DR. CHRISTIAN HEDRICH (Orcid ID : 0000-0002-1295-6179)
DR. DIRK FOELL (Orcid ID : 0000-0002-1946-3916)

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Innately adaptive or truly autoimmune

Is there something unique about systemic JIA?

Christoph Kessel, PhD[1], Christian M Hedrich, MD PhD[2,3], Dirk Foell, MD[1]

[1]Department of Pediatric Rheumatology and Immunology, University of Muenster, Muenster, Germany
[2]Department of Paediatric Rheumatology, Alder Hey Children's Hospital, Liverpool, UK
[3]Department of Women's & Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Corresponding author: Prof. Dirk Foell, Department of Pediatric Rheumatology and Immunology, University of Muenster, Domagkstr. 3, D-48149 Muenster. Germany, Phone ++49-251-8358178, Fax ++49-251-8358104, Email dfoell@uni-muenster.de

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Abstract

Systemic juvenile idiopathic arthritis (sJIA) is a form of arthritis in childhood that is initially dominated by innate driven systemic inflammation and is thus considered a polygenic autoinflammatory disease. However, sJIA can progress towards an adaptive immunity driven afebrile arthritis.

Based on this observation of bi-phasic disease progression, a "window-of-opportunity" for optimal, individualized and target-directed treatment has been proposed. This hypothesis requires testing and in this review we summarize current evidence regarding molecular factors that may contribute to the progression from an initially predominantly autoinflammatory disease phenotype to autoimmune arthritis. We consider the involvement of innately adaptive γδT and NKT cells that express γδ or αβ T cell receptors but can be neither classified as purely innate or adaptive cells, versus classical B and T lymphocytes in this continuum. Finally, we discuss our understanding of how and why some primarily autoinflammatory conditions can progress towards autoimmune-mediated disorders over the disease course while others do not and how this knowledge may be used to offer individualized treatment.

1. Introduction

The concept of autoinflammation was proposed 20 years ago with the characterization of genetic alterations that cause monogenic hereditary fever syndromes (1). Today, at least 8 categories of autoinflammatory diseases have been defined: IL-1β activation disorders (inflammasomopathies), NF-κB activation syndromes, protein misfolding disorders, complement regulatory diseases, cytokine signaling disturbances, macrophage activation syndromes, ubiquitination disorders, and type I interferonopathies (2). Following the historic definition, autoinflammatory disorders are characterized by seemingly unprovoked episodes of systemic or organ-specific inflammation, in the absence of high-titer autoantibodies or self-reactive lymphocyte populations. In a conceptional divide, autoimmunity has historically been seen as the consequence of (isolated) adaptive immune dysregulation. This divide was also applied to polygenic/multifactorial disorders, in which the absence of disease-causing mutations in single genes makes it challenging to identify molecular pathways.

Today, advances in understanding the polygenic autoinflammatory Still's disease or systemic juvenile idiopathic arthritis (SJIA) can provide new insights into the complex bidirectional interplay between innate and adaptive immunity (**figure 1**).

2. Systemic JIA in the conceptual divide of autoinflammation versus autoimmunity

SJIA is the childhood counterpart to adult-onset Still's disease (AOSD) and usually considered a prototypic polygenic autoinflammatory disease (3, 4). About 10% of chronic idiopathic arthritis cases occurring during childhood can be classified as SJIA. Although the name implies the disease to be a systemic variant of juvenile idiopathic arthritis (JIA), and regardless of SJIA being classified as one of seven JIA subtypes according to the International League Against Rheumatism's (ILAR), recent studies indicate SJIA to be fundamentally different to other forms of JIA. Indeed, its unique genetic architecture manifests in a distinct clinical spectrum, indicating that the underlying pathomechanistic pathways significantly differ from other JIA subtypes (5).

Early in disease the clinical presentation of SJIA is dominated by "autoinflammatory features" resembling a classical fever syndrome. Common symptoms comprise quotidian spiking fever accompanied by erythematous rash while arthritis may be minimal or even absent. Further,

hepatosplenomegaly, lymphadenopathy and/or serositis are clinical hallmarks of the disease that separate SJIA from other JIA subtypes (3). During the systemic inflammatory phase SIJA can be complicated by macrophage activation syndrome, a severe hyperinflammatory condition characterized by a "cytokine storm" that can result in multi-organ failure with significant mortality. More recently, an association of SJIA with pulmonary artery hypertension, interstitial lung disease and alveolar proteinosis as severe and mostly fatal complications, potentially resulting from uncontrolled systemic disease activity and inflammation has been recognized (6).

Disease courses in SJIA can be monophasic and self-limiting, polycyclic, or persistent and - if inadequately or not treated - SJIA can progress to a disease mainly characterized by aggressive/destructive arthritis, a feature more typical for autoimmune conditions. Indeed, though no specific autoantibodies have yet been detected, a genetic association of SJIA with the major histocompatibility complex (MHC) class II specific allele, *HLA-DRB1*11* (7) as well as alterations in adaptive immune cell signatures (8), including a skewed ratio of Th1 and Th17 cells (9) and increased IL-17A serum levels (10), suggests an autoimmune component to SJIA (11, 12).

Further indicative evidence for a close interplay between innate and adaptive immune responses is provided by treatment responses. While traditional SJIA therapy was limited to steroidal and non-steroidal anti-inflammatory medication, current treatment regimens mainly rely on drugs interfering with either IL-1 or IL-6 signaling. Therapeutic IL-1 blockade significantly improves disease outcomes (13) and seems particularly effective when initiated as first-line therapy during the systemic disease phase (14-16). In contrast, children with established polyarthritis less likely respond to treatment with recombinant IL-1 receptor antagonist (IL-1Ra; anakinra) (17, 18). Current clinical trial results suggest that these patients may benefit from therapeutic IL-6 receptor (IL-6R) blockade (tocilizumab) instead (19). However, a true head-to-head comparison of drugs interfering with either IL-1 or IL-6 signaling is still lacking.

Taken together, differential response to treatment as well as genetic and immunological findings suggest that dysbalanced expression of innate molecules may link autoinflammation with autoimmunity in SJIA and finally drive autoimmune arthritis on the basis of an initial autoinflammatory disease context (10, 11).

3. Mechanisms linking autoinflammation and autoimmunity in SJIA

3.1 Autoinflammation in SJIA: the role of inflammasome dysregulation

A key observation from the investigation of monogenetic autoinflammatory diseases is their strong association with mutations in genes encoding for proteins involved in inflammasome assembly. Inflammasomes are cytoplasmic multiprotein complexes that can sense a wide range of pathogen- (PAMPs) or danger-associated molecular patterns (DAMPs) (20). Activation of NOD-like receptors (NLRs), NLRP3 (or cryopyrin), NLRP1, NLRC4 or AIM2 (absent in melanoma 2) mediate conformational changes, some of which are allowing for interaction with an inflammasome-adaptor protein, ASC, through pyrin domains (PYD) (20). Once assembled, ASC binds pro-caspase 1 through its caspase recruitment domain (CARD) and assists in assembly and caspase 1 activation, which, in turn, cleaves inactive pro-IL-1β and pro-IL-18 and activates the cytosolic protein gasdermin D (GSDMD) (21). Cleaved GSDMD forms pores in the plasma membrane, which induces pyroptotic cell death and permits the release of mature IL-1β and IL-18 to the extracellular space (22). Prototypic autoinflammatory diseases, such as Familial Mediterranean Fever (FMF) or cryopyrin-associated periodic syndrome (CAPS), are associated with mutations in *MEFV* (encoding pyrin) or *NLRP3*. Aberrant inflammasome activation results in excessive IL-1β and/or IL-18 processing. Consequently, drugs such as colchicine as specific inhibitor of the pyrin inflammasome can interfer with cytokine release and thus alleviate clinical symptoms of systemic inflammation in individuals affected (23).

Though a large proportion of SJIA patients benefit from IL-1 blocking therapy, to our knowledge, gain-of-function inflammasome polymorphisms in SJIA have not been reported and it remains difficult to measure/quantify increased IL-1 expression as a key autoinflammatory factor. Several studies, including the seminal paper by Pascual *et al.* introducing the concept of IL-1 blockade in SJIA (13), failed to detected elevated IL-1β levels in patients' sera (10), or whole blood (24). Stimulation of *ex vivo* isolated monocytes or whole blood using designated PRR-ligands, such as LPS and others (tollgene.org), did not reveal increased IL-1 release when compared to controls (24, 25) or demonstrate decreased cytokine secretion, possibly due to an intermediate regulatory/anti-inflammatory (M2) phenotype of circulating SJIA monocytes (25). However, complex stimulation conditions using patients' sera can induce IL-1 specific gene signatures as well as IL-1β release from

healthy donor PBMCs (13). Furthermore, on the transcriptional or translational level both patients' mono- and neutrophils exhibited increased IL-1β expression (26, 27) or protein accumulation over time (24, 25). This may be caused by decreased expression of the IL-1 inhibiting aryl hydrocarbon receptor in SJIA cells (24). In response to a prolonged stimulus (24h) by a strong stimulant such as PMA/ionomycin, this can result in enhanced cytokine release from patients' cells when compared to controls (13). Gene expression studies in neutrophils from SJIA patients further indicated overexpression of inflammasome components such as *AIM2* and *NLRC4* (26, 27).

In contrast to limited detection of circulating IL-1 in SJIA, several studies report massive overexpression of the IL-1 family member IL-18 (28-30). However, while the role of IL-18 as SJIA biomarker is well established (28, 30) and recent studies suggest IL-18 as critical driver of MAS (30, 31), its cellular sources as well as expression control in SJIA remain poorly understood. IL-18 is expressed by a wide range of tissues, including cells of the myeloid lineage but also epithelial cells, and (in contrast to IL-1) IL-18 mRNA expression and translation into its pro-peptide appear to be constitutive (32). However, beyond constitutive expression, a recent murine study (33) and human data from our lab (Verweyen *et al*., in revision (34)) indicate type I interferon signaling to play a vital role in controlling IL-18 expression.

3.2 Dysregulation of interferon expression and signaling

In the context of SJIA, impaired expression of interferons and altered interferon signaling is usually associated with the type II interferon IFN-γ. IFN-γ is predominantly produced by adaptive immune cells, namely Th1 $CD4^+$ lymphocytes but also NK and CD8+ T cells. Their role, particularly in MAS, has been extensively discussed elsewhere (30, 31, 35). More recently, observations on gene expression levels in response to IL-1 inhibition and data on the control of IL-18 by the interferon family suggested a previously underestimated role for type I interferons IFN-α and -β, another arm of the innate immune system, in SJIA pathogenesis. Type I interferons are produced by a multitude of cells and tissues. Their main cellular source, however, are plasmacytoid dendritic cells (pDCs) which produce type I interferons in response to viral infections (36).

Physiologically, type I interferon expression is induced by viral DNA or RNA, which is sensed by pattern recognition receptors such as endosomal TLR3, 7, 8 and/or 9. In addition to TLRs, cytosolic

sensors for DNA and RNA such as the retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs) as well as AIM2-like receptors (ALRs) induce type I interferons expression (37). Cyclic GMP-AMP (cGAMP) synthase (cGAS) was recently identified as a cytosolic PRR that detects DNA and leads to the production of cGAMP (38, 39). Activation of TLRs or cytosolic nucleotide sensors triggers interferon expression which in turn mediates phosphorylation of transcription factors initiating the expression of interferon stimulated genes (ISGs). Indeed, transcription levels of selected ISGs in blood cells can be used as complementary biomarker to generate an interferon signature (37, 40). In fact, while even in type I interferonopathies high-sensitivity assays, such as digital ELISAs, are required to produce measurable (fg/ml) serum levels of IFN-α (40), most patients display an interferon signature on the mRNA level in PBMCs (40, 41).

Interestingly, though SJIA is not readily associated with type I interferon expression and signaling, blockade of IL-1 signaling induces a type I interferon signature in SJIA patients, independent of the clinical response to IL-1 blockade (18). Similar observations regarding the relationship of IL-1 blockade in SJIA and type I interferon expression were obtained from a recent study assessing interferon signatures in a variety of pediatric inflammatory conditions (41). On a cellular level, transcriptome analysis of SJIA neutrophils reveal – among other genes – an upregulation of transcripts associated with type I interferon signaling (26). Monocytes from SJIA patients exhibit defective STAT1 phosphorylation downstream of IFN-α or IFN-γ stimulation, while expressing higher transcript levels of SOCS1, an inhibitor of interferon signaling (42). In patients responsive to IL-1 blockade, SOCS1 levels reduce while STAT1 levels increase. The opposite was observed in individuals who fail to respond to IL-1 blockade, suggesting that response to cytokine blocking therapy is associated with effects on type I interferon signaling pathways that may in turn result in increased pSTAT1/IFN responses (42). However, as type I interferons have yet not been mechanistically linked with SJIA, it is debatable whether effects observed are primarily or secondarily associated with disease. Pro-inflammatory IL-1 and type I interferons are key players of two types of inflammatory responses, which can efficiently counter-regulate each other (43). Thus, increased type I interferon expression following IL-1 but also TNF-α blockade (44, 45) may just reflect the presence of feedback loops induced by cytokine-blockade (41). Nonetheless, it has been speculated whether

decreased ability of SJIA monocytes to respond to IFN-γ and IFN-α may set the stage for the excessive IL-1β activity evident in disease (42).

3.3 DAMPs and the relevance of sterile inflammation

A hallmark of SJIA and other autoinflammatory diseases is the extremely increased secretion of myeloid cell-derived S100 proteins. S100A8/A9 and S100A12 are present in the cytoplasm of monocytes and granulocytes and play an incompletely understood role in the homeostasis of these phagocytes (46). Serum levels of S100A8/A9 and S100A12 strongly correlate with peripheral blood neutrophil counts, and neutrophils from SJIA patients exhibit elevated inflammatory gene expression, including inflammasome components and *S100A8* and *S100A12* (26, 27). Furthermore, these cells revealed enhanced PMA-induced S100A8/A9 release as compared to controls (26).

When released during the activation of the innate immune system or in the context of tissue damage, S100 proteins function as DAMPs and recruit to pattern recognition receptors (47, 48). In SJIA and other autoinflammatory diseases, dysregulation of alternative secretory pathways may furthermore contribute to disease pathogenesis and lead to hypersecretion of S100 proteins (46). Thus, in the absence of infectious pathogens, S100 proteins can generate a sterile inflammatory environment and initiate downstream pro-inflammatory effects on innate immune cells that feed into amplifying loops, which may perpetuate disease (46). Along these lines, depletion of S100A8/A9 from SJIA patients‘ serum or prevention of the Ca^{2+}/Zn^{2+}-induced inflammatory complex formation by S100A12 reduces the release of IL-1 and other inflammatory cytokines from immune cells (whole blood or monocytes) of SJIA patients or controls (47, 49).

3.4 Innate molecules fueling adaptive immunity

Apart from driving innate immune responses, IL-1β and IL-18 can have a prominent role in shaping adaptive immune responses. In fact, IL-18 was initially described as IFN-γ inducing factor (50), since it can induce IFN-γ expression from NK cells and Th1 lymphocytes, while blocking regulatory IL-10 expression in the Th1 compartment (51). IL-1β is involved in the differentiation of Th17 cells (52) and IFN-γ/IL-17 co-expressing T lymphocytes (53). Furthermore, IL-1β strongly suppresses T cell derived IL-10 expression and promotes IFN-γ production in human Th17 cells, thus influencing the

balance between pro- and anti-inflammatory cellular functions (54, 55). However, particularly human IL-1-mediated Th17 differentiation also requires IL-23 and T cell receptor engagement (56). The presence of IL-6, which is also massively overexpressed in SJIA, however, appears to be of secondary importance (52). Apart from its vital role in Th cell differentiation, IL-1R signaling stabilizes cytokine transcripts to enable productive and rapid effector functions across effector Th1, Th2 and Th17 lymphocyte subsets (57). Independent from T cells, IL-1β can also enhance B cell proliferation and antibody production, while IL-18 promotes self-reactive antibody responses (58).

However, despite strong effects of IL-1 and IL-18 on T cell differentiation and activity, evidence for altered CD4+ T cell function in SJIA or AOSD remains scarce. While some reports suggest increased numbers of Th1 and Th17 cells in SJIA (9) and AOSD (59, 60), other studies indicate that this may be - if at all present – just a trend (8, 10, 61). Controversial data on Th1 and Th17 cell numbers furthermore reflect uncertainty regarding a stimulating autoantigen, despite the association with MHC class II variant *HLA-DRB1*11* (7). Indeed, Th cell subsets in SJIA may rather benefit from increased IL-1R signaling, which can prevails effector functions of CD4+ T cells by stabilizing cytokine transcripts and thus may allows for rapid response to unspecific stimulation in cell culture and flow cytometry assays (57).

In addition to the potential involvement of classical adaptive immune cells in SJIA pathogenesis, recent studies highlight a role of innately adaptive cells bridging innate and adaptive immune responses (62), such as γδT or invariant ~~chain~~ (i)NKT cells (**figure 2**). In SJIA patients, iNKT cell numbers are strongly increased (8), while peripheral γδT cell counts - particularly during active disease - remain reduced when compared to healthy individuals (8, 10, 61). This may be explained by the recruitment of cells from the peripheral circulation to sites of inflammation (10, 61). Immunological changes in both cell subsets have been identified to be a primary predictor of JIA (8). γδT cells, but not Th17 lymphocytes from SJIA patients express increased levels of IL-17, which corroborates findings in a murine SJIA model (63). Importantly, IL-1β is critically involved in IL-17 expression from both γδT and iNKT cells (10, 64, 65). In this context it is noteworthy that mice lacking endogenous IL-1Ra expression develop spontaneous IL-17-driven arthritis (66, 67). In this model γδT cells serve as main source of IL-17 in inflamed joints, but require CD4+ T cells for tissue homing (68). Concurrent reduction of circulating γδT and IL-17/IFNγ double-expressing CD4+ T

cells during SJIA flares when compared to patients in remission or healthy controls may indicate a relevance for this observation also in humans (10). Once happening in the joint, inflammatory Th cell activation can occur independent of conventional TCR signaling (69). Thinking along such lines may also explain recent findings in patients with oligo- or polyarticular JIA, in who an IL-17 signature in synovial fluid is driven by a whole potpourri of contributors comprising γδT lymphocytes, receptor negative innate lymphoid cells, but also CD4+ and CD8+ lymphocytes (70).

Importantly, γδT cell expansion, but also iNKT cell activation can be driven by IL-18. Both cell types – in contrast to CD4+ T cells – express high levels of IL-18R (10, 64, 71). Both in humans, (Verweyen *et al.*, in revision (34)) and in mice (33) it has been demonstrated that type I interferon signaling is associated with the production of IL-18. Thus, it can be speculated whether tilting the IL-1/type I interferon balance towards increasing interferon-signaling in response to IL-1 blockade (18, 41) may benefit IL-18 associated effects on innate and adaptive immune cells. Indeed, full restoration of the type I interferon/IL-l balance inhibits autoimmunity in NOD mice (72).

Lastly, also in this context S100 proteins may play a central role. While certainly IL-1, IL-6 and IL-18 may be the main autoinflammation-related effector molecules promoting adaptive immune cell differentiation and activation in SJIA, these effector cytokines are part of an S100 protein induced sterile inflammatory environment that promotes Th17 (73) and γδ17T cell (10) development or directly induces autoreactive IL-17 expressing CD8+ T cells (74).

4. Adaptive immunity in other autoinflammatory disease: Fact or fake news?

Key pathophysiological features of mono- and polygenic autoinflammatory diseases are either inflammasome dysregulation leading to uncontrolled IL-1 and/or IL-18 release or molecular defects resulting in altered type I interferon responses. While involvement of innate immune mechanisms in B and T cell-driven autoimmunity is well accepted, the fate of these adaptive immune cells in autoinflammation and related cytokine expression seems – apart from SJIA - far less clear or investigated.

Almost a decade ago, two seminal papers were published back-to-back in a single issue of *Immunity* (75, 76): A study on two *Nlrp3* mutant knock in mouse strains modelling CAPS reported that the systemic inflammatory phenotype required an intact inflammasome, however, was only partially

dependent on IL-1β, and independent of T cells (76). A second study suggested that a mutation in the *Nlrp3* gene leading to murine CAPS resulted in massive IL-1β production, augmenting Th17 differentiation and resulting in a Th17 cytokine-dominant immune response. Authors reasoned that the *Nlrp3* mutation investigated results in inflammasome hyperactivation and consequently Th17-mediated immunopathology in autoinflammation (75). Corresponding to these murine data, untreated CAPS patients reveal elevated IL-17 serum levels and increased Th17 cell numbers when compared to healthy controls (77). Both were reversed in response to anti-IL-1 treatment. Similarly, TLR stimulation of monocyte-derived dendritic cells from CAPS patients triggered enhanced secretion of IL-1β and IL-23, which normalized after the introduction of anti-IL-1 treatment, suggesting a central role of IL-1β in Th17 differentiation in human inflammatory conditions (77). Recent data on the IL-1/IL23-induced differentiation and activation of human T cells even in absence of TCR engagement or costimulatory signals support this (52, 69).

Elevated serum IL-17 and increased numbers of Th17 cells also occur in patients with FMF. Part of the increased IL-17 secretion was related to the deleterious homozygous *MEFV* p.M694V genotype (78). Another study suggests Th1 polarization in FMF patients, which could be driven by elevated IL-12 and IL-18 levels in FMF patients' serum (79).

Finally, in Schnitzler syndrome, a polygenic autoinflammatory condition in adults, systemic overproduction of IL-1β translates into a profound loss of anti-inflammatory Th17 cell functionalities, which can be reversed by IL-1 blocking treatment (55).

5. From autoinflammation to autoimmunity: Is there something unique about SJIA?

Evidence for the activation of innately or classical adaptive immune cells in autoinflammatory diseases apart from sJIA is scarce albeit the cytokine environment and pathologically activated innate immune cells should have full potential to prime and activate lymphocytes. Thus, it is worth exploring whether specific mechanisms that can either promote or counter-act ‚spill-over' of inflammation may be uniquely involved in sJIA pathogenesis.

The immune regulatory cytokine IL-10 can limit both the duration and intensity of PRR-signaling in innate immune cells, which also affects inflammasome-dependent IL-1 and IL-18 release (80). Indeed, IL-10 regulates the inflammasome-driven augmentation of inflammatory arthritis and joint destruction

(81). In fact, two independent studies reported increased prevalence of *IL10* promoter haplotypes in SJIA cohorts that encode for low IL-10 expression (82, 83). Recently, cell-specific IL-10 defects were observed in SJIA patients and a murine disease model, resulting in insufficient IL-10 production to counterbalance proinflammatory cytokines (84).

While the relevance of decreased IL-10 expression due to genetic variations can be debated as recent SNP genotype data from the 9 case–control populations of the INCHARGE SJIA collection could not reproduce this association (85), data on IFN-γ as another potential regulatory factor in SJIA appear more consistent. Reduced serum and plasma levels of IFN-γ and CXCL-9, a surrogate for IFN-γ-signaling, have been described in SJIA as compared to healthy controls (10, 86), and decreased IFN-γ-induced transcriptional signatures in sJIA monocytes have been reported, suggesting limited *in vivo* IFN-γ exposure (18, 87). Defective IFN-γ release has been observed in NK cells from SJIA patients (86, 88), while Th1 cells – although increased in numbers in the peripheral blood of disease-active patients (9, 10) - reveal a remarkable decrease in intracellular IFN-γ expression which is partly corrected in response to IL-1 blockade (10). Furthermore, mice deficient of IFN-γ develop SJIA-like disease in response to inflammatory challenge with Complete Freund's adjuvant (63, 86). Surprisingly, iNKT cells from IFN-$\gamma^{-/-}$ animals promote arthritis rather than protecting from inflammation (89). Similarly, iNKT cells in RA patients' synovial fluid have been reported to express only low levels of IFN-γ, consistent with the hypothesis that active arthritis is correlated with a decreased cellular ability to produce this cytokine (89). Thus, aberrantly low IFN-γ levels in concert with a dysbalanced innate immune cell derived pro-inflammatory cytokine environment in SJIA may contribute to the progression to an autoimmune phenotype with a prominent role for IL-17 (90) (**figure 2**). As no such findings have yet been reported from other autoinflammatory conditions, this may indeed be unique to SJIA.

To date, the dichotomy of this very limited role of IFN-γ in the arthritis of sJIA as compared to its prominent role in MAS is not understood. MAS develops in approximately 10-20% of patients with sJIA and resembles a severe hyperinflammatory condition characterized by a catastrophic cytokine storm resulting in multiple organ failure and high mortality (extensively reviewed elsewhere (35)). In contrast to sJIA, IFN-γ as well as IFN-γ induced chemokines are markedly elevated during MAS (91) and IFN-γ neutralization can revert clinical and laboratory features of MAS in a preclinical murine

model (92). Furthermore, in a pilot open label single arm international study (NCT03311854) therapeutic IFN-γ neutralization proofed effective in controlling MAS (93). It is an intriguing future research question to understand the cause for low IFN-γ expression during active sJIA and to investigate whether a disturbed IL-18:IFN-γ axis can set the stage for fulminant IFN-γ expression and signaling during MAS.

6. Getting it right for patients: Translating molecular complexity into therapeutic strategies

In the absence of formally approved drugs for the treatment of the majority of (ultra-)rare autoinflammatory or autoimmune diseases, there is no shortage of recommendations for the treatment of more common polygenic chronic-inflammatory diseases. In the current "treat-to-target" era, medical care focuses on the achievement of remission or low disease activity (94, 95).

However, in many SJIA patients, treatment responses could be better if effective therapies were established earlier. Precise definition of relevant subgroups and introduction of tailored preventative strategies and/or treatments are the most important and pressing challenges for translational research. Understanding inflammatory mechanisms that drive autoimmunity, especially during early disease progression, gave rise to the "window-of-opportunity" paradigm (11). This promises potential to prevent the onset of clinically manifest chronic autoimmune/inflammatory disease in susceptible individuals. Moreover, future use of biological signatures to steer treat-to-target therapies based on the involvement of autoinflammation and/or autoimmunity will allow for disease phenotype and/or stage specific individualized precision medicine. Finally, predictive (demographic, clinical, genetic, serologic, etc.) markers may allow for early intervention in susceptible individuals that can prevent the development of chronic autoimmune/inflammatory disease. However, finding the right balance between over- and under-treatment means moving along very thin lines. Without doubt, getting it right for the patient will only be possible if we break down dogmatic barriers diverting immune dysregulation underlying inflammatory disease into antipodes of autoimmunity or autoinflammation. Potentially, innately adaptive cell populations and the molecules involved in their complex interplays to both sides should be considered for molecular characterization of disease stages and patient sub-populations, and they may even offer attractive targets for future therapies.

Figure legends

Figure 1. Examples of polygenic arthritic disorders with differing degree of autoinflammation and/or autoimmunity. Arthritic conditions can be dominated by innate (sJIA/AOSD at onset, gout) or adaptive immune mechanisms (poly/oligoarthritic JIA, RA, sJIA/AOSD in course of disease progression) with or without B cell activation and autoantibody expression or resemble mixed pattern diseases (PsA, AS). Where reported, identified HLA-association are indicated. JIA: (systemic) juvenile idiopathic arthritis; (s)JIA; AOSD: adult onset Still's disease; RA: rheumatoid arthritis.

Figure 2. Innately adaptive or truly autoimmune: a pathophysiological model for disease progression in SJIA. Innate immune cells, such as myeloid (granulocytes, monocytes) and NK cells, are relevant during the acute febrile phase of SJIA. (1) Myeloid cells release IL-1-family (IL-1β, IL-18) but also other pro-inflammatory cytokines which can be either triggered by infection (pathogen associated molecular patterns, PAMPs) or be the result from pattern recognition receptor activation by damage associated molecular patterns (DAMPs) released from stressed or necrotic cells. (2) Together with γδTCR-activation by endogenous (i.e. isopentenyl pyrophosphate, IPP) or bacterial ligands, IL-1 and IL-18 can trigger IL-17 expression from γδT cells, while (3) IL-18 fails to trigger IFN-γ expression from NK cells due to a defective IL-18R. (4) Similarly, SJIA Th1 cells express only low levels of IFN-γ. Both cell types may contribute to hypophysiological IFN-γ levels, potentially promoting IL-17 expression in disease. Albeit a genetic association or alterations in frequencies have been reported, the pathomechanistic roles of (5) HLA-DRB1*11 (antigen presentation or intracellular function?) or (6) (i)NKT and (7) CD4+ T cells in disease progression is yet largely unclear. Thus, current data imply that innately adaptive immune cells bridging innate and adaptive immunity rather than classical B or T lymphocytes have a central role in promoting disease progression in SJIA.

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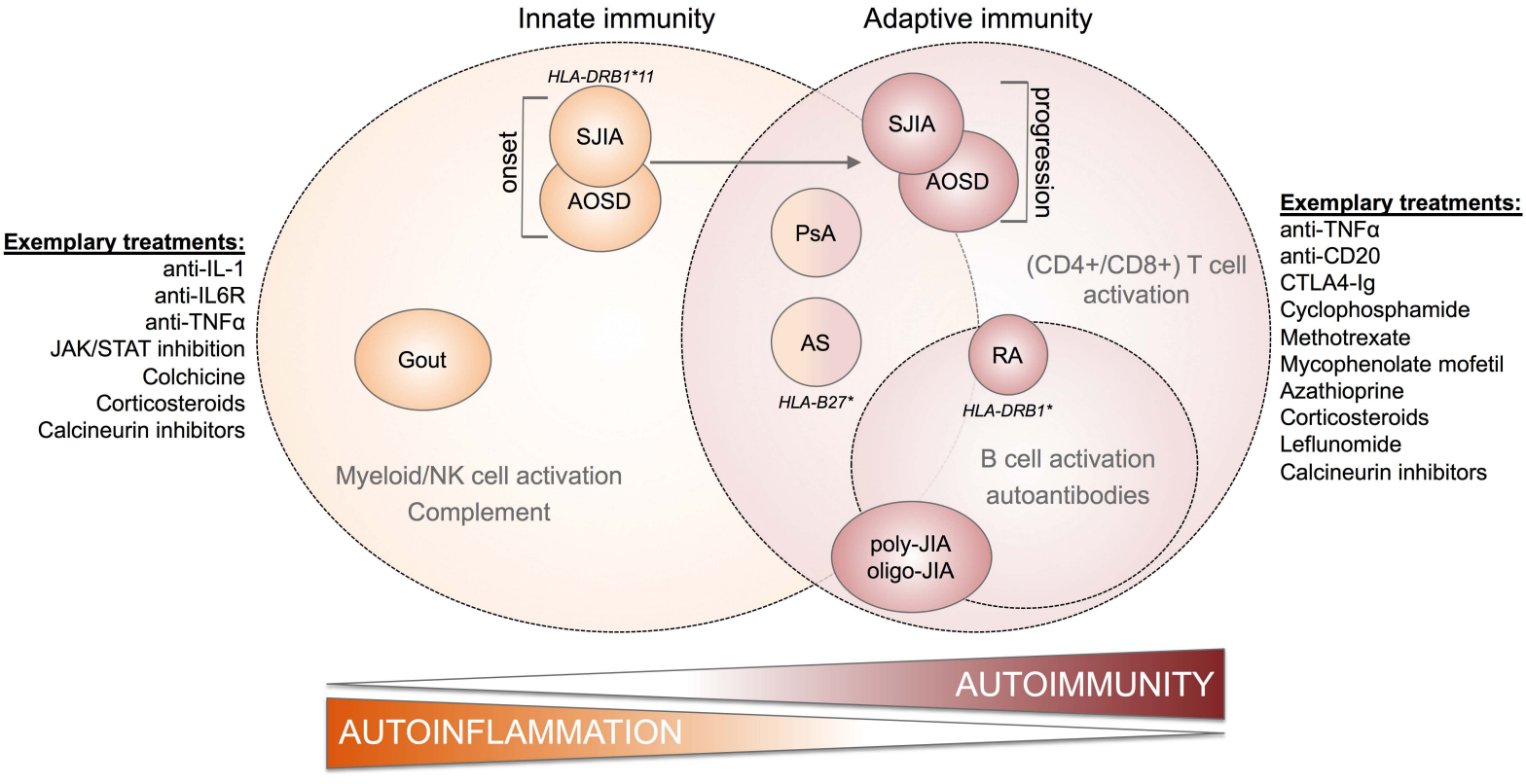
Innate immunity
Adaptive immunity
HLA-DRB1*11
onset
SJIA
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progression
SJIA
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PsA
AS
HLA-B27*
RA
HLA-DRB1*
(CD4+/CD8+) T cell activation
Gout
Myeloid/NK cell activation
Complement
B cell activation
autoantibodies
poly-JIA
oligo-JIA
Exemplary treatments:
anti-IL-1
anti-IL6R
anti-TNFα
JAK/STAT inhibition
Colchicine
Corticosteroids
Calcineurin inhibitors
Exemplary treatments:
anti-TNFα
anti-CD20
CTLA4-Ig
Cyclophosphamide
Methotrexate
Mycophenolate mofetil
Azathioprine
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Leflunomide
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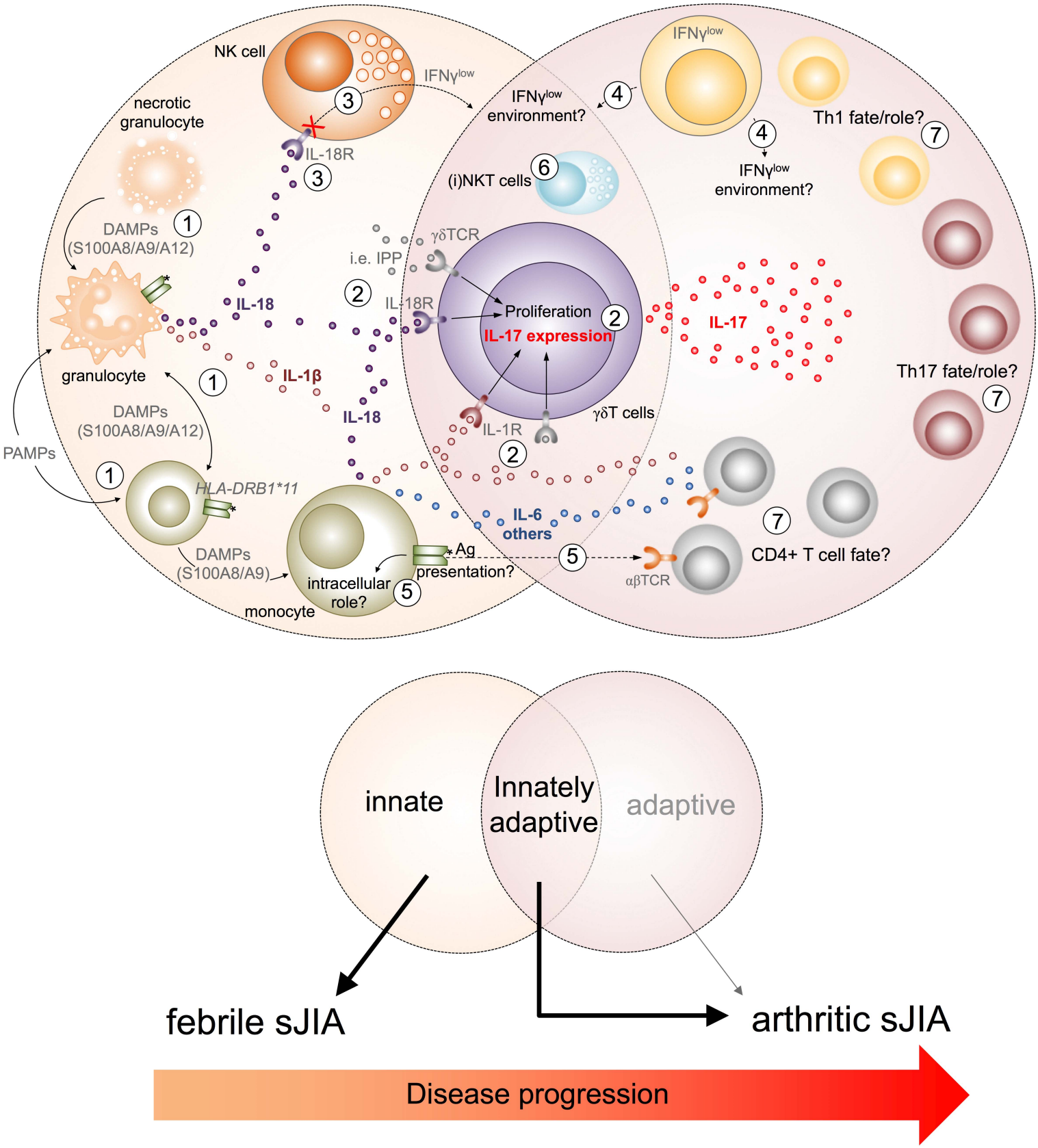
NK cell
IFNγlow
necrotic granulocyte
IL-18R
DAMPs (S100A8/A9/A12)
IL-18
granulocyte
IL-1β
IL-18
PAMPs
HLA-DRB1*11
DAMPs (S100A8/A9)
intracellular role?
monocyte
Ag presentation?
IFNγlow environment?
IFNγlow
Th1 fate/role?
IFNγlow environment?
(i)NKT cells
γδTCR
i.e. IPP
IL-18R
Proliferation
IL-17 expression
IL-17
γδT cells
IL-1R
Th17 fate/role?
IL-6
others
CD4+ T cell fate?
αβTCR
innate
Innately adaptive
adaptive
febrile sJIA
arthritic sJIA
Disease progression