Special Issue "Autoinflammation vs Autoimmunity"

Mini Review

Systemic JIA as an Autoinflammatory Disease

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Autoinflammatory diseases have recently been recognized as diseases characterized by systemic inflammation mediated by abnormalities in the molecules of the innate immune system. Clinical features of the systemic onset juvenile idiopathic arthritis (sJIA), the most common rheumatic disease in Japan, mimic those of autoinflammatory disease. In addition, a large number of evidence indicates the pathogenesis of sJIA to be closely associated with abnormalities in the innate immune system rather than with the classic autoimmune system. Based on these findings, a consensus is now emerging that sJIA may be a autoinflammatory disease.

In order to deepen our understanding of human innate immunity, and to offer more targeted therapies for patients with sJIA, further studies on the genetics and molecular pathophysiology of sJIA and autoinflammatory diseases are essential.

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A fever is one of the most common signs of illness in children. In most cases where febrile episodes are repeated frequently or prolonged beyond two to three weeks, specific infections, malignancies, or autoimmune rheumatic diseases are the main cause of the condition. Systemic juvenile idiopathic arthritis (sJIA) is one such febrile disease in children, and is characterized by systemic inflammatory features such as a spiking fever, skin rash, serositis, and hepatosplenomegaly, in addition to persistent arthritis[1]. According to two nation-wide surveys conducted in Japan, sJIA is the major subtype of JIA; with 42-54% of JIA patients being diagnosed with sJIA, and the number of sJIA patients is estimated to be more than 1,000[2-3]. Therefore, sJIA is the most common disease among pediatric rheumatologists in Japan.

Table1: Comparison between autoimmunity and innate immunity

	Adaptive Autoimmunity	Innate Immunity
Pathogenic cells	Tcells, B cells	Monocytes, Macrophages, Granurocyte, NK cells
Mechanism	Failure of peripheral or central T cells tolelance to self-antigens	Aberrant sensor activation or failure of inhibitory mechanisms
Other features	Autoantibodies	No Autoantibodies
	Autoreactive T cells (Th1/Th2)	No Autoreactive T cells
	HLA class II association	No HLA Class II association

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Table2:Autoinflammatory Diseases

Ⅰ Hereditary Periodic Fever Syndrome
- ■Familiar Mediterranean Fever (FMF)
- ■Hyper IgD syndrome (HIDS)
- ■TNFReceptor associated periodic fever syndrome (TRAPS)
- ■Cryopyrin associated periodic ever syndrome (CAPS)
  - CINCA/NOMID
  - Muckle-Wells syndrome (MWS)
  - Familiar cold uriticaria syndrome (FCU/FCAS)

Ⅱ Idiopathic eriodic Fever Syndrome
- ■PFAPA
- ■systemic JIA
- ■Adult onset Still Disease (AOSD)

Ⅲ Granulomatous Disease
- ■Early onset sarcoidosis (EOS)/Blau sydr me
- ■Chron's disease

Ⅳ Febrile Diseases
- ■PAPA
- ■Majeed syndrome
- ■SAPHO syndrome

Ⅴ Hemophagocytic syndrome
- ■Hemophagocytic lymphohistiocytosis (HLA)
- ■Macrophage activating syndrome (MAS)

Ⅵ Complement Disease
- ■Hereditary angioneurotic edema (HANE)

Ⅶ Vasucular Disease
- ■Behcet's disease

Ⅷ Metabolic Disease
- ■Gout
- ■Pseudo Gout

CINCA:Chronic infantile neurologic cutaneous and articular syndrome
NOMID:Nenonatal-onset multisystem inflammatory disease
PFAPA:Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
PAPA:Pyogenic ster le arthritis, pyoderma gangrenosum, and acne syndrome
SAPHO:Synovitis, acne, pustulosis, hyperostosis, and osteomyelitis

Table 3a: Hereditary periodic fever syndrome

	Famillial Mediterranean fever FMF	Mevalonate kinase deficiency syndrome HID	TNF receptor-associated periodic syndrome TRAPS
Onset	Chidhood or adolescence	Infancy (first year of life)	3-20 years
Inheritance	Resessive	Resessive	Dominant
Gene	*MEFV*	*MVK*	*TNFRSF1A*
Chromosome	16p13.3	12q24	12p13.3
Usual ethnicity	Non-Sephardic Jewish, American, Arab, Turish	Dutch and other Northern European	Northern European, any ethnicity
Protein involved	Pyrin	Mevalonate kinase	TNF receptor 1 (p55) or CD120a
Fever duration	1-4 days	3-7 days	1 or more weeks
Abdominal distress	Very common (sterile peritonitis)	Very common (abdominal pain, vomiting, diarrhea)	Common (abdominal pain, diarrrhea, constipation)
Chest involvement	Pleurisy, often unilateral	Infrequent	Pleuritis
Skin involovement	Erysipelas-like rash	Polymorphic rash	Painful migratory eruption, edematous plaques
Articular involvement	Arthritides, or arthraligia	Arthralgias	Migratory arthralgia, non-erosive arthritides
Other signs	Pericardial effusion, scrotal pain	Cephalalgia, lymph node enlargement	Periorbital edema, conjunctivitis, localized myalgia, muscle tenderness, monocytic fascitis
Elevated IgD	15% of cases	Almost all (> 100 IU/ml)	10% of cases (< 100 IU/ml)
Elavated IgA	20% of cases	85% of cases	-
Treatment	Colchicine	Anakinra, simvastatine	Corticosteroid, etanercept, anakinra
Amyloidosis	Common in colchicine-resistant and in untreated patients	Rare (5% of patients)	15-25% of patients

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Although the clinical features resemble to many infectious diseases, sJIA has not been consistently associated with any pathogen. In addition, no auto-antibodies or auto-reactive T cells are detected in patients with sJIA. Furthermore, genetic associations with human leukocyte antigen (HLA) class I or II alleles have not been identified at present. On the other hand, a large amount of evidences of cells and cytokines of innate immune response have been accumulating in sJIA. Based on these recent data, a new consensus is now emerging that sJIA may be an autoinflammatory disease[4].

Autoinflammatory Diseases

The autoinflammatory diseases are a group of recently recognized diseases characterized by systemic inflammation mediated by the cells and molecules of the innate immune system, with a significant host predilection[5]. Patients with this disease exhibit repeated or prolonged febrile episodes affecting the skin, joints, the gastrointestinal tract, or serous

membranes, without signs of infection or autoimmune phenomena. These inflammatory symptoms are caused by aberrant sensor activation or failure of the inhibitory mechanism of the innate immune response. Therefore, monocytes, macrophages, granulocytes, or natural killer (NK) cells are the pathogenic cells in autoinflammatory disease, in contrast to autoimmune diseases in which T cells and B cells play the major pathogenic role (Table 1).

The term 'systemic autoinflammatory syndrome' was first used by Kastner et al in 1999 in the report about TNF receptor-associated periodic syndrome (TRAPS)[5]. Thereafter, the spectrum of the autoinflammatory diseases has been spreading; it now includes periodic fever syndromes (hereditary or non-hereditary), some chronic granulomatous diseases, vascular diseases, and metabolic diseases. In addition, some rheumatic diseases with sero-negative features such as Behcet disease and sJIA are now being considered as autoinflammatory diseases (Table 2). The clinical features of these autoinflammatory diseases are summarized in Tables 3a-d.

Table 3b: Cryopyrin associated periodic syndrome (CAPS)

	Famillial cold autoinflammatory syndrome	Muckle-Wells syndrome	CINCA syndrome (Neonatal-onset multisystem inflammatory disease (NOMID)
Onset	Infancy	Infancy or adolescence	Early neonatal period
Inheritance	Dominant	Domina t	Dominant
Gene	*CIAS1*	*CIAS1*	*CIAS1*
Chromosome	1q44	1q44	1q44
Usual ethnicity	Any	Northern European	European
Protein involved	Cryopyrin	Cryopyrin	Cryopyrin
Fever duration	< 24 hours	1-2 days	Continuous (with flares)
Skin involovement	Cold-induced urticarial rash	Evanescent urticarial rash	Polymorphic urticaria-like rash
Articular involvement	Aarthraligias or joint stiffness	Non erosive transient polyarthritides	Deforming knee osteo-arthropathy
Neurological involvemnt	-	-	Chronic meningitis, hydrocephalus, pseudopapilledema, uveitis
Neurosensorial deafness	-	Present	Present
Treatment	Cold avoidance, anakinra	Anakinra, rilonacept, canakimumab	Anakinra, rilonacept, canakimumab
Amyloidosis	2-4%	25%	20%

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Clinical Mimicry of Autoinflammatory Diseases by sJIA

1) The epidemiology and clinical manifestations of sJIA

JIA is defined as arthritis in one or more joints persisting for 6 weeks or longer, which begins before the 16th birthday and has no other known cause[1]. It includes 6 subtypes of diseases including sJIA. The incidence of sJIA patients in all JIA was 42% in Japanese subjects in a nation-wide survey[2]. This is a relatively high incidence rate compared with that of the US or European countries (usually < 10%). In addition, the peak age of onset in sJIA patient is 2-4 years, which is the youngest among patients with other subtypes of JIA. These findings may indicate that there is a genetic background responsible for the pathogenesis of sJIA.

Table 3c: Granulomatous disease

	Blau syndrome/EOS	Crohn's disease
Onset	Infancy (before 4 years)	All ages
Inheritance	Dominant/ none	Complex non-Mendelian genetic trait
Gene	*NOD2/CARD15*	*NOD2/CARD15, MDR1, PXR/NRII2, DLG5, OCT1-2,etc*
Chromosome	16p12.1-13	16q12, 7q21, 3q13, 10q22, 5q31, etc
Protein involved	NOD2/CARD15	NOD2/CARD15, P-glycoprotein 170, nuclear hormone receptor, MAGUK, organic cation transportes 1$2, etc
Fever duration	variable	variable
Abdominal distress	Absent	Chronic relapsing interstinal inflammation with epithelioid granulomata
Skin involovement	Erythematous papular rash, painful panniculitis	Pyoderma gangrenosum, erythema multiforme/nodosum, necrotizing vasculitis
Articular involvement	Non-erosive granulomatous synovitis with painless cysts, "boutonniere" deformities of fingers, camptodactyly	Migratory polyarthritis, sacroileitis, ankylosing spondylitis
Ocular involvement	Granulomatous uveitis, risk of post-iritic blindness	Conjunctivitis, episcleritis, iritis, keratitis, xerophthalmia
Treatment	Corticosteroids, methotrexate, infliximab	Sulfasalazine, corticosteroids, azathioprine, infliximab, oral antibiotics, dietary arrangement

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The clinical features of sJIA are similar to those seen in patients with autoinflammatory diseases[6]. In the active phase of sJIA, the patient's body temperature suddenly rises to 39°C or higher, and is accompanied by severe malaise and tachycardia, with a rapid return to baseline or below the baseline (spiking fever) on a daily or twice-daily basis (quotidian pattern). The intermittent fever persists for at least 2 weeks, and is almost always accompanied by a non-fixed evanescent erythematous rash that has been described as being salmon pink in color. Some patients in the active phase develop systemic serositis such as pericarditis, pleuritis, or pan-peritonitis. Hepatosplenomegaly or systemic lymphadenitis is frequently observed. About 8% of sJIA patients develop macrophage activating syndrome (MAS) which is also recognized to be an autoinflammatory disease.

2) Disease course in sJIA

The systemic inflammation in sJIA is essentially self-limited. The acute manifestations, such as fever or rash, tend to subside during the initial months to years of the disease. Studies over the last 30 years have consistently shown that about half of the children with sJIA have attained drug-free remission after a variable period[7-10]. According to our follow-up data of 50 sJIA patients observed for a mean 7.9 years, 32% of the sJIA children followed a monocyclic disease course and eventually recovered after a variable period. In the follow-up study, 24% of children had a polycyclic course characterized by recurrent episodes of active disease interrupted by periods of remission without treatment. The disease course of sJIA is compatible with that of some autoinflammatory diseases. For example, the cyclic episodes ceased after a mean of 5.4 years from the onset in patients with periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) and; approximately one third of patients stopped having episodes, and the

symptoms became less intense and less frequent with the passage of time in the rest of the patients[11-12].

Table 3d: Miscellaneous autoinflammatory disease

	Systemic-onset juvenile idiopathic arthritis sJIA	Periodic fever, aphtosis, pharyngitis, adenitis syndrome PFAPA	Behçet syndorme
Onset	Any age	Childhood (especially children aged < 5 yeas)	Any age
Genetic association	-	-	HLA-B51
Fever reccurence	At leat 2 weeks' duration	Fever of 3-6 days duration with 4/6-week frequecy	unpredictable
Musculo-skeletal involvement	Arthritis in one or more joints (compulsory sign)	-	Arthralgias, arthritides
Skin involovement	Non-fixed evanescent erythematous rash.	-	Nodous erythema, acne, folliculitis, positive pathergy test
Oral involvement	-	Pharyngitis, aphthous stomatitis	Recurrent oral ulcers
Systemic signs	Generalized lymphnode enlargement, hepatomegaly and/or splenomegaly, Serositis	Cervical lymph node enlargement	Thrombophlebitis
Neurological involvement	Risk of macrophage activation syndrome	-	CNS vasculitis
Ocular involvement	-	-	Uveitis, retinal vasculitis, optic neuritis
Genital involvement	-	-	Recurrent genital ulcers, epididymitis
Laboratory involvement	Increased acute phase reactants, leukocytosi, anemia	Increased acute phase reactant, leukocytosis	Non-specific abnormalities
Treatment	Corticosteroids, NSAIDs, MTX, anakinra, canakinumab, tociizumab	Single-dose of corticosteroid (at the onset of fever), tonsillectomy	Interferon-α, cyclosporin, infliximab

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3) Initial diagnosis in patients with autoinflammatory diseases.

Due to the clinical symptoms and the disease course, a number of children with other autoinflammatory diseases might be misdiagnosed as having sJIA. In fact, 9 of 13 patients diagnosed as having an autoinflammatory disease by gene examination in the past 5 years in our clinic were initially diagnosed with sJIA (Table 4). Two cases of tumor necrosis factor receptor-associated periodic syndrome (TRAPS), shown in Table 4, were siblings, which provide a clue that helped us make a proper diagnosis[13].

Table 4: Initial diagnosis of patients with autoinflammatory disease

Disease	Patient	Sex	Age at onset	At diagnosis		Initial diagnosis
				Age	year	
Early onset sarcoidosis (EOS)						
	NT	M	1y	19y	2006	sJIA
	NK	M	8m	12y	2006	sJIA
	MK	M	6m	15y	2006	RF negative PoJIA
	UE	M	1y	9y	2009	sJIA
	YA	F	3y	8y	2006	RF negative PoJIA
	AA	F	3y	10y	2009	RF negative PoJIA
	TE	F	7y	16y	2009	sJIA
Familiar mediterranean fever (FMF)						
	TY	F	7y	20y	2009	HSP
	SK	F	4y	9y	2009	sJIA
	TM	F	4y	17y	2010	sJIA
TNF receptor assciated periodic syndrome (TRAPS)						
	NM	M	6m	10y	2004	sJIA
	NA	F	3y	4y	2004	sJIA
CINCA sydrome/NOMID						
	MR	M	1m	13y	2007	sJIA

sJIA:systemic JIA, poJIA: polyarticular JIA, RF:rheumatoid factor

HSP:Henoch Shonlein Purpura, EOS:Early onset sarcoidosis

CINCA:Chronic infantile neurologic cutaneous and articular syndrome

NOMID:Nenonatal-onset multisystem inflammatory disease

The Pathophysiological Course of sJIA is Similar to Autoinflammatory Diseases

1) Prominent innate immunity in sJIA

Several studies have indicated that the role of the adaptive immune system in sJIA may be rather limited compared with the other JIA subtypes, while the contribution of the innate immune system may be much more prominent[14-19].

Several studies using the microarray technology that allows for simultaneous assessment of the expression of thousands of genes have shown that sJIA is distinguished from other subtypes of JIA by the up-regulation of innate immune pathways, including IL-6, TLR/IL1R, and the peroxisome proliferator-activated receptor (PPAR) signaling pathways associated with down-regulation of the gene networks involving natural killer (NK)-T cell and major histocompatibility complex (MHC) antigen-related biological process, including antigen presentation[14, 16-20].

2) Major effector cells in sJIA

The main pathogenic cells in sJIA are neutrophils, macrophages, monocytes, and NK cells, which are all closely involved in the innate immune response.

In the active phase of sJIA, an increased number of neutrophils and monocytes associated with the expansion of immature myelomonocytoid precursors of CD34+cells or CD33+cells are often seen[16]. In addition, extremely high levels of S100 proteins derived from activated neutrophils and monocytes are reported in both patients with sJIA and those with familial Mediterranean fever (FMF), which is the most common Mendelian autoinflammatory disease that is characterized by autosomal recessive mutations in the MEFV locus[21-22].

Macrophage activation syndrome (MAS) is the most devastating condition related to sJIA, and is associated with serious morbid-

ity and sometimes death. It occurs in at least 7% of sJIA patients during the disease course, but rarely occurs in patients with other subtypes of JIA[23]. MAS most often occurs during the active phase of sJIA, but has been reported to occur at the time of disease onset[24-25].

3) Pivotal cytokines involved in sJIA

Potent pro-inflammatory cytokines, including IL-1, IL-6, and IL-18, have been reported to be pivotal cytokines in the inflammatory process of both autoinflammtory diseases and sJIA. The inflammatory process observed in some autoinflammtory diseases is explained by the formation of an abnormal inflammasome complex that eventually activates the caspase 1 pathway, which resulted in excessive IL-1ß and IL-18 production.

In the pathogenesis of sJIA, an important role for IL-1 was first reported by Pascual et al[14]. They showed that the serum from sJIA patients induced the transcription of various innate immunity genes, including IL-1beta, in peripheral blood mononuclear cells obtained from healthy individuals.

High levels of serum IL-18 were also reported in sJIA patients not only in the active phase, but also in the convalescent phase of the disease[26-27]. In addition, the high levels of IL-18 were derived from CD 68+ macrophages in the bone marrow[26].

On the other hand, high levels of IL-6 in serum or synovial fluids in patients with sJIA was described beginning in the 1990s, and the level of IL-6 correlates well with the overall clinical activity of the disease.

Table 5: Anti-IL-1 therapy in autoinflammatory diseases and sJIA

Blocking agents						Reports used for autoinflammatory diseases and sJIA				
		Target	Administration, interval	Dose (mg/kg)	FDA approved use	CAPS	FMF	TRAPS	sJIA	Adult onset Still
Anakinra (Kineret®)	**fully-humanized anti-IL-1Ra**	IL-1R	sc, daily	1-2 (max 100 mg)	RA	CINCA 10 cases (31), FCAS 4 cases (32), MWS case report (33)	ase report (38-39)	5 cases (40)	22 cases (29), 20 cases (37), 15 cases (35)	15 cases (37)
Rilonacept (Arkalist®)	**IL-1R/IgG2 Fc fusion protein**	IL-1α /β	sc, weekly	2.2-4.4	FCAS, MWS Age ≥ 12y	FCAS 44 cases, MWS 3 cases (34)			21 cases (36)	
Canakinumab (Ilaris®)	**fully-humanized anti-IL-1β Mab**	IL-1β	sc or iv, every 8w	2		CAPS 35 cases (30), On international clinical study	On international clinical study		On international clinical study	

(reference number), sc:sub cutaneous, iv: intravenous

RA: rheum toid arthritis, FCAS: familiar cold associated syndrome, MWS: Muckle-Wellis syndrome

CAPS: cryopyirin-associated periodic syndrome, TRAPS: tumor necrosis factor receptor associated periodic syndrome

FMF: familiar Mediterrenean fever, sJIA: systemic onset juvenile idiopathic arthritis.

These findings provide a rationale for the use of biological blocking agents for IL-1 and IL-6. A clinical trial for sJIA patients was first conducted in Japan using an anti-IL-6 receptor antibody, tocilizumab (TCZ). The results were completely successful in terms of its efficacy and safety[28], and the Japanese Ministry of Health, Labor and Welfare ap-

proved its use in children with refractory sJIA in 2008.

In 2008, the FDA also approved rilonacept, an IL-1 blocking agents, for patients with cryopyrin-associated periodic syndrome (CAPS) which is an autoinflammatory disease. The IL-1 blockers are now recognized as an effective biologics in both patients with autoinflammatory diseases and sJIA[29-40] (Table 5).

Conclusions

It is clear that the pathogenesis of sJIA is closely associated with abnormalities in the innate immune system, rather than with classic auto-immunity. Patients with sJIA should therefore be viewed as having a pathophysiological condition similar to that observed in autoinflammatory diseases. Further studies on the genetics and molecular pathophysiology are essential in order to deepen our understanding of human innate immunity, and to offer more targeted therapies for patients with sJIA.

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