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Pathogenesis of Systemic Inflammatory Diseases in Childhood: "Lessons From Clinical Trials of Anti-Cytokine Monoclonal Antibodies for Kawasaki Disease, Systemic Onset Juvenile Idiopathic Arthritis, and Cryopyrin-Associated Periodic Fever Syndrome"

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Abstract

Inflammation has often been considered a non-specific response, and to play only a bridging role in the activation of adaptive immunity. However, it is now accepted that inflammation is the product of an independent innate immune system closely linked to the adaptive immune system. The key mediators of inflammation are inflammatory cytokines, as determined by multiple lines of evidence both *in vitro* and *in vivo*. Due to the crucial role of inflammatory cytokines in the pathogenesis of autoimmune disorders, anti-cytokine treatment has been developed as a therapy for rheumatoid arthritis, juvenile idiopathic arthritis (JIA), and inflammatory bowel disease. We recently completed several clinical trials of anti-cytokine treatment for children with systemic inflammatory diseases: anti-IL-6 receptor monoclonal antibody (tocilizumab) for children with 2 subtypes of JIA (poly-JIA and systemic JIA), anti-TNF-alpha monoclonal antibody (infliximab) for children with Kawasaki disease, and anti-IL-1-beta monoclonal antibody (canakinumab) for children with cryopyrin-associated periodic syndrome. This review summarizes the basis of inflammation in terms of innate immunity and adaptive immunity in these systemic inflammatory diseases, clinical efficacy and tolerability of these biologic agents, and attempts to determine the roles of individual inflammatory cytokines in disease pathogenesis.

Keywords: Innate immunity; Inflammation; Kawasaki disease; Systemic-onset juvenile idiopathic arthritis; Cryopyrin-associated periodic syndrome

Abbreviations: IFN-γ: Interferon-γ; Th1: T helper cell; Treg: Regulatory T cell; PAMPs: Pathogen Associated Molecular Patterns; DAMPs: Damage Associated Molecular Patterns; TLR: Toll Like Receptor; MDA5: Melanoma Differentiation Associated Gene-5; NLRs: Nod Like Receptor; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; MyD88: Myeloid Differentiation Primary Response Protein-88; IRAK-4: Interleukin-1 Receptor Associated Kinase-4; NEMO: NF-kB Essential Modulator; MHC: Major Histocompatibility; TCRs: T cell receptors; CRP: C-reactive protein; SAA: Serum Amyloid A; ESR: Erythrocyte Sedimentation Rate; IVGG: Intravenous Gamma Globulin; PE: Plasma Exchange; HSP-65: Heat Shock Protein-65; MMP-3: Matrix Metalloproteinase-3; MCP-1: Monocyte Chemo-attractant Protein-1; ICAM-1: Intrecellular Adhesion Molecule-1; TFs: Tissue Factors; CAPS: Cryopyrin Associated Periodic Syndrome; FCAS: Familial Cold Autoinflammatory Syndrome; MWS: Muckle-Wells Syndrome; CINCA: Chronic Infantile Neurological Cutaneous and Articular Syndrome; NOMID: Neonatal Onset Multisystem Inflammatory Disease

Introduction

Infectious diseases, in which defenses against an infectious agent are established and can later be recalled, account for practically all childhood illnesses. Inflammatory pathogenesis depends initially on the balance between invasiveness of an infectious agent such as a bacterium or virus, and inflammatory processes triggered in the host in defense [1]. On the other hand, inflammation such as that seen in rheumatic diseases, though unclear how it is triggered, damages and destroys organs and tissues, resulting in fibrotic changes caused by repair.

Inflammation is systemically manifested as fever and sickness behaviors such as malaise and anorexia, and locally as redness, warmness, swelling and pain at the affected area. Corresponding pathological changes at a local inflammatory site irrespective of the organ, are infiltration by inflammatory cells such as neutrophils in the acute phase and mononuclear cells in the chronic phase, tissue edema, and a mixture of tissue destruction and fibrosis in longstanding inflammation. It is interesting and valuable for establishing the therapeutic concept to understand what the common inducing factor(s) are for inflammation in human diseases, and how the inflammatory cytokines play a role in inflammation under pathological as opposed to physiological conditions.

In this review, we consider typical inflammatory diseases such as Kawasaki disease, systemic-onset juvenile idiopathic arthritis and cryopyrin-associated periodic fever syndrome. We review efficacy as well as adverse effects of novel therapeutic agents designed to inhibit individual cytokines and, in turn, roles of individual inflammatory cytokines in inflammatory pathogenesis.

Inflammation and Immunity

The innate immune system and disease

Inflammation has been considered to be a nonspecific and unsophisticated system, and to play only a bridging role in the

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activation of the more specific and sophisticated adaptive immune system. However, it was very recently clarified that inflammation was an independent system though it was closely linked to the immune system [2].

Thus, the system to generate inflammatory cytokines and type I interferon (IFN) as an effector molecule is called innate immunity while the classical immune system with memory is called adaptive immunity [3]. It is unquestionable that both systems are intimately connected to one another and that their interactions contribute to inflammatory pathogenesis.

Inflammation is a functional manifestation of innate immunity, whose immunocompetent cells include dendritic cells, monocytes/macrophages, neutrophils in a broad sense, and humoral factors such as chemokines and complement in addition to inflammatory cytokines and type I IFN. Conversely, adaptive immunity is mediated by specific T cell subsets including Th1, Th2, Treg and Th17 cells, and B cells [4]. B cells differentiate eventually into plasma cells, which yield antigen-specific antibodies as a final product of adaptive immunity.

Two kinds of stimuli are known to bring about inflammation involving dendritic cells and monocytes/macrophages: one is pathogen-associated molecular patterns (PAMPs) where a virus or bacterium is the pathogen; the other is damage-associated molecular patterns (DAMPs) where the triggers are intracellular proteins, enzymes, nucleic acids and nuclear proteins which are released into surrounding tissues as a result of host cell apoptosis and/or necrosis [5]. Contrary to adaptive immunity, neither PAMPs nor DAMPs are specific for any antigen, but each binds to a receptor that recognizes it according to the pattern.

Dendritic cells and macrophages express Toll-like receptors (TLRs; TLR2, TLR4, TLR5) residing on their surfaces and have intracellular sensors such as TLRs (TLR3, TLR7/8, TLR9), melanoma differentiation-associated gene-5 (MDA5), retinoic acid–inducible gene-I (RIG-I) and Nod-like receptors (NLRs) as well. These receptors or sensors recognize inflammation-provoking factors, PAMPs and DAMPs. Dendritic cells and macrophages are activated by recognition of such inflammation-provoking factors to ultimately produce and release type I IFN and such inflammatory cytokines as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, interferon (IFN)-γ and IL-18 [6].

Thus, in the inflammation system, PAMPs and DAMPs are provoking factors, which are bound by receptors borne on dendritic cells and macrophages. These cells eventually release inflammatory cytokines and type I IFN that trigger inflammation. Among genetic variants of this system causing disease are myeloid differentiation primary-response protein-88 (MyD88) deficiency, interleukin-1 receptor-associated kinase (IRAK)-4deficiency, NF-κB essential modulator (NEMO) deficiency, and IkBα-deficiency [7]. Autoinflammatory syndrome is a prime example of a phenotype of individual amino acid substituted protein components of the inflammasome that activates pro-IL-1β and pro-IL-18 [8]. Moreover, there are diseases that are caused by an excessive amount of cytokines produced presumably due to functional abnormality of production and regulation, although the mechanisms responsible are unclear: hemophagocytic lymphohistiocytosis, septic systemic inflammatory response syndrome, and macrophage activation syndrome [9].

Adaptive immunity and disease

Antigens are the triggers of adaptive immunity. An antigen is first taken up by antigen-presenting cells, i.e., monocytes/macrophages and B cells, processed and presented to $CD4^+$T cells. These recognize the antigen via T cell receptors (TCRs) restricted by self major histocompatibility complex (MHC) molecules. Naïve $CD4^+$T cells can then differentiate into Th1 cells in the presence of IL-12 to produce IFN-γ which plays a role in anti-viral and anti-tumor activities. Naïve $CD4^+$T cells can also differentiate into Th2 cells under the influence of IL-4 to release IL4 itself, and support IgE production, potentially contributing to allergic illness development. Furthermore, naïve T cells may also differentiate into Th17 cells in the presence of TGF-β together with IL-6 to release IL-17 which plays a role in inflammation and autoimmunity. These naïve $CD4^+$T cells may also differentiate into Treg cells in the presence of TGF-β to release IL-10 as well as TGF-β which are involved in the control of T cell activation [10]. In this way, a variety of effector cells including Th1, Th2, Th17, Treg and $CD8^+$T cells develops under the influence of essential T-cell cytokines and TGF-β and regulates information and reactions to eventually promote differentiation/proliferation of B cells that produce an antigen-specific antibody.

his system constitutes adaptive immunity. In other words, adaptive immunity may be regarded as a system that generates an antibody maintaining antigenic specificity after processing information on that antigen restricted by self-MHC. Autoimmunity represents a "functional abnormality" of this system as follows: an antibody produced by B cells, if it targets self-components, is bound to self-cells or self-tissues to cause chronic inflammation. Primary immunodeficiency syndrome is a set of symptoms that occur due to gene mutation of individual functional proteins formed at individual steps of this system [11].

Clinical Symptoms/Laboratory Data on Inflammation

Inflammation manifests itself systemically as fever, malaise and anorexia. It is known from animal experiments that costimulation with IL-1β and IL-6 is essential for fever development [12]. It was also reported that both malaise and anorexia were triggered only when a trace amount of both IL-1βand IL-6 were concurrently administered, as seen in experiments using rats whose cerebral ventricles were injected with various inflammatory cytokines through indwelling catheters to monitor food intake and quantity of motion as a reflection of malaise and anorexia [12].

In human beings as well, administration of an anti-IL-6 receptor monoclonal antibody (tocilizumab) results in prompt improvement of fever, sickness behavior, skin rash, and laboratory abnormalities seen in inflammatory responses through specific blockade of IL-6 activity in patients with systemic-onset juvenile idiopathic arthritis in which excessive production of IL-6 plays a critical role in pathogenesis (see later discussion). Similarly, anti-IL-1βmonoclonal antibody (canakinumab) administration results in blockade of the specific inflammatory cytokine, IL-1β, and is effective in relieving various symptoms including fever, chronic sterile meningitis and arthropathy in CAPS cases where an excessive amount of IL-1β is produced (see later discussion). Thus, it is clear that physical manifestations of inflammation including fever, malaise, and anorexia are the functional expression of inflammatory cytokines.

At the bedside, C-reactive protein (CRP), serum amyloid A (SAA), and erythrocyte sedimentation rate (ESR) are used as markers of inflammation. Information on the production of hepatic CRP and SAA can be obtained by means of quantitative estimation of mRNA using hepatic cells cultured in the presence of different inflammatory cytokines [13,14]. The quantity of CRP-mRNA is slightly increased by IL-6 alone but is maximally increased by concomitant addition of IL-6 and IL-1β [13]. On the other hand, the maximal amount of SAA-

mRNA is produced when IL-6+IL-1β or IL-6+TNFα are added to the medium [14]. Consequently, it is clear that inflammatory markers frequently used at the bedside reflect quantities of inflammatory cytokines produced by the innate immune response.

Moreover, chronic inflammatory disease is without exception associated with iron deficiency anemia. In a hepatic cell culture system, addition of IL-6 stimulates *de novo* synthesis of hepcidine which has recently been found to inhibit iron release in the reticuloendothelial system and to suppress gastrointestinal absorption of iron [15]. It was known empirically in the clinical setting that iron administration was ineffective in the treatment of the chronic anemia seen in chronic inflammation. It was also reported that the level of hepcidine was inversely correlated with the degree of anemia in Castleman's disease [16].

Kawasaki Disease and TNF-α

Characteristics of symptoms and interpretation of laboratory data

Kawasaki disease is an acute inflammatory illness that subsides in about 2 weeks. Its diagnosis is made based on a combination of clinical symptoms as follows: persisting fever, skin rash, indurative edema in the peripheral limbs, ocular hyperemia, cervical lymphadenopathy, red fissures and bleeding of the lips, strawberry tongue and redness and ulceration of BCG vaccination scars. These signs and symptoms develop with diverse kinetics over the course of the illness, eventually coalescing into the complete clinical picture. Coronary artery lesions are still a serious complications in 5-10% of affected children despite the administration of intravenous high-dose gamma globulin. The pathogenic basis of each symptom is clear: fever and skin rash reflect reactions of inflammatory cytokines; ocular hyperemia or vascular dilatation in the eyeball is an expression of vasculitis; and indurative edema results from plasma extravasation due to endothelial disruption of the medium-sized vessels [17]. A BCG vaccination scar results from a delayed-type hypersensitivity reaction against inflammation-inducing factors which are cross-reactive with BCG.

Membranous desquamation begins to appear at the boundary between the skin and nails 12 days after disease onset, which finding establishes the final diagnosis of Kawasaki disease. During the course of the disease, coronary artery lesions develop as a reflection of systemic inflammation usually 10 days or more after the onset but around 7 days in some cases with severe inflammation.

Blood laboratory data also run a unique course. The white blood cell count ranges from 10,000 to 15,000/Ml or more, with neutrophils accounting for over 70% or often 80 to 90%. Left shift of white blood cells (ratio of nature to immature cells) is not observed with about 1 to 5% stab neutrophils and over 95% hypersegmented neutrophils. Such characteristic features of white blood cell differentiation are frequently seen in other systemic vasculitides, eg., Takayasu disease and polyarteritisnodosa, suggesting that Kawasaki disease is not of infectious etiology but represents a sterile inflammatory comdition. The level of fibrinogen-fibrin degradation product rises up to 200 to 500 μg/mL in the FDP-E fraction (normal range <60 μg/mL), and 3-8 μg/mL in the D-dimer fraction, indicating endothelial dysfunction [18].

The blood stream containing such inflammatory cytokines as IFN-γ, TNF-α, IL-6 and IL-1β continuously bathes the surface of endothelial cells, the structures of which are injured due to induced inflammation. FDP and D-dimer levels, reflecting the extent of damaged endothelial cells [19,20], are not as markedly increased as in virus-associated hemophagocytic syndrome and macrophage activation syndrome, presumably because inflammation is relatively limited to the medium-sized vessels in Kawasaki disease.

As the disease progresses, the serum albumin level declines often down to 2 g/dL or lower in parallel with progression of indurative edema in the peripheral limbs. Increased levels of CRP and SAA are reflected by elevations of IL-1β and IL-6 [13,14] while LDH levels from 300 to 500 IU/L indicate destruction of over-mature neutrophils, disruption of endothelial cells and injury of other organs and cells.

Therapy of Kawasaki disease

In 1991, Newburger proposed high-dose intravenous gamma globulin (IVGG) therapy (2 g/kg body weight), which is now the first-line treatment [21]. Although its mechanism of action remains unclear, IVGG is considered to re-adjust excessive inflammatory cytokines to a balanced level. Thus, it was shown that IVGG decreased the IL-6 level to normal although the soluble IL-6 receptor level remained rather high and the TNFα level was unchanged (although the prior high level of soluble TNFα receptor was markedly reduced) [22]. Nevertheless, 5 to 10% of cases have a sequel of coronary artery lesions despite additional IVGG therapy. Therefore, steroid therapy including methylprednisolone pulse treatment was reportedly tried, but its efficacy was hard to evaluate according to a meta-analysis [23,24]. Another therapy using ulinastatin, which prevents activated neutrophils from releasing elastase and suppresses elastase activity, was reported [25] but, although it is useful as complementary treatment, there is little pathophysiological rationale for its use.

Plasma exchange

In Kawasaki disease, plasma levels of a plethora of inflammatory cytokines including IL-6, IL-10, IL-17, IFNγ, TNFα and soluble E-selectin change markedly from the acute to the recovery period [26]. It was demonstrated that inflammatory cytokines are essential factors for the pathogenesis of inflammation in Kawasaki disease and that coronary artery lesions were caused by abnormal activation of endothelial cells, progressive injury of the arterial media and activation/disruption of the coagulation and fibrinolysis systems [27,28].

If inflammatory cytokines play a central role in the pathogenesis of inflammation and coronary artery lesions in Kawasaki disease, it would be a reasonable therapeutic strategy to comprehensively deplete them or to specifically eliminate the major leading ones. The former strategy corresponds to plasma exchange while the latter represents anti-cytokine monoclonal antibody therapy. Additionally, it will be of value to stabilize the cytokine-producing cells, although this may not be essential because Kawasaki disease is a febrile acute syndrome, but is not a persistent or chronic illness.

Plasma exchange (PE) has been performed in our department since 2000 for the purpose of depleting all of the inflammatory cytokines, chemokines and potential inflammation-provoking factors [29]. Evaluation of its therapeutic efficacy requires reference indexes, and to this end we have been using post-treatment types of fever and fractional changes proposed by Mori et al. in our department [30].

Coronary artery lesions are likely to develop with a probability of ca. 70% in cases that have a recurrent fever over 38°C within 24 hours after a second IVGG infusion with persistent positivity for fractional changes [30]. A total of 125 Kawasaki disease patients refractory to IVGG were treated by PE. Of these, 105 (84.0%) whose coronary arteries were normal before PE had no sequelae. Dilatation was present before PE in 14 patients (11.2%), but persisted only in two (1.6%) in the late period.

In 4 of the 6 patients (4.8%) in whom aneurysms had already formed before PE, the lesions had advanced into giant aneurysms, but in the other 2 patients (1.6%) they returned to the normal range. Thus, the efficacy of PE for Kawasaki disease refractory to IVGG is remarkable, particularly if it is initiated before coronary artery lesions arise [31].

Infliximab therapy (TNFα inhibition therapy)

Infliximab is a chimeric (human and mouse) monoclonal antibody that directly binds to TNF-α and blocks its function. The biological function of TNF-α is (1) it induces other inflammatory cytokines such as IL-1β and IL-6; (2) it acts on vascular endothelial cells to enhance vascular permeability and stimulate leukocyte migration from the blood stream into surrounding tissues; (3) it promotes expression of adhesion molecules on the surface of endothelial cells and increases their release (E- and L-selectin, ICAM-1, etc.); (4) it binds to TNFα receptors on the cell membrane to induce cellular apoptosis by mitochondrial permeability transition; and (5) it stimulates ferritin production in the reticuloendothelial system [32-36].

In addition, since infliximab administration cures synovitis in rheumatoid arthritis and juvenile idiopathic arthritis, this agent has been approved for the treatment of chronic inflammatory diseases including Crohn's disease, ankylosing spondylitis, psoriasis, ulcerative colitis and arthritis.

In 2005, Burns et al. made a retrospective analysis of 16 cases of Kawasaki disease gathered from around the USA that were treated with infliximab [37]. These 16 cases had not responded to 2 or 3 courses of IVGG but infliximab administration immediately reduced their temperature and lowered the CRP level in all of them. However, 12 of them developed coronary artery dilatation/aneurysm although 4 improved later. All 4 cases without a coronary artery lesion had been treated with infliximab within 11 days of disease onset, whereas the 12 cases with lesions had been similarly treated but 11 days or more after onset. This suggests a narrow "window of opportunity" for such treatment. Thereafter, a prospective clinical study of infliximab efficacy was performed in 24 Kawasaki disease patients who did not respond to IVGG [38]. Half of these patients were treated with a second round of IVGG and if they again failed to respond, they were treated with infliximab. The other half were first treated with infliximab and non-responders then given a second course of IVGG. A reduction in body temperature was observed in 8 cases of the first group and 11 of the second. The effect on coronary artery lesions was not different between the two groups.

Subsequently, we performed an open-label trial of infliximab in 20 cases unresponsive to IVGG [39]. This clinical trial was characterized by rescue plasma exchange planned to be implemented in patients where IVGG-infliximab failed. When infliximab was administered to patients with fever but in whom fractional changes (+) persisted after IVGG, inflammatory symptoms were improved and indexes of inflammation normalized rapidly in all cases. Fever recurrence and re-elevation of laboratory values were seen within 48 hours in two cases, who were then additionally treated by plasma exchange without any sequelae. Thus, in this trial, alleviation of inflammation was achieved in all patients. Plasma exchange improved two cases with coronary artery dilatation at the time of infliximab administration.

More recently, the infliximab-PE study was expanded to 76 patients with Kawasaki disease refractory to IVGG. Seventy of these patients rapidly responded to infliximab without any sequelae. Six patients refractory to infliximab were additionally treated with PE, with only one dilatation and no aneurysms [in preparation].

According to these results, it should be possible to almost completely prevent the development of coronary artery lesions in patients with Kawasaki disease using a sequential therapeutic regimen consisting of IVGG infusion, infliximab and plasma exchange provided that this is carried out within 10 days of onset even in intractable cases if initiated before coronary artery lesions arise.

Conclusions on Kawasaki disease

In Kawasaki disease, inflammation can be negated by comprehensive removal of inflammatory cytokines involved in acute inflammation (using plasma exchange) or by selective removal of leading cytokines (using infliximab). Conversely, it is well understood that Kawasaki disease is caused by rapid, excessive generation of inflammatory cytokines. Such generation of inflammatory cytokines occurs via activation of innate immunity although the factors responsible therefore are not known. As mentioned above, inflammation in Kawasaki disease will be triggered by PAMPs or DAMPs.

We previously proposed that heat shock protein (HSP)-65, which strong evokes inflammation, is a candidate causative factor in Kawasaki disease [40]. HSP-65 is an inflammatory/immunoactive protein expressed in all bacteria including BCG, and similar to the P1 antigen in human cells [41]. HSP-65 was thereafter proposed to cause Kawasaki disease [42,43]. The following scenario is conceivable: bacterial infection causes inflammation via PAMPs and at the same time DAMPs such as bacterial cells/nuclear proteins, HSP-65, HMGB-1 and S100 trigger inflammation via different routes [44], resulting in an excessive amount of inflammatory cytokines which are not appropriately controlled because of disordered (or immature?) immunoregulatory function in these young patients (>85% of whom are <5 years old). We anticipate that the triggering factors involved in the initial phase of the disease will be the subject of extensive studies in future.

Systemic-onset Juvenile Idiopathic Arthritis and IL-6

Characteristic symptoms and interpretation of laboratory data of systemic-onset juvenile idiopathic arthritis (systemic JIA)

Systemic JIA is a type of JIA the main symptoms of which are remittent fever, skin rash and arthritis. Severe cases may be associated with hepatosplenomegaly, systemic lymphadenopathy and serositis [45]. Arthritis is likely to affect the shoulder and hip joints unlike in articular JIA. Advanced articular JIA is characterized by narrowing of the joint space as occurs in adult rheumatoid arthritis, whereas systemic JIA progresses to markedly advanced osteoporosis and poor growth/deformity of the epiphyseal nucleus, suggesting that the two types of JIA are different disease entities [46]. A problematic complication is macrophage activation syndrome, which is regarded as a pathological condition indicating a poor prognosis [47].

Blood values are reported to specifically show an elevation of inflammatory factors such as CRP and SAA, leukocytosis usually >15,000/μL with 70 to 90% mature neutrophils with no left shift, elevated levels of IL-6 and IL-18, an increased level of hemoxygenase (HO)-1 [48] and an elevation of the ferritin level [49]. Its clinical diagnosis, however, is made by exclusion of infectious disease, other rheumatic disease or malignancy including leukemia.

The diagnosis is established based on the following: clinical manifestations of fever, skin rash and arthritis, especially physical findings of arthritis, hyperplasia of the synovial membrane evidenced by joint echography, synovial fluid retention, increased blood supply

verified by power Doppler, exclusion of malignancy by bone marrow aspiration and, if possible, exclusion of malignancy or deep infection using 18F-FDG-PET. If available diagnostic tools are restricted to establishment of blood values, the following data are gathered together: an elevation of inflammatory markers such as CRP and ESR, amatrix metalloproteinase-3 (MMP-3) value that informs on synovitis as well as cartilage destruction, determination of HO-1, ferritin and cytokines including IL-6 and IL-18, and NK cell activity.

Macrophage activation syndrome

Clinical features of macrophage activation syndrome: Macrophage activation syndrome is not a disease entity in itself but a pathological condition associated with systemic JIA as reported by Stephan in 1993 [50]. This first report already described a high level of urinary TNF-α. This pathological condition runs a short course but cannot be diagnosed by a single laboratory value or at a single time point. Laboratory data must be gathered over time and include platelet counts/white blood cell counts, D-dimer/FDP-E (fibrin degradation product in the blood), aspartate transaminase/lactate dehydrogenase, ferritin/β2-microglobulin, total cholesterol/triglycerides, and others. Fluctuations of such laboratory data are very common in this pathological condition and also among cases of hemophagocytic lymphohistiocytosis or familial (hereditary) hemophagocytic syndrome, as well as systemic inflammatory response syndrome. Hemophagocytic events are common findings among the above-mentioned pathological conditions. These findings can be reasonably explained by excessive production of inflammatory cytokines common to these syndromes, contributing to inflammatory pathogenesis by being produced and released in a certain order [51].

It was also reported that NK cells as well as $CD8^+$T cells had abnormally low perforin levels [52,53] in this pathological condition. Macrophages and dendritic cells infiltrating organs are activated to produce/release an uncontrolled large amount of inflammatory cytokines while vascular endothelial cells are activated and disrupted, and tissue and cellular apoptosis/necrosis progresses. It should, therefore, be assumed as an underlying etiology that NK cells and CD8+ T cells have ceased to function properly. Stephan et al. suggested that transition from systemic JIA to macrophage activation syndrome can be triggered by virus infection or a change of medication [47], which remains to be confirmed.

Endothelial cell activation/disruption and activation of the coagulation and fibrinolytic system: In systemic inflammation, overproduced inflammatory cytokines circulate in the blood. Consequently, endothelial cells are activated by these inflammatory cytokines that are released by activated monocytes-macrophages and, in turn, endothelial cells themselves release cytokines such as IL-1β, IL-8, monocyte chemo-attractant protein-1 (MCP-1) and chemokines. Such interactive activation of macrophages and endothelial cells has recently attracted much attention [54]. Because certain cytokines, especially IFN-γ, upregulate the expression of HLA class I molecules on the endothelial cells membarane, H and L chains are increasingly translated. As a result, a large amount of L chains that fail to assemble with H chains are excreted in the urine as β2-microglobulin [55].

Endothelial cells activated by inflammatory cytokines also express elevated levels of adhesion molecules such as intercellular adhesion molecule-1(ICAM-1) and E-selectin, which direct activated neutrophils as well as cytotoxic mononuclear cells to sites of inflammation [56]. Endothelial cells continuously trap these activated cells via adhesion molecule/ligand interactions; some then release lysosomes, proteases, and reactive oxygen species into their immediate surroundings, resulting in destruction of the endothelial cells compromising endothelial integrity. They may be further damaged by tissue factor release. Because vascular endothelial cells' ability to adjust permeability plays a vital role in homeostasis, it is important to attempt to repair them immediately [57]. Such damaged endothelial cells themselves and activated macrophages release tissue factors (TFs), which in turn activate coagulation factor VII (TF-VIIa) as well as the extrinsic pathway [58]. Platelets adhere to and via von Willbrand factor agglutinate collagen exposed on damaged endothelial cells. Collagen activates coagulation factor XII as well as the intrinsic pathway. Injured vascular walls then become covered by fibrin nets and thrombi are formed, promoted by the activated extrinsic and intrinsic pathways, and platelet adhesion and aggregation, and eventually leading to blockage of plasma flow into tissues [59,60].

The fibrinolytic system is also activated to excise fibrins formed on endothelial cells, increasing the amount of FDP-E/D-dimer, a fibrin degradation product, in the blood. Levels of FDP-E/D-dimer reflect the extent of vascular endothelial cell damage. Endothelial cells thus activate the fibrinolytic system via inflammation [61]. If this activation goes beyond the bounds of physiological homeostasis, PT/APTT collapses and may progress to the development of disseminated intravascular coagulation (DIC) .

Tissue/cell injury by TNF-α: TNF-α function as an inflammatory cytokine and also as the next most important apoptosis inducer after Fas/Fas-ligand interactions [62]. If TNF-α is produced to a degree that overwhelms the neutralizing capacity of TNFRI, a soluble receptor, it binds to its specific receptors on the cell membrane, stimulates the intracellular signal transduction pathway and promotes the mitochondrial permeability transition [35]. Cytochrome C released from mitochondria then activates enzymes of the caspase family, one of which, caspase-3, is finally activated in cells to randomly cleave DNA, leading to cellular apoptosis/necrosis. On the other hand, since serum ferritin production by the reticulo endothelial system is controlled by TNF-α [36], the serum ferritin level, reflecting the amount of systemic TNF-α, provides a rough idea of the degree of TNF-activation in the clinical setting.

As vascular endothelial cells become more badly damaged and the coagulation and fibrinolysis systems are activated to repair them, activation of coagulation may come to predominate. Dysregulated coagulation control involving antithrombin, activated protein C/protein S, and thrombomodulin results in the systemic pre-DIC state transitioning to the DIC state. This manifests itself as prolonged PT/APTT and the tendency to bleed. Because lipoprotein lipase activity is under the control of TNF-α [63], persistent high levels of TNF-α in the circulation can lead to abnormal lipid metabolism. Eventually, multiple organ failure via a series of events occurs in the following order: an elevation of the serum triglyceride level, a reduction of the serum total cholesterol level, renal failure as reflected by an increase of serum creatinine, liver dysfunction as evidenced by increased levels of alanine transaminase/total bilirubin, and pancreatic insufficiency represented by an elevation of serum amylase and lipase levels.

Treatment

Systemic-onset juvenile idiopathic arthritis: In the past, there was no alternative but to treat this disease by long-term administration of high-dosecorticosteroids to suppress severe systemic inflammation. This regimen greatly affected the quality of life of these children due to the following side effects: obesity, growth retardation, osteoporosis,

compression fractures of the vertebrae, femur head necrosis and steroid diabetes. TNF-α blocking agents known to be effective for rheumatoid arthritis and articular JIA, were tried but unfortunately they were found to have limited efficacy. In contrast, an IL-1 receptor antagonist (IL-1Ra), anakinra, was reported to be effective [64].

It was reported in the 1990s that IL-6 was the major factor involved in the pathogenesis of systemic JIA. It was shown blood IL-6 levels peaked one hour before fever onset and that reduction of the feverparalleleddecreasedIL-6 level [65]. An anti-IL-6 receptor monoclonal antibody, tocilizumab, was developed in Japan. After it was first administered to pediatric patients on acompassionate use basis, it proved to have impressive efficacy in phase II and III clinical trials [66,67] as discussed later and was the first in the world to gain regulatory agency approval.

Macrophage activation syndrome: Previously, the prognosis of patients with macrophage activation syndrome was extremely poor as in virus-associated hemophagocytic syndrome and septic systemic inflammatory syndrome. However, the pathophysiological mechanisms in macrophage activation syndrome have gradually become apparent, and clinical manifestations and the fluctuating laboratory parameters can be explained by the presence of excessive amounts of inflammatory cytokines [9]. Thus, macrophage activation syndrome can be managed at this time by the following approaches: alleviation of activated macrophages and dendritic cells by corticosteroids in addition to anticoagulant therapy; inhibition of the mitochondrial permeability transition by cyclosporine to deal with tissue/cellular injury caused by inflammatory cytokines; and plasma exchange to reduce excessive inflammatory cytokines [49]. These treatments are life-saving for most patients in our hospital.

Tocilizumab therapy (anti-IL-6 therapy)

IL-6 alone is not sufficient to cause inflammation, but when complexed with the soluble IL-6 receptor or the membrane-bound IL-6 receptor, gp130, is triggered to transduce inflammatory signals [68]. Consequently, tocilizumab blocks the IL-6 binding site and inhibits signaling by binding to both soluble and membrane-bound IL-6 receptors [69].

Tocilizumab has such a strong anti-inflammatory effect that a dose of 8 mg/kg already decreases fever within hour's administration and alleviates malaise and anorexia. About one week after treatment initiation, the CRP level returns almost to normal, and arthritis starts to improve in a couple of weeks [66]. The IL-6 level may rise temporarily because of the lack of soluble IL-6 receptors in addition to the smoldering inflammation, but is generally reduced to undetectable levels in 3 to 6 months. Biweekly administration of tocilizumab, if repeated for a period of several months to several years, achieves an improvement rate of around 90% as evaluated by ACR Pedi 70 [67]. Briefly, it can be safely said that IL-6 has a leading role in systemic inflammation of systemic JIA, as evidenced by an anti-IL-6 receptor monoclonal antibody effectively depressing inflammation through blocking IL-6 signaling [70]. Recently, the efficacy and tolerability of tocilizumab for systemic JIA patients has been confirmed by De Benedetti and the European group [71].

Conclusions on systemic JIA

Blockade of signaling by the single cytokine IL-6 can abrogate inflammation in systemic JIA, which documents that IL-6 has a leading role in this disease. In vitro studies of CRP or SAA using hepatic cell cultures revealed the requirement for cooperation between IL-6 and IL-1β, implicating IL-1β as well as IL-6 in the pathogenesis of inflammation in systemic JIA. The efficacy of anakinra [64], and more recently canakinumab [72] is consistent with such a role for IL-1β.

Macrophage activation syndrome is a pathological condition which progresses from systemic JIA due to dysregulation of multiple inflammatory cytokines including TNF-α and IFN-γ. This results in cell/tissue damages and disruption of endothelial cells. However, the sequence and quantity of each cytokine remain to be investigated, and, more importantly, mechanisms regulating the production of each cytokine and their mutual effects are completely unknown. Hopefully, a way to comprehensively block the production of inflammatory cytokines will be developed in future, possibly an NF-kB blocking agent, or a way to block the augmentative loop of inflammatory response or to restore the negative feedback loop will be established [73,74].

Cryopyrin-Associated Periodic Syndrome and IL-1β

Clinical manifestations and changes of laboratory data

Patients with cryopyrin-associated periodic syndrome (CAPS) present with periodic fever, urticaria-like skin rash, inflammation of the central nervous system and joint symptoms. They present with a variety of clinical symptoms such as amyloidosis because of the inflammation sustained over a prolonged course [75].

CAPS isdivided into the following three categories according to the severity of the clinical symptoms [76]: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA; also known asneonatal-onset multisystem inflammatory disease (NOMID)). Each is caused by the same gene mutation, *C1AS1* [75].

Familial cold autoinflammatory syndrome (FCAS): FCAS is regarded as the mildest form of CAPS [77]. It has an onset immediately after birth or before 6 months of age in 95% of cases. The onset is precipitated by exposure to low temperatures for 2 to 3 hours. Clinical manifestations include urticaria-like skin rash that appears first in the limbs, spreading over the trunk. The skin rash is not urticaria itself but represents perivascular neutrophilic invasion in the skin as observed histologically. Concurrently, it is accompanied by fever, arthralgia, conjunctivitis, digestive symptoms, severe thirst, sweating and headache. The complication of amyloidosis is rarely seen (2 to 4% of cases).

Muckle-Wells syndrome (MWS): MWS is of intermediate severity among the categories of CAPS and its onset is at a later age than FCAS. It develops in adults as well as children, but with a preponderance in adolescence. It is characterized by a sudden onset of fever, accompanied by skin rash, arthritis/arthralgia, muscle pain, headache, conjunctivitis, episcleritis, uveitis, and other symptoms. A paroxysm of fever lasts for nearly three days. Fifty to 70% of patients eventually suffer hearing impairment or deafness, and progression to amyloidosis occurs in 25% of cases [75]. The *NLRP3* (*CIAS1*) mutation is detected in 65 to 70% of cases.

Neonatal-onset multisystem inflammatory disease (NOMID): NOMID is also called chronic infantile neurocutaneous articular syndrome (CINCA) and is the most severe form of CAPS [76]. About half of CINCA cases are born premature or have very low birth weight, with disease onset at birth or within several weeks. Fever and urticaria-like skin rash appear almost every day. Chronic aseptic meningitis causes repetitive irritability, vomiting and headache. As the patient

grows, neurological disorders, including hydrocephalus, developmental disorder, mental retardation and hearing disorder progress.

Ophthalmologic findings include conjunctivitis, uveitis, optic pupillitis and visual disturbance. Skeletal/cartilaginous dysgenesis brings about severe arthropathy before about 2 years of age. Excessively hypertrophied/ossified bone/cartilage of the distal end of the femur can be felt like a hard mass. X-rays shows remarkable ossification, flaring, and abnormality as well as deformity of the epiphyseal nucleus of the distal end of the femur [78]. The patient is not able to walk due both to joint deformity and pain. The body shape is affected by disorders of the joints at different sites, resulting in short stature, prominent forehead, microcephaly, saddle nose, clubbed fingers and wrinkled skin. NOMID has the poorest CAPS prognosis and around 20% of patients die before 20 years while the remainder progress to amyloidosis [79]. The gene mutation responsible for CAPS is detected in 50 to 60% of cases.

CIAS-1 gene mutation and pathological conditions caused by IL-1β

CAPS is caused by the *CIAS-1* gene mutation resulting in changed cryopyrin protein in NLRP3 (which forms a core protein of the inflammasome complex that controls production as well as release of IL-1β) [76]. Physiologically, the NLRP3 protein, when stimulated by PAMPs and DAMPs, forms an inflammasome complex associating pro-caspase-1 and ASC proteins. Stimuli mediated via Toll-like receptors results in pro-IL-1β and pro-IL-18 production, ie. precursors of IL-1β and IL-18, respectively [80]. Casapase-1 activated by the inflammasome then cleaves pro-IL-1β and pro-IL-18 to produce mature secreted forms of IL-1β and IL-18. IL-1β secreted from cells binds to IL-1 receptors and causes inflammation [80]. Such extracellular secretion of IL-1β requires $P2X_7$ receptor activation by ATP, a second stimulatory molecule [81]. Gene mutation-induced alteration of the NLRP3 protein maintains the inflammasome in an active state for IL-1β production and secretion, in a gain-of-function fashion [75]. In CAPS, the excessive amount of IL-1β produced and secreted is implicated in the pathogenesis of chronic inflammation.

In 2009, a clinical trial of the anti-IL-1β monoclonal antibody canakinumab [82], was started in Japan to treat 19 CAPS patients (MWS 7 patients and NOMID 11 patients) in whom the *CIAS1* gene mutation had been confirmed [83]. Eleven of these patients were aged 2 to 16 years and 9 were over 16 years with the oldest being 48 years of age. Therapeutic efficacy was evaluated by improvement of clinical symptoms and the inflammatory markers CRP, and SAA. Complete remission was assessed from the point of view of both clinical and serological remission: clinical remission was assessed by comprehensive scoring of autoinflammatory disease activity and dermatological symptomatology, and serological as CRP <1 mg/dL and SAA <10 μg/mL.

The initial canakinumab administration achieved a complete remission in 89.5% (17/19 cases) within 4 weeks and with a further remission by 24 weeks. A dramatic effect was thus seen in 95% of the patients, especially the improvement of skin symptoms, headache, conjunctivitis and lassitude. Central nervous system disorders went into remission in 33.3% (4/12 cases) 8 days after starting therapy, and in 75% at the end of the clinical trial. In all cases, the CRP and SAA levels were decreased within 14 days of administration. However, 18patients (95%) experienced at least one adverse event during the treatment course. Nasopharyngitis (36.8%), gastroenteritis (31.6%), upper respiratory tract infection (15.8%) and nasal discharge (15.8%) were most frequently observed. Additionally, diffuse vasculitis and pneumonia were seen in one patient. This clinical trial has confirmed a previous European trial [84].

Conclusions on cryopyrin-associated periodic syndrome

Systemic inflammation subsides after anti-IL-1β monoclonal antibody administration in CAPS, showing that IL-1β is the leading cytokine in the pathogenesis of CAPS. Thus, it has been demonstrated that the idea of inflammasomopathy is not misplaced when considering mechanisms of CAPS development [85].

Although there are protein abnormalities in the inflammasome in CAPS, questions arise as to why fever is periodic not sustained, and the major question of what triggers inflammasome activation. Can we not develop any therapeutic method to eliminate triggering factors? This will probably become the major task for the future.

Single-Cytokine Blocking Therapy and its Prospects

Inflammation is caused by inflammatory cytokines. These cytokines may be implicated in the pathogenesis of certain diseases if produced and released in excess, although they are engaged in essential biological defense mechanisms under normal circumstances. Typical diseases of excess inflammatory cytokine production are Kawasaki disease, systemic JIA and CAPS. In these diseases, different patterns of inflammatory cytokines are produced by known mechanisms of interactive stimulation. Each disease entity seems to have one specific *leading cytokine* in the clinical setting. We showed that we could end inflammation by blocking the appropriate leading cytokine in these

	Autoinflammatory disease	Autoimmune disease
Pathogenetic basis	Innate immunity	Adaptive immunity
Competent cells	Dendritic cells, Monocytes/Macrophages, Neutrophils	$CD4^+$T cells-Th1/Th2/Th17/Treg, $CD8^+$T cells, Macrophages, B cells
Activators	PAMPs/DAMPs	Antigens
Receptors	TLR/MDA5/RIG-I/NLR	TCR
Reaction specificity	Comprehensive/Pattern recognition	MHC-restricted/Antigen-specific
Gene products	Type I interferon	Antibodies Inflammatory cytokines
Disease due to gene mutation	Congenital innate immunodeficiency (MyD88 deficiency, NEMO, DIRA, IkBα deficiency, IRAK-4 deficiency, etc.)	Primary immunodeficiency diseases (CVID, agamma globulinemia, WAS, SCID, HIDS, HIES, CGD, etc.)
Representative	Autoinflammatory diseases Periodic fever syndrome (FMF, PFAPA,TRAPS, MVK, CAPS), Systemic-onset JIA Juvenile dematomyositis, Chronic recurrent multifocal osteomyelitis, Behcet's disease, etc.	Autoimmune diseases Systemic lupus erythematosus, Mixed connective tissue disease, Kawasaki disease, Sjogren syndrome, Juvenile systemic sclerosis, etc.
Therapy	Removal of inflammatory cytokines, Suppression of activated macrophages/Dendritic cells	Immunosuppressive therapy, Depletion of B cells

Abbreviations: PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; TLR: Toll-like receptor; MDA5: Melanoma differentiation-associated gene-5; RIG-I: Retinoic acid-inducible gene-I; NLR: Nod-like receptor; NEMO: NF-kB essential modulator; DIRA: Deficiency of the interleukin-1 receptor antagonist; FMF: Familial Mediterranean fever; PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; TRAPS: Tumor necrosis factor receptor-associated periodic syndrome; MVK: Mevalonate kinase deficiency; CAPS: Cryopyrin-associated periodic syndrome; JIA: Juvenile idiopathic arthritis; TCR: T cell receptor; CVID: Common variable immunodeficiency; WAS: Wiscott-Aldrich syndrome; SCID: Severe combined immunodeficiency; HIES: Hyper-immunoglobulin E syndrome; CGD: Chronic granulomatous disease.

Table 1: Differences between autoinflammatory disease and autoimmune disease.

diseases: first, in Kawasaki disease, an acute inflammatory disease, and where TNF-α appears to be the leading cytokine for systemic inflammation and coronary arterial vasculitis; second, in systemic JIA, in which an excessive amount of IL-6 is implicated in the pathogenesis; third, in CAPS which is caused by overproduction of IL-1β due to a single-gene mutation. Currently, inflammatory cytokine blocking therapy using appropriate monoclonal antibodies specific for the leading cytokine is proving effective. However, such therapy can deal only with the cytokine already as it is produced and secreted, without addressing the causative factors responsible for this. There must be regulatory mechanisms in the innate immune system controlling the expression level as well as the order of expression of individual cytokines. It is therefore important to determine negative feed-back mechanisms or down-regulatory mechanisms for already-activated inflammation and inflammatory cytokine production. In the long run, establishment of techniques to control the regulatory system would make disease management easier from the clinical view point (Table 1).

Conclusion

Inflammation is the manifestation of important innate immune mechanisms, different from the classic adaptive immune system. Consequently, since inflammatory disease involving innate immunity cannot be effectively treated with immunosuppressant, the major therapeutic strategy is to control inflammatory cytokines. Clarification of the dysregulated mechanisms responsible for excessive inflammatory cytokine production at the cellular level remains a task for the future.

Conflict of Interest Statement

Shumpei Yokota and Takako Miyamae hold a patent for tocilizumab and receive royalties for Actemra.

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