. Sarzi-Puttini, P. Emery, J.H. Barrett, A.W. Morgan, M.F. McDermott, Evidence of NLRP3-inflammasome activation in rheumatoid arthritis (RA); genetic variants within the NLRP3-inflammasome complex in relation to susceptibility to RA and response to anti-TNF treatment, Ann. Rheum. Dis. 73 (2014) 1202–1210, https://doi.org/10.1136/annrheumdis-2013-203276.

[64] P. Dieude, M. Guedj, J. Wipff, B. Ruiz, G. Riemekasten, M. Matucci-Cerinic, I. Melchers, E. Hachulla, P. Airo, E. Diot, N. Hunzelmann, J. Cabane, L. Mouthon, J.L. Cracowski, V. Riccieri, J. Distler, O. Meyer, A. Kahan, C. Boileau, Y. Allanore, Association of the TNFAIP3 rs5029939 variant with systemic sclerosis in the European Caucasian population, Ann. Rheum. Dis. 69 (2010) 1958–1964, https://doi.org/10.1136/ard.2009.127928.

[65] P. Dieude, M. Guedj, J. Wipff, B. Ruiz, G. Riemekasten, P. Airo, I. Melchers, E. Hachulla, M.M. Cerinic, E. Diot, N. Hunzelmann, P. Caramaschi, J. Sibilia, K. Tiev, L. Mouthon, V. Riccieri, J.L. Cracowski, P.H. Carpentier, J. Distler, Z. Amoura, I. Tarner, J. Avouac, O. Meyer, A. Kahan, C. Boileau, Y. Allanore, NLRP1 influences the systemic sclerosis phenotype: a new clue for the contribution of innate immunity in systemic sclerosis-related fibrosing alveolitis pathogenesis, Ann. Rheum. Dis. 70 (2011) 668–674, https://doi.org/10.1136/ard.2010.131243.

[66] D. McGonagle, A. Aziz, L.J. Dickie, M.F. McDermott, An integrated classification of pediatric inflammatory diseases, based on the concepts of autoinflammation and the immunological disease continuum, Pediatr. Res. 65 (2009) 38R–45R, https://doi.org/10.1203/PDR.0b013e31819dbd0a.

[67] R.E. Petty, T.R. Southwood, P. Manners, J. Baum, D.N. Glass, J. Goldenberg, X. He, J. Maldonado-Cocco, J. Orozco-Alcala, A.M. Prieur, M.E. Suarez-Almazor, P. Woo, International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, edmonton, 2001, J. Rheumatol. 31 (2004) 390–392 doi:0315162X-31-390 [pii].

[68] A. Martini, A. Ravelli, T. Avcin, M.W. Beresford, R. Burgos-Vargas, R. Cuttica, N.T. Ilowite, R. Khubchandani, R.M. Laxer, D.J. Lovell, R.E. Petty, C.A. Wallace, N.M. Wulffraat, A. Pistorio, N. Ruperto, Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus, J. Rheumatol. 46 (2019) 190–197, https://doi.org/10.3899/jrheum.180168.

[69] M.S. Fife, A. Gutierrez, E.M. Ogilvie, C.J. Stock, J.M. Samuel, W. Thomson, L.F. Mack, C.M. Lewis, P. Woo, Novel IL10 gene family associations with systemic juvenile idiopathic arthritis, Arthritis Res. Ther. 8 (2006) R148, https://doi.org/10.1186/ar2041.

[70] F. De Benedetti, C. Meazza, M. Vivarelli, F. Rossi, A. Pistorio, R. Lamb, M. Lunt, W. Thomson, A. Ravelli, R. Donn, A. Martini, B.P.R.S. Group, Functional and prognostic relevance of the -173 polymorphism of the macrophage migration inhibitory factor gene in systemic-onset juvenile idiopathic arthritis, Arthritis Rheum. 48 (2003) 1398–1407, https://doi.org/10.1002/art.10882.

[71] R.P. Donn, E. Shelley, W.E. Ollier, W. Thomson, A novel 5'-flanking region polymorphism of macrophage migration inhibitory factor is associated with systemic-onset juvenile idiopathic arthritis, Arthritis Rheum. 44 (2001) 1782–1785, https://doi.org/10.1002/1529-0131(200108)44:8<1782::AID-ART314>3.0.CO;2-#.

[72] C.J.W. Stock, E.M. Ogilvie, J.M. Samuel, M. Fife, C.M. Lewis, P. Woo, Comprehensive association study of genetic variants in the IL-1 gene family in systemic juvenile idiopathic arthritis, Genes Immun. 9 (2008) 349–357, https://doi.org/10.1038/gene.2008.24.

[73] D. Fishman, G. Faulds, R. Jeffery, V. Mohamed-Ali, J.S. Yudkin, S. Humphries, P. Woo, The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis, J. Clin. Invest. 102 (1998) 1369–1376, https://doi.org/10.1172/JCI2629.

[74] Y. Date, N. Seki, S. Kamizono, T. Higuchi, T. Hirata, K. Miyata, M. Ohkuni, O. Tatsuzawa, S. Yokota, K. Joo, K. Ueda, T. Sasazuki, A. Kimura, K. Itoh, H. Kato, Identification of a genetic risk factor for systemic juvenile rheumatoid arthritis in the 5'-flanking region of the TNFalpha gene and HLA genes, Arthritis Rheum. 42 (1999) 2577–2582, https://doi.org/10.1002/1529-0131(199912)42:12<2577::AID-ANR10>3.0.CO;2-O.

[75] M.J. Ombrello, E. Remmers, A.A. Grom, W. Thomson, A. Martini, M. Gattorno, S. Ozen, S. Prahalad, J.F. Bohnsack, A. Zeft, N.T. Ilowite, E.D. Mellins, R.A.G. Russo, C. Len, S.K. Oliveira, R.S.M. Yeung, L.R. Wedderburn, J.A. Lopez, C. Satorius, I. Tachmazidou, C.D. Langefeld, E. Zeggini, S.D. Thompson, P. Woo, D.L. Kastner, Genome-wide association meta-analysis of eight independent systemic juvenile idiopathic arthritis collections reveals regional association spanning the major histocompatibility complex class II and III gene cluster, Arthritis Rheum. 64 (2012) S1126 http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71000653.

[76] A. Arthur, V.L. Shuldiner, E. Remmers, E.F. Hinks, S. Grom, A. Foell, D. Martini, A. Gattorno, M. Özen, N. Prahalad, S. Zeft, A.S. Bohnsack, J.F. Ilowite, R. Mellins, E.D. Russo, R. Len, C. Oliveira, S. Yeung, J. Rosenberg, A.M. Wedderburn, L.R. Anton, J. Haas, I. Rösen-Wolff, A. Minden, K. Szymanski, A.M.P. Thomson, W. Kastner, D.L. Woo, M. Ombrello, IL1RN variation influences both disease susceptibility and response to human recombinant IL-1RA therapy in systemic juvenile idiopathic arthritis, Arthritis Rheumatol. (2018).

[77] M.J. Ombrello, E.F. Remmers, I. Tachmazidou, A. Grom, D. Foell, J.-P. Haas, A. Martini, M. Gattorno, S. Ozen, S. Prahalad, A.S. Zeft, J.F. Bohnsack, E.D. Mellins, N.T. Ilowite, R. Russo, C. Len, M.O.E. Hilario, S. Oliveira, R.S.M. Yeung, A. Rosenberg, L.R. Wedderburn, J. Anton, T. Schwarz, A. Hinks, Y. Bilginer, J. Park, J. Cobb, C.L. Satorius, B. Han, E. Baskin, S. Signa, R.H. Duerr, J.P. Achkar, M.I. Kamboh, K.M. Kaufman, L.C. Kottyan, D. Pinto, S.W. Scherer, M.E. Alarcon-Riquelme, E. Docampo, X. Estivill, A. Gul, P.I.W. de Bakker, S. Raychaudhuri, C.D. Langefeld, S. Thompson, E. Zeggini, W. Thomson, D.L. Kastner, P. Woo, HLA-DRB1*11 and variants of the MHC class II locus are strong risk factors for systemic juvenile idiopathic arthritis, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 15970–15975, https://doi.org/10.1073/pnas.1520779112.

[78] S. Vastert, B. Prakken, Update on research and clinical translation on specific clinical areas: From bench to bedside: How insight in immune pathogenesis can lead to precision medicine of severe juvenile idiopathic arthritis, Best Pract. Res. Clin. Rheumatol. 28 (2014), https://doi.org/10.1016/j.berh.2014.05.0024.

[79] D. Holzinger, C. Kessel, A. Omenetti, M. Gattorno, From bench to bedside and back again: translational research in autoinflammation, Nat. Rev. Rheumatol. 11 (2015) 573–585, https://doi.org/10.1038/nrrheum.2015.79.

[80] V. Pascual, F. Allantaz, E. Arce, M. Punaro, J. Banchereau, Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade, J. Exp. Med. 201 (2005) 1479–1486, https://doi.org/10.1084/jem.20050473.

[81] F. Allantaz, D. Chaussabel, D. Stichweh, L. Bennett, W. Allman, A. Mejias, M. Ardura, W. Chung, E. Smith, C. Wise, K. Palucka, O. Ramilo, M. Punaro, J. Banchereau, V. Pascual, Blood leukocyte microarrays to diagnose systemic onset juvenile idiopathic arthritis and follow the response to IL-1 blockade, J. Exp. Med. 204 (2007) 2131–2144, https://doi.org/10.1084/jem.20070070.

[82] N. Fall, M. Barnes, S. Thornton, L. Luyrink, J. Olson, N.T. Ilowite, B.S. Gottlieb, T. Griffin, D.D. Sherry, S. Thompson, D.N. Glass, R.A. Colbert, A.A. Grom, Gene expression profiling of peripheral blood from patients with untreated new-onset systemic juvenile idiopathic arthritis reveals molecular heterogeneity that may predict macrophage activation syndrome, Arthritis Rheum. 56 (2007) 3793–3804, https://doi.org/10.1002/art.22981.

[83] C.H. Hinze, N. Fall, S. Thornton, J.Q. Mo, B.J. Aronow, G. Layh-Schmitt, T.A. Griffin, S.D. Thompson, R.A. Colbert, D.N. Glass, M.G. Barnes, A.A. Grom, Immature cell populations and an erythropoiesis gene-expression signature in systemic juvenile idiopathic arthritis: implications for pathogenesis, Arthritis Res. Ther. 12 (2010) R123, https://doi.org/10.1186/ar3061; 10.1186/ar3061.

[84] E.M. Ogilvie, A. Khan, M. Hubank, P. Kellam, P. Woo, Specific gene expression profiles in systemic juvenile idiopathic arthritis, Arthritis Rheum. 56 (2007) 1954–1965, https://doi.org/10.1002/art.22644.

[85] N. Ruperto, H.I. Brunner, P. Quartier, T. Constantin, N. Wulffraat, G. Horneff, R. Brik, L. McCann, O. Kasapcopur, L. Rutkowska-Sak, R. Schneider, Y. Berkun, I. Calvo, M. Erguven, L. Goffin, M. Hofer, T. Kallinich, S.K. Oliveira, Y. Uziel, S. Viola, K. Nistala, C. Wouters, R. Cimaz, M.A. Ferrandiz, B. Flato, M.L. Gamir, I. Kone-Paut, A. Grom, B. Magnusson, S. Ozen, F. Sztajnbok, K. Lheritier, K. Abrams, D. Kim, A. Martini, D.J. Lovell, PRINTO, PRCSG, Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis, N. Engl. J. Med. 367 (2012) 2396–2406, https://doi.org/10.1056/NEJMoa1205099; 10.1056/NEJMoa1205099.

[86] T. Lequerre, P. Quartier, D. Rosellini, F. Alaoui, M. De Bandt, O. Mejjad, I. Kone-Paut, M. Michel, E. Dernis, M. Khellaf, N. Limal, C. Job-Deslandre, B. Fautrel, X. Le Loet, J. Sibilia, S.F. pour la R. et les M.I. en P. (SOFREMIP), C.R. et I. (CRI), Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France, Ann. Rheum. Dis. 67 (2008) 302–308, https://doi.org/10.1136/ard.2007.076034.

[87] S.J. Vastert, Y. Jamilloux, P. Quartier, S. Ohlman, L. Osterling Koskinen, T. Kullenberg, K. Franck-Larsson, B. Fautrel, F. de Benedetti, Anakinra in children and adults with Still's disease, Rheumatology (Oxford) 58 (2019) vi9–vi22, https://doi.org/10.1093/rheumatology/kez350.

[88] F. Gohar, C. Kessel, M. Lavric, D. Holzinger, D. Foell, Review of biomarkers in systemic juvenile idiopathic arthritis: helpful tools or just playing tricks? Arthritis Res. Ther. 18 (2016) 163, , https://doi.org/10.1186/s13075-016-1069-z.

[89] P.A. Nigrovic, Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? Arthritis Rheumatol. (Hoboken, N.J.). 66 (2014) 1405–1413, https://doi.org/10.1002/art.38615.

[90] R.A. Brown, M. Henderlight, T. Do, S. Yasin, A.A. Grom, M. DeLay, S. Thornton, G.S. Schulert, Neutrophils from children with systemic juvenile idiopathic arthritis exhibit persistent proinflammatory activation despite long-standing clinically inactive disease, Front. Immunol. 9 (2018) 2995, https://doi.org/10.3389/fimmu.2018.02995.

[91] N.M. ter Haar, T. Tak, M. Mokry, R.C. Scholman, J.M. Meerding, W. de Jager, A. Verwoerd, D. Foell, T. Vogl, J. Roth, P.H.C. Leliefeld, J. van Loosdregt, L. Koenderman, S.J. Vastert, S. de Roock, Reversal of sepsis-like features of neutrophils by interleukin-1 blockade in patients with systemic-onset juvenile idiopathic arthritis, Arthritis Rheumatol. (2018), https://doi.org/10.1002/art.40442.

[92] A.A. Grom, J. Villanueva, S. Lee, E.A. Goldmuntz, M.H. Passo, A. Filipovich, Natural killer cell dysfunction in patients with systemic-onset juvenile rheumatoid arthritis and macrophage activation syndrome, J. Pediatr. 142 (2003) 292–296, https://doi.org/10.1067/mpd.2003.110.

[93] J. Villanueva, S. Lee, E.H. Giannini, T.B. Graham, M.H. Passo, A. Filipovich, A.A. Grom, Natural killer cell dysfunction is a distinguishing feature of systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome, Arthritis Res. Ther. 7 (2005) R30–R37, https://doi.org/10.1186/ar1453.

[94] K. Put, J. Vandenhaute, A. Avau, A. van Nieuwenhuijze, E. Brisse, T. Dierckx, O. Rutgeerts, J.E. Garcia-Perez, J. Toelen, M. Waer, G. Leclercq, A. Goris, J. Van Weyenbergh, A. Liston, L. De Somer, C.H. Wouters, P. Matthys, Inflammatory gene expression profile and defective interferon-gamma and granzyme K in natural killer cells from systemic juvenile idiopathic arthritis patients, Arthritis Rheumatol. (Hoboken, N.J.). 69 (2017) 213–224, https://doi.org/10.1002/art.39933.

[95] W. De Jager, S.J. Vastert, J.M. Beekman, N.M. Wulffraat, W. Kuis, P.J. Coffer, B.J. Prakken, Defective phosphorylation of interleukin-18 receptor ?? causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis, Arthritis Rheum. 60 (2009) 2782–2793, https://doi.org/10.1002/art.24750.

[96] S.W. Canna, A.A. de Jesus, S. Gouni, S.R. Brooks, B. Marrero, Y. Liu, M.A. DiMattia, K.J.M. Zaal, G.A.M. Sanchez, H. Kim, D. Chapelle, N. Plass, Y. Huang, A. V Villarino, A. Biancotto, T.A. Fleisher, J.A. Duncan, J.J. O'Shea, S. Benseler, A. Grom, Z. Deng, R.M. Laxer, R. Goldbach-Mansky, An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome., Nat. Genet. 46 (2014) 1140–1146. doi:https://doi.org/10.1038/ng.3089.

[97] G. Prencipe, C. Bracaglia, F. De Benedetti, Interleukin-18 in pediatric rheumatic diseases, Curr. Opin. Rheumatol. 31 (2019) 421–427, https://doi.org/10.1097/BOR.0000000000000634.

[98] K. Put, A. Avau, E. Brisse, T. Mitera, S. Put, P. Proost, B. Bader-Meunier, R. Westhovens, B.J. Van den Eynde, C. Orabona, F. Fallarino, L. De Somer, T. Tousseyn, P. Quartier, C. Wouters, P. Matthys, Cytokines in systemic juvenile idiopathic arthritis and haemophagocytic lymphohistiocytosis: tipping the balance between interleukin-18 and interferon-gamma, Rheumatology (Oxford) 54 (2015) 1507–1517, https://doi.org/10.1093/rheumatology/keu524.

[99] E.S. Weiss, C. Girard-Guyonvarc'h, D. Holzinger, A.A. de Jesus, Z. Tariq, J. Picarsic, E.J. Schiffrin, D. Foell, A.A. Grom, S. Ammann, S. Ehl, T. Hoshino, R. Goldbach-Mansky, C. Gabay, S.W. Canna, Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome, Blood. 131 (2018) 1442–1455, https://doi.org/10.1182/blood-2017-12-820852.

[100] P.A. Nigrovic, M. Mannion, F.H. Prince, A. Zeft, C.E. Rabinovich, M.A. van Rossum, E. Cortis, M. Pardeo, P.M. Miettunen, G. Janow, J. Birmingham, A. Eggebeen, E. Janssen, A.I. Shulman, M.B. Son, S. Hong, K. Jones, N.T. Ilowite, R.Q. Cron, G.C. Higgins, Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series, Arthritis Rheum. 63 (2011) 545–555, https://doi.org/10.1002/art.30128; 10.1002/art.30128.

[101] F. De Benedetti, H. Brunner, R. Allen, D. Brown, J. Chaitow, M. Pardeo, G. Espada, B. Flato, G. Horneff, C. Devlin, A. Kenwright, R. Schneider, P. Woo, A. Martini, D. Lovell, N. Ruperto, The efficacy of tocilizumab in patients with systemic juvenile idiopathic arthritis: 52-Week data from a phase 3 clinical trial, Rheumatology (United Kingdom) 51 (2012) iii76 http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70953786.

[102] F. De Benedetti, H.I. Brunner, N. Ruperto, A. Kenwright, S. Wright, I. Calvo, R. Cuttica, A. Ravelli, R. Schneider, P. Woo, C. Wouters, R. Xavier, L. Zemel, E. Baildam, R. Burgos-Vargas, P. Dolezalova, S.M. Garay, R. Merino, R. Joos, A. Grom, N. Wulffraat, Z. Zuber, F. Zulian, D. Lovell, A. Martini, Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis, N. Engl. J. Med. 367 (2012) 2385–2395, https://doi.org/10.1056/NEJMoa1112802.

[103] S.J. Vastert, W. de Jager, B.J. Noordman, D. Holzinger, W. Kuis, B.J. Prakken, N.M. Wulffraat, Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a Prospective Cohort Study, Arthritis Rheumatol. 66 (2014) 1034–1043, https://doi.org/10.1002/art.38296.

[104] N.M. Ter Haar, E.H.P. van Dijkhuizen, J.F. Swart, A. van Royen-Kerkhof, A. El Idrissi, A.P. Leek, W. de Jager, M.C.H. de Groot, S. Haitjema, D. Holzinger, D. Foell, J. van Loosdregt, N.M. Wulffraat, S. de Roock, S.J. Vastert, Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study, Arthritis Rheumatol. (Hoboken, N.J.). 71 (2019) 1163–1173, https://doi.org/10.1002/art.40865.

[105] P.A. Nigrovic, M. Mannion, A.S. Zeft, E.C. Rabinovich, M.A.J. Van Rossum, E. Cortis, M. Pardeo, Anakinra as first-line disease modifying therapy in systemic juvenile idiopathic arthritis report of 46 patients from an international multicenter series, Arthritis Rheum. 62 (2010) 209 http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70380266.

[106] K. Oen, P.N. Malleson, D.A. Cabral, A.M. Rosenberg, R.E. Petty, M. Cheang, Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort, J. Rheumatol. 29 (2002) 1989–1999.

[107] E. Silverman, L. Spiegel, D. Hawkins, R. Petty, D. Goldsmith, L. Schanberg, C. Duffy, P. Howard, V. Strand, Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis, Arthritis Rheum. 52 (2005) 554–562, https://doi.org/10.1002/art.20861.

[108] L.R. Spiegel, R. Schneider, B.A. Lang, N. Birdi, E.D. Silverman, R.M. Laxer, D. Stephens, B.M. Feldman, Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study, Arthritis Rheum. 43 (2000) 2402–2409, https://doi.org/10.1002/1529-0131(200011)43:11<2402::AID-ANR5>3.0.CO;2-C.

[109] J. Guzman, K. Oen, L.B. Tucker, A.M. Huber, N. Shiff, G. Boire, R. Scuccimarri, R. Berard, S.M.L. Tse, K. Morishita, E. Stringer, N. Johnson, D.M. Levy, K.W. Duffy, D.A. Cabral, A.M. Rosenberg, M. Larche, P. Dancey, R.E. Petty, R.M. Laxer, E. Silverman, P. Miettunen, A.-L. Chetaille, E. Haddad, K. Houghton, L. Spiegel, S.E. Turvey, H. Schmeling, B. Lang, J. Ellsworth, S. Ramsey, A. Bruns, S. Campillo, S. Benseler, G. Chedeville, R. Schneider, R. Yeung, C.M. Duffy, The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort, Ann. Rheum. Dis. 74 (2015) 1854–1860, https://doi.org/10.1136/annrheumdis-2014-205372.

[110] F. Fantini, V. Gerloni, M. Gattinara, R. Cimaz, C. Arnoldi, E. Lupi, Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup, J. Rheumatol. 30 (2003) 579–584.

[111] M. Gattorno, A. Piccini, D. Lasiglie, S. Tassi, G. Brisca, S. Carta, L. Delfino, F. Ferlito, M.A. Pelagatti, F. Caroli, A. Buoncompagni, S. Viola, A. Loy, M. Sironi, A. Vecchi, A. Ravelli, A. Martini, A. Rubartelli, The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis, Arthritis Rheum. 58 (2008) 1505–1515, https://doi.org/10.1002/art.23437; 10.1002/art.23437.

[112] B. Hugle, C. Hinze, E. Lainka, N. Fischer, J.-P. Haas, Development of positive antinuclear antibodies and rheumatoid factor in systemic juvenile idiopathic arthritis points toward an autoimmune phenotype later in the disease course, Pediatr. Rheumatol. Online J. 12 (2014) 28, https://doi.org/10.1186/1546-0096-12-28.

[113] B. Hugle, A. Schippers, N. Fischer, K. Ohl, B. Denecke, F. Ticconi, B. Vastert, I.G. Costa, J.-P. Haas, K. Tenbrock, Transcription factor motif enrichment in whole transcriptome analysis identifies STAT4 and BCL6 as the most prominent binding motif in systemic juvenile idiopathic arthritis, Arthritis Res. Ther. 20 (2018) 98, , https://doi.org/10.1186/s13075-018-1603-2.

[114] E. Omoyinmi, R. Hamaoui, A. Pesenacker, K. Nistala, H. Moncrieffe, S. Ursu, L.R. Wedderburn, P. Woo, Th1 and Th17 cell subpopulations are enriched in the peripheral blood of patients with systemic juvenile idiopathic arthritis, Rheumatology (Oxford) 51 (2012) 1881–1886, https://doi.org/10.1093/rheumatology/kes162.

[115] C. Kessel, K. Lippitz, T. Weinhage, C. Hinze, H. Wittkowski, D. Holzinger, N. Fall, A.A. Grom, N. Gruen, D. Foell, Proinflammatory cytokine environments can drive interleukin-17 overexpression by gamma/delta T cells in systemic juvenile idiopathic arthritis, Arthritis Rheumatol. (Hoboken, N.J.). 69 (2017) 1480–1494, https://doi.org/10.1002/art.40099.

[116] L.A. Henderson, K.J. Hoyt, P.Y. Lee, D.A. Rao, A.H. Jonsson, J.P. Nguyen, K. Rutherford, A.M. Julé, L.-M. Charbonnier, S. Case, M.H. Chang, E.M. Cohen, F. Dedeoglu, R.C. Fuhlbrigge, O. Halyabar, M.M. Hazen, E. Janssen, S. Kim, J. Lo, M.S. Lo, E. Meidan, M.B.F. Son, R.P. Sundel, M.L. Stoll, C. Nusbaum, J.A. Lederer, T.A. Chatila, P.A. Nigrovic, Th17 reprogramming of T cells in systemic juvenile idiopathic arthritis, JCI Insight. 5 (2020), https://doi.org/10.1172/jci.insight.132508.

[117] A. Avau, T. Mitera, S. Put, K. Put, E. Brisse, J. Filtjens, C. Uyttenhove, J. Van Snick, A. Liston, G. Leclercq, A.D. Billiau, C.H. Wouters, P. Matthys, Systemic juvenile idiopathic arthritis-like syndrome in mice following stimulation of the immune system with Freund's complete adjuvant: regulation by interferon-gamma, Arthritis Rheumatol. (Hoboken, N.J.). 66 (2014) 1340–1351, https://doi.org/10.1002/art.38359.

[118] P. Pignatti, L. Ciapponi, P. Galle, M.B. Hansen, M. Massa, C. Meazza, G. Paonessa, D. Novick, G. Ciliberto, A. Martini, F. De Benedetti, High circulating levels of biologically inactive IL-6/SIL-6 receptor complexes in systemic juvenile idiopathic arthritis: evidence for serum factors interfering with the binding to gp130, Clin. Exp. Immunol. 131 (2003) 355–363, https://doi.org/10.1046/j.1365-2249.2003.02052.x.

[119] K. Boniface, B. Blom, Y.-J. Liu, R. de Waal Malefyt, From interleukin-23 to T-helper 17 cells: human T-helper cell differentiation revisited, Immunol. Rev. 226 (2008) 132–146, https://doi.org/10.1111/j.1600-065X.2008.00714.x.

[120] A. Jain, R. Song, E.K. Wakeland, C. Pasare, T cell-intrinsic IL-1R signaling licenses effector cytokine production by memory CD4 T cells, Nat. Commun. 9 (2018) 3185, , https://doi.org/10.1038/s41467-018-05489-7.

[121] A. Akitsu, H. Ishigame, S. Kakuta, S.-H. Chung, S. Ikeda, K. Shimizu, S. Kubo, Y. Liu, M. Umemura, G. Matsuzaki, Y. Yoshikai, S. Saijo, Y. Iwakura, IL-1 receptor antagonist-deficient mice develop autoimmune arthritis due to intrinsic activation of IL-17-producing CCR2(+)Vgamma6(+)gammadelta T cells, Nat. Commun. 6 (2015) 7464, , https://doi.org/10.1038/ncomms8464.