Published in final edited form as:
Best Pract Res Clin Rheumatol. 2009 October ; 23(5): 655–664. doi:10.1016/j.berh.2009.08.003.

Systemic JIA: New Developments in the Understanding of the Pathophysiology and Therapy

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Abstract

Systemic juvenile idiopathic arthritis (sJIA) is a rare, systemic inflammatory disease classified as a subtype of JIA. Besides arthritis, it is characterised by systemic features like spiking fever, skin rash, hepatosplenomegaly or serositis. It is becoming clear now that abnormalities in the innate immunity (cytokines like IL-1, IL-6 and IL-18, and neutrophils and monocytes/macrophages rather than

Acknowledements and conflicts of interest
No sources of funding were used to assist in the preparation of this review.
The authors declare that there are no conflicts of interests.

Practice points

- sJIA is a systemic (probably auto-) inflammatory disorder
- Diagnosis is by clinical classification criteria and still requires exclusion of other diseases in patients with a spiking fever, other systemic features and arthritis
- The pathophysiological mechanisms underlying sJIA begin to be unraveled, with strong indications for a pivotal role of cells, components and genes involved in the innate immune system
- Sofar, corticosteroids have been the mainstay of the treatment for sJIA. However, both IL-1 and IL-6 targeted therapies hold great promises in phase II and III studies.

Research agenda

- Further progress in the unraveling of the pathophysiological mechanisms is needed, focusing on both genetic and environmental factors triggering the inflammatory pathways in sJIA
- New possible biomarkers for diagnosis and disease severity have to be evaluated prospectively in multi-center trials
- Controlled trials, set up in international collaboration given the rarity of the disease, are needed to define the optimal treatment strategies for all sJIA patients. This relates especially to the order and timing of the IL-1 and IL-6 targeted therapies in relation to glucocorticoids.

lymphocytes) play a major role in the pathogenesis of sJIA, distinguishing sJIA from other JIA-subtypes. Another distinctive feature of sJIA is its strong association with macrophage activation syndrome (MAS). Based on this, consensus is emerging that sJIA should be viewed as an auto-inflammatory syndrome rather than a 'classic' autoimmune disease.

As a consequence of the progression in understanding the underlying mechanisms of sJIA, major changes in the management are evolving. Sofar, treatment has been based on glucocorticosteroids in combination with disease modifying drugs like methotrexate. Recently, remarkable improvement has been observed with IL-1 and IL-6 targeted therapies. These therapies might also change the long term outcome of this disease. However, controlled trials set up in international collaboration are needed to determine the optimal treatment strategies for all sJIA patients.

Keywords

systemic juvenile idiopathic arthritis; innate immunity; myeloid related proteins (MRP´s); IL-1; IL-6; Macrophage Activation Syndrome (MAS)

Introduction

In 1897 while being a Registrar at the Hospital for Sick Children at Great Ormond Street in London, Sir George Frederick Still described 19 patients with three patterns of childhood arthritis one of which came to be known later as Still's disease or Systemic Juvenile Idiopathic Arthritis (SJIA) [1]. Although over the following decades it became clear that this clinical entity is very different from other forms of childhood arthritis, the unique pathogenetic pathways leading to the development of SJIA remained obscure until recent years. Profound changes in the understanding of this disease that have occurred over the last decade are the main topic of this review.

At onset, SJIA which constitutes about 10% of all JIA patients, is distinguished clinically from other forms of JIA by the prominence of extra-articular features such as spiking fevers, typical fleeting pink macular rash, generalized lymphadenopathy, hepatosplenomegaly, and occasionally, polyserositis [2]. The typical laboratory features include marked polymorphonuclear leukocytosis and thrombocytosis. The clinical course at later stages of SJIA is highly variable [2]. The systemic features tend to subside during the initial months to years of the disease in the majority of patients. In North America, about half of the children with SJIA recover almost completely. The other half continue to show progressive involvement of more joints. Even the joint disease seen in these SJIA patients is in some respects quite different from the other subtypes of JIA. The distinctive features include early destructive changes in the joints and ankylosis involving cervical spine, wrists, and mid-foot [3].

Another perplexing feature of SJIA is the strong association with so called macrophage activation syndrome [4] a condition that bears close resemblance to a group of histiocytic disorders collectively known as hemophagocytic lymphohistiocytosis (HLH) [5–9].

Innate immunity in SJIA

It is now becoming increasingly clear that the markedly distinct clinical presentation of the systemic form of JIA is associated with distinct immunologic abnormalities. Thus, several lines of evidence suggest that the role of the adaptive immune system in SJIA may be rather limited compared to the other JIA subtypes, while the contribution of the innate immunity may be much more prominent [10–15]. For instance, several recent studies utilizing the microarray technology that allows for simultaneous assessment of expression of thousands of genes have shown that systemic JIA is distinguished from other sybtypes of JIA by up regulation of the

innate immune pathways including IL-6, TLR/IL1R, and PPARγ signaling pathways associated with down regulation of the gene networks involving NK-, T cell and MHC antigen-related biological processes including antigen presentation [10,12–16].

Over the last decade there has been a trend to distinguish “classic” (adaptive) versus innate autoimmunity based on the relative contribution of the adaptive and innate immunity respectively [17](Table 1). The development of classic autoimmunity is typically associated with the emergence of autoreactive antigen-specific T lymphocytes and high-titer autoantibodies leading to a destructive immune response to self antigens. These diseases typically show strong MHC class II associations. Obviously, the abnormalities in the adaptive immune system play the pivotal role in the pathogenesis of these conditions. SLE, Grave’s disease, and autoimmune thyroiditis are some examples in this group of diseases.

In contrast to classic autoimmunity, abnormalities in innate immunity pathways may lead to the development of a distinct group of pathologic conditions now known as autoinflammatory syndromes [18,19]. Familial Mediterranean Fever (FMF) and Neonatal Onset Multisystem Inflammatory Disease (NOMID) are some examples in this group. These conditions lack strong MHC associations. High-titer auto-antibodies or antigen specific T cells are usually not seen in these patients. Predominance of monocytes and neutrophils rather than lymphocytes as effector cells is another important feature of these diseases. Clinically, the autoinflammatory syndromes are characterized by recurrent episodes of inflammation not associated with infection or malignancy. Fever is prominent. Multisystem involvement including joints, skin, gastrointestinal tract, eyes etc is common. Nontraditional triggers such as changes in temperature, stress, or exercise are frequently reported. Amyloidosis is a common complication in this group of conditions.

SJIA as an autoinflammatory disease

The emerging consensus in pediatric rheumatology is that since the abnormalities in the innate immunity play a major role in the pathogenesis of SJIA this disease should be viewed as an autoinflammatory syndrome rather than a “classic” autoimmune disease. Indeed, many clinical features of SJIA are similar to those seen in autoinflammatory syndromes [2]. This includes fever, multisystem involvement as well as a polycyclic course in some patients. Autoreactive lymphocytes are usually not detected in systemic JIA patients. Only rare patients have positive ANA test. Rheumatoid Factor is usually absent. Finally, as in autoinflammatory syndromes, patients with SJIA are at risk for amyloidosis.

On a genomic level, one distinctive feature of the systemic form of JIA is the lack of strong MHC Class II associations [20]. This is very different from other clinical forms of JIA in which the contribution of the MHC genes is quite significant. In fact, a recently completed genome-wide screen showed that most of the genetic predisposition to oligo-JIA is contributed by the MHC loci [21]. In contrast in systemic JIA, the most consistently reported genetic effects have been limited mainly to mild contributions from cytokine/chemokine gene polymorphisms involving the promoter elements and genes encoding TNF-α, IL-6 [22–24] and MIF [25–26].

Effector cells in SJIA

Furthermore, increasing evidence suggest that as in autoinflammatory syndromes, the main effector cells in SJIA are monocytes and neutrophils rather than lymphocytes. Increased numbers of circulationg neutrophils and monocytes associated with peripheral expansion of immature myelomonocytoid precursors ($CD34^+$ $CD33^+$) are often seen in active systemic disease [12], and strikingly high levels of neutrophil- and monocyte-derived S100 proteins appear to distinguish systemic JIA from many other febrile illnesses [27]. Calcium-binding proteins S100A8 (myeloid-related protein or MRP8), S100A9 (MRP14) and S100A12 are

secreted during activation of neutrophils and monocytes and contribute to the perpetuation of the innate inflammatory responses. For instance, one important pathway is related to the ability of MRP8 and MRP14 to form a complex which may serve as an endogeneous TLR agonist and trigger TLR4 signaling pathways playing a major role in the innate immune responses [28–29].

Pivotal cytokines networks

The cytokines critical to the perpetuation of the inflammatory process in the systemic form of JIA also appear to be different from those in other JIA subtypes. Both clinical and translational studies suggest the pivotal role for the two potent pro-inflammatory cytokines: Interleukin-1 (IL-1) and Interleukin -6 (IL-6). Il-18 is another important cytokine that may contribute to the inflammatory process as well [30].

The important role for IL-6 in the pathogenesis of SJIA has been suspected since the 1990's [31]. IL-6 is markedly elevated in both peripheral blood and synovial fluid of patients with SJIA, and the levels of IL-6 expression appear to correlate with the overall clinical activity of the disease and such distinctive clinical features as thrombocytosis, microcytic anemia, growth retardation, and osteopenia [31–33]. Furthermore, studies of the unique quotidian fever pattern of systemic JIA show that IL-6 concentrations rise and fall in concert with the temperature spikes. Consistent with these observations, preliminary clinical experience with a biologic agent neutralizing IL-6 activity is very promising [see further].

The importance of IL-1 in the pathogenesis of SJIA had been appreciated more recently. First, Pascual et al [10] showed that the serum from SJIA patients induced transcription of various innate immunity genes including IL-1β in peripheral blood mononuclear cells (PBMC) obtained from healthy individuals. This observation combined with earlier clinical reports describing the effect of Kineret in similar patients [35–37] provided a rationale for the use of this drug in SJIA. Kineret is a soluble IL-1 receptor antagonist similar to the naturally occurring IL1ra. Interestingly, in the first report describing the existence of naturally occurring IL-1 inhibitors (that eventually turned out to be IL1ra), these factors were detected in a urine sample from a febrile patient with SJIA[38] It is now recognized that a substantial proportion of patients with SJIA do respond to IL-1 blocking agents, and the response is reminiscent to that seen in NALP3 associated auto-inflammatory syndromes. Consistent with this observation, in another recent study that utilized the microarray technology, the list of genes differentially expressed between PBMC from patients and control showed a much greater overlap between SJIA and NOMID (one of the NALP3 associated auto-inflammatory syndromes) compared to the overlaps between SJIA and other rheumatological illnesses including systemic lupus erythematosus, polyarticular JIA, and Kawasaki disease [13]. Since the genetic defect underlying NOMID leads to spontaneous release of active IL-1β it has been suspected that similar mechanisms may be involved in the pathogenesis of SJIA as well [10,13].

Remarkably, none of the above mentioned gene expression studies noted increased expression of IL-1β in freshly isolated PBMC [10,12,13,15,16], consistent with some functional studies performed by another group [39]. However, the reported gene expression profiles in SJIA did contain some elements of the IL-1 signature [10,12,13,15,16]. This was particularly prominent in the gene expression profiles reported by Fall et al [12]. This study included untreated patients with new onset SJIA. The clustering analysis of the differentially expressed genes revealed several interesting groups of genes one of which was highly enriched for the markers of the monomyelocytoid cell lineage, as well as the genes whose expression appears to be induced by the triggering of the IL1R/TLR signaling pathways including various anti-microbial peptides. Particularly prominent in the cluster were the genes involved in the negative feedback regulation of innate immune responses including SOCS3 and IL-10. SOCS3 is induced by a

number of inflammatory cytokines, most notably IL-1 and IL-6. It interferes with signaling pathways of these cytokines thus providing a negative feed back loop in inflammatory cascades induced by IL-6/IL-1.

Distinct phenotypes of monocytes and macrophages in SJIA/MAS

Another intriguing finding in the study performed by Fall et al is the co-regulated expression of the genes involved in the negative feedback regulation of innate immune responses including SOCS3 and the markers of the alternative pathway of macrophage differentiation (e.g. MS4A4A, CD163) [12]. This is consistent with the recent reports describing expansion of alternatively activated $CD163^+$ macrophages in the bone marrow of a large proportion of patients with new onset systemic JIA [40]. Since hemophagocytic macrophages seen in MAS also express CD163, this feature may provide some new clues to the understanding of the high prevalence of MAS in systemic JIA [40–43].

MAS association

A strong association with MAS is a perplexing feature of SJIA. MAS is a severe, potentially life-threatening complication characterized by the excessive activation of well-differentiated macrophages, resulting in fever, hepatosplenomegaly, lymphadenopathy, severe cytopenia, serious liver disease, intravascular coagulation, and neurological involvement [4]. One of the early events in MAS is an uncontrolled, and persistent, expansion of activated T lymphocytes and hemophagocytic macrophages. These macrophages express CD163 [40–43], a scavenger receptor that recognizes Haptoglobin-Hemoglobin (HP-Hb) complexes [44]. CD163 appears to be expressed mainly on alternatively activated phagocytic macrophages performing “scavenger” functions [45,46]. Increased uptake of HP-Hb complexes by macrophages leads to upregulation of heme-oxygenase (HO) enzymatic activity. HO degrades the heme subunit of Hb into biliverdin that is subsequently converted to bilirubin, CO (carbon monoxide), and free iron. The free iron is either sequestered in association with ferritin within the cell or transported and distributed to red blood cell precursors in the bone marrow. Increased uptake of Hp-Hb complexes by macrophages leads to increased synthesis of ferritin. Interestingly, very high level of HO activity in freshly isolated PBMC appears to distinguish SJIA from other febrile illnesses [47] and highly elevated level of serum ferritin is an important diagnostic feature of hemophagocytic syndromes. The fact that haemophagocytic macrophages in MAS are $CD163^+$ and extreme hyperferritinaemia is an important diagnostic feature of haemophagocytic syndromes suggest that this pathway is important in the pathogenesis of MAS.

As discussed earlier, the expansion of $CD163^+$ macrophages in the bone marrow may be seen not only in full-blown MAS but also is a as many as 30–50% of patients with active SJIA without clinically apparent MAS [40,41]. Since these macrophages appear to have the potential to become hemophagocytic, it has been suggested that such expansion may represent the early stages of MAS. Consistent with this notion, the hierarchical clustering analysis of the differentially expressed genes reported by Fall et al, revealed heterogeneity of patients that correlated with serum levels of ferritin, and the signature of the alternatively activated macrophages was particularly strong in the group of patients with very high levels of ferritin [12].

The fact that these CD163 macrophages exhibit many characteristics of the alternative (or M2) pathway of activation is intriguing. In the current literature, mirroring the Th1/Th2 paradigm, many refer to polarized activation of macrophages as M1 and M2 pathways [45,46]. Classically activated M1 macrophages participate as inducers and effectors in polarized Th1 responses, and IFNγ is the key cytokine driving this pathway of macrophage differentiation. These macrophages are highly pro-inflammatory. In contrast, M2 macrophages participate in Th2

immune responses, perform scavenger functions and promote tissue remodeling. The pro-inflammatory activity of M2 macrophages appears to be relatively low [45]. Given the highly inflammatory nature of SJIA and MAS associated with abundance of IFN-γ (the main driving force of M1 pathway of differentiation), the emergence of alternatively activated M2 macrophages in these diseases is surprising. One possible explanation is the altered responsiveness of monocytes/macrophages to IFN-γ. Indeed, one intriguing finding in the gene expression profiles seen in SJIA is that the IFN-induced gene expression signature is conspicuously absent [10,12,13]. Another consistent feature is over expression of SOCS3, a suppressor of cytokine signaling protein that interacts with the JAK/STAT signaling pathway, leading to decreased responsiveness of monocytes/macrophages to IFN-γ. Therefore, overexpression of SOCS3 in monocytes as shown by Ogilvie et al, combined with the abundance of cytokines implicated in the alternative pathway of macrophage activation (such as IL-10 and IL-6) may lead to the overall cytokine milieu that favors the alternative M2 pathway [12]. This view may certainly be an oversimplification given the complexity of the factors with different temporal patterns the monocytes are exposed to in such a complex disease as SJIA, but the analysis of the described gene expression profiles does suggest that the mononuclear phagocytes in SJIA may have a distinct phenotype that need to be defined better in future studies.

Cytolytic pathway in SJIA and MAS

In the study reported by Fall et al, the comparison between “ferritin high” versus “ferritin normal” also revealed statistically significant differences in the levels of expression of several genes whose products are critical to the activation of the cytolytic pathway [12]. Some examples include MUNC13-4, Rab27a, and SH2D1A. Since, the most consistent underlying immunologic defect reported in patients with genetic hemophagocytic syndromes such as primary HLH has been impairment of cytotoxic functions [8,48–53], these observations suggest that the pathways that distinguish “ferritin high” versus “ferritin normal” SJIA patients may also be relevant to the development of cytolytic abnormalities and MAS in SJIA.

In primary HLH, the uncontrolled proliferation of T cells and macrophages has been linked to decreased NK-cell and cytotoxic T-cell function [8] often due to mutations in the gene encoding perforin [48]. Perforin is a protein which cytolytic cells utilize to induce apoptosis of target cells such as tumor cells or cells infected by viruses. More recently, mutations in another gene, MUNC13-4, have been implicated in the development of hemophagocytic lymphohistiocytosis in 10% of patients with inherited HLH [49]. The protein encoded by the MUNC13-4 gene is involved in the delivery and fusion of the perforin-containing granules with the plasma membrane [49]. Therefore, it is an important player in the intracellular transport of perforin. Although the cytolytic cells of the patients with FHLH caused by MUNC13-4 mutations produce sufficient amounts of perforin, the poor ability to deliver perforin to the surface of the cells leads to profoundly decreased cytolytic activity against target cells. The presence of defects in the granule-dependant cytotoxic activity of lymphocytes in diseases associated with hemophagocytic syndromes highlights the importance of this function in restoring the immune system to a state of equilibrium during some inflammatory responses

The exact mechanisms that would link deficient cytolytic functions with expansion of activated macrophages are not clear. Two alternative explanations have been suggested in the literature [54,55]. One is related to the fact that HLH and MAS patients appear to have diminished ability to control some infections. More specifically, NK cells and cytotoxic T lymphocytes fail to kill infected cells and, thus, to remove the source of antigenic stimulation. Such persistent antigen stimulation leads, in turn, to persistent antigen-driven activation and proliferation of T-cells associated with escalating production of cytokines that stimulate macrophages. It also has been hypothesized by some authors that abnormal cytotoxic cells may fail to provide

appropriate apoptotic signals for removal of activated macrophages and T cells during the contraction stage of the immune response. This leads to persistent expansion of T cells and macrophages secreting proinflammatory cytokines.

Remarkably, immunologic abnormalities similar to those seen in genetic hemophagocytic syndromes, i.e. poor NK cell cytolytic activity often associated with abnormal levels of perforin expression, have been reported to distinguish SJIA from other clinical forms of childhood arthritis as well [56,57] and it has been suggested that this the presence of such cytolytic dysfunction may identify patients at risk for MAS. Since SJIA is not a monogenic inherited disease like primary HLH, it is likely that multiple interacting factors, both genetic and acquired are responsible for the development of the cytolytic dysfunction in SJIA patients. Thus, Zhang et al recently reported an association with single-nucleotide polymorphisms (SNPs) in the MUNC13-4 gene inherited as an extended haplotype in the majority of MAS patients (58). In another report, Vastert et al described the association between MAS in SJIA and SNPs and/or heterozygous mutations in gene encoding perforin [Vastert et al, submitted]. It has also been suggested that decreased NK cell function in SJIA could be induced by the rather unique cytokine environment present in this disease. It is well known that excessive activity of some cytokines may affect the behavior of various transcription factors in lymphocytes in downstream signaling pathways. As previously noted, SJIA is associated with strong signatures induced by IL-1, IL-6 and IL-18. De Jager et al recently studied the relationship between defective NK cell function and high plasma levels of IL-18 in SJIA (De Jager et al, Arhritis & Rheumatism 2009, in press). It was determined that IL-18 present in plasma of SJIA patients binds its cognate receptor and stimulates activation of NK cells obtained from healthy controls. In contrast, NK cells obtained from SJIA patients failed to upregulate cell mediated killing molecules such as perforin, and IFNγ after IL-18 stimulation. Furthermore, in contrast to healthy controls, IL-18 treatment did not induce phosphorylation of receptor activated MAP kinases in NK cells obtained from SJIA patients. Immunoprecipitation of the IL-18 receptor beta unit showed that NK cells from SJIA patients could not phosphorylate this receptor after IL-18 stimulation. Further research is necessary to determine whether this abnormality is a reversible phenomenon induced by excessive IL-18 activity as seen in SJIA or whether it is caused by a genetic defect in either the receptor or in the downstream signalling pathway. Interestingly, a negative role of IL-18 on NK cell homeostasis was also noted in HIV- infected patients [60].

New treatment paradigms

The recent insights into the pathophysiological mechanisms in SJIA have led to major changes in the management of this disease. Until recently, the treatment algorithms in SJIA included mainly steroids and methotrexate [61]. Since their introduction in the late 90s, TNF- inhibiting agents have also been frequently used in these patients. Thalidomide [62], Cyclosphosphamide [63] or even autologous stem cell transplantation [64] have been used in patients with a particularly severe disease. However, Methotrexate, the first choice second line agent in JIA, is now recognized to be less effective for both the systemic and articular manifestations of SJIA [65–67]. TNF-inhibiting agents also show significantly lower response rates in SJIA compared to other JIA subtypes [68–72].

In contrast, the preliminary experience with new biologics blocking IL-1β and IL-6 looks very promising. Initially, in uncontrolled studies in patients with refractory SJIA resistant to methotrexate and TNFα-blockade, the treatment with Kineret led to a rapid and sustained remission within a few days [10,33–35]. However, the initial optimism for this treatment has been somewhat diminished by more recent reports suggesting that not all the patients with SJIA respond to the treatment and the response is not always sustained 73,74]. These observations suggest that there might be different subsets within the disease [39] and studies

aimed at the identification of biologic markers that would predict response are in progress. Another possible reason for the poor response to Kineret in some patients is that the utilization of the naturally occurring IL-1 receptor antagonists may not be the best strategy to inhibit IL-1 activity [75]. Indeed, it may be difficult to occupy the large number of IL1 receptors expressed on many different cell types. In addition, IL-1 receptor antagonists are rapidly excreted by the kidney, while new IL-1Rs are being generated every day. These problems are likely to be overcome with the new long-acting agents that block IL-1 more efficiently. One of these new agents, Rilonacept (or IL-1 Trap) is a fusion protein consisting of the two human IL1 receptor extracellular domains and the Fc portion of human IgG1. It incorporates in a single molecule the extracellular domains of both receptor chains required for IL-1 signaling: the IL-1 type I receptor and the IL-1 receptor accessory protein. Because of this, the IL-1 Trap molecule might be a more efficient inhibitor of in vivo IL-1 signalling than Kineret. Recently, Rilonacept has been proven to be effective in a phase II trial in familial cold autoinflammatory syndrome [76], and a Phase III trial of this agent in SJIA is in progress. A fully human anti-interleukin-1β (anti-IL-1β) monoclonal antibody is another new IL-1 inhibiting agent currently studied in SJIA in the USA and Europe. The preliminary experience with the anti-IL-6 receptor antibody (Toculizumab) in two independent Phase II studies [77,78] in SJIA shows even greater promise. However, the safety profiles of these agents still need to be determined.

Currently in clinical practice, the increasing enthusiasm for the IL-1 and IL-6 inhibiting agents has led to a rapid decrease in the use of Methotrexate and TNF-inhibitors in SJIA while early administration of the IL-1 and IL-6 inhibiting agents is becoming more and more common. There is a hope that the early administration of the IL-1 and IL-6 inhibiting agents will also allow to decrease or even avoid the use of steroids in at least some of the patients with SJIA.

In conclusion, similarly to the autoinflammatory syndromes such as FMF, and NOMID, the abnormalities in the innate rather than adaptive immunity play a major role in the pathophysiology of SJIA. Based on this, the emerging consensus is that SJIA should be viewed as an auto-inflammatory syndrome. The utilization of the new IL-1 and IL-6 blocking agents is likely to become the main treatment of SJIA and, perhaps, change the long term outcome in this still often devastating disease.

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Table 1

Innate *versus* Adaptive Autoimmunity

Adapted from Beutler: Nature 2004;430:257-63

- **Adaptive**
  - **Pathogenic cells**:
    - T cells, B cells
  - **Mechanism**:
    - Failure of peripheral or central T cell tolerance to self-antigens
  - **Other features**
    - Autoantibodies
    - Autoantibodies
    - Autoreactive T cells (Th1/Th2)
    - HLA Class II associations
  - **Examples:** Graves disease, Lupus
- **Innate**
  - **Pathogenic cells**:
    - Monocytes, Macrophages, Granulocytes, NK cells
  - **Mechanism**:
    - Aberrant sensor activation or failure of inhibitory mechanisms
  - **Other features:**
    - No autoantibodies
    - No autoreactive T cells
    - No HLA Class II associations
  - **Examples**: autoinflammatory syndromes (FMF, NOMID, MWS, FCU, TRAPS) Systemic JIA ?