

**Special Issue “Autoinflammation vs Autoimmunity”****Mini Review****Autoinflammatory diseases and the inflammasome: mechanisms of IL-1 $\beta$  activation leading to neutrophil-rich skin disorders**

Naotomo Kambe \*, Takashi Satoh, Yuumi Nakamura, Mari Iwasawa, and Hiroyuki Matsue

Department of Dermatology, Chiba University Graduate School of Medicine, Chiba, Japan

Autoinflammatory diseases were initially assigned to the hereditary recurrent fevers that were characterized by unprovoked episodes of inflammation without antigen-specific T cells or high titers of auto-antibodies, in contrast to the autoimmune diseases in which acquired immunity played an essential role. Except for Blau syndrome and early-onset sarcoidosis that are associated with granuloma due to NOD2 mutations and classified as NF- $\kappa$ B activation disorders, the major types of autoinflammatory diseases are defined as IL-1 $\beta$  activating disorders or inflammasomopathies. This is based on accumulating evidence for the efficacy of anti-IL-1 therapy. These diseases include intrinsic cryopyrin-associated periodic syndrome (CAPS), extrinsic familial Mediterranean fever, hyper IgD syndrome, pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome, and deficiency of an IL-1 receptor antagonist. Knowledge obtained these autoinflammatory disorders should also be pertinent to a number of common disorders. For example, neutrophil migration is observed in autoinflammatory CAPS common inflammatory keratoses represented by psoriasis. Abnormal regulation of the innate immune response and Th17 cell differentiation via IL-1 signaling may be associated with the molecular pathogenesis of these conditions.

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Corresponding author: Naotomo Kambe, MD, PhD.  
Department of Dermatology, Chiba University Graduate School of Medicine  
1-8-1 Inohana, Chuo-ku, Chiba 270-8670, Japan  
Tel: +81-43-226-2505 Fax: +81-43-226-2128 E-mail: [nkambe@faculty.chiba-u.jp](mailto:nkambe@faculty.chiba-u.jp)

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## Introduction

During the last decade, hereditary recurrent fever syndrome with unexplained inflammation involving the skin and joints has become a model of autoinflammatory mechanisms in nature<sup>1,2</sup>. The term “autoinflammatory” was introduced by Kastner after mutations of the p55 tumor necrosis factor (TNF) receptor were identified in patients with autosomal dominant periodic fever syndrome, which was designated TNF receptor-associated periodic syndrome (TRAPS)<sup>3</sup>. The so-called autoinflammatory diseases were initially assigned to hereditary recurrent fevers that were characterized by unprovoked episodes of inflammation without antigen-specific T cells or high titers of auto-antibodies, in contrast to the autoimmune diseases in which acquired immunity played an essential role.

In this post-genome era, advances in our knowledge of and techniques in genetics have allowed for detection of the genes responsible for autoinflammatory diseases. Mutations have mainly been identified in the genes that encode for pattern recognition receptors or accessory molecules involved in inflammatory pathways associated with the regulation of innate immune responses. Both basic scientists and clinical physicians are interested in autoinflammatory diseases because biologics that target inflammatory cytokines, particularly IL-1 $\beta$ , can dramatically relieve clinical symptoms and also extend our knowledge of the molecular mechanisms of autoinflammatory diseases.

## Autoinflammatory diseases and anti-IL-1 therapy

Among the autoinflammatory diseases, familial Mediterranean fever (FMF; Mendelian inheritance in man [MIM] #249100) is the most commonly occurring and most representative disease. The clinical manifestations of FMF are self-resolving recurrent attacks of high spiking fevers along with serositis that usually lasts 1 to 3 days. Recurrent fever may be the only symptom in childhood, although most patients ultimately complain of abdominal pain associated with board-like rigidity of the abdominal muscles, rebound tenderness, constipation, and/or diarrhea. Chest pain due to pleural or pericardial involve-

ment also occurs. Some patients experience painful skin lesions, so-called erysipelas-like erythema, usually located on the lower legs. Histological examination shows edema of the superficial dermis and perivascular inflammatory cell infiltrations comprised of neutrophils, nuclear dust, and a few lymphocytes<sup>4</sup>. Vasculitis is not observed. These symptoms can be effectively reversed with colchicine, while systemic amyloidosis can gradually occur, particularly in untreated or colchicine-resistant patients<sup>5-6</sup>.

Attacks of FMF occur irregularly and, in some patients, asymptomatic periods can last a few years, although they might be provoked by physical and emotional stress. The gene causing FMF was found to be *MEFV* that encodes pyrin and that is specifically expressed in the cytoplasm of myeloid cells. Pyrin is postulated to act as a negative regulator of IL-1-mediated inflammation. Several reports suggested that IL-1 inhibition with a recombinant IL-1 receptor antagonist (IL-1Ra), anakinra, was effective for preventing attacks of FMF<sup>7</sup>, although its effect was not as pronounced in FMF as it was in cryopyrin-associated periodic syndrome (CAPS) mediated by a gain-of-function mutation of *NLRP3*. Of great interest would be the effect of therapy that targets IL-1 for preventing AA amyloidosis<sup>8</sup>. However, long-term studies are needed to determine whether or not progressive renal diseases due to amyloidosis can be prevented.

TRAPS (MIM #142680), also known as Hibernian fever, is characterized by repeated febrile attacks involving multiple organs. These patients have episodes of recurrent fever accompanied by migrating skin lesions that are swollen, with painful erythema localized to the trunk and extremities. Febrile attacks continue for approximately 2 days, although they can last for weeks. It is also accompanied by chest and abdominal pain, arthralgia, testicular pain, lymphadenopathy, headache, and ocular involvement with periorbital edema.

The *TNFRSF1A* gene is involved, which encodes for the 55-kDa TNF receptor superfamily 1A (also known as TNFR1 or CD120a). Although the molecular pathogenesis of TRAPS was initially proposed as a “shedding defect” due to TNFR1 cleavage leading to prolonged, sustained TNF signaling, other TRAPS-associated mutations may produce



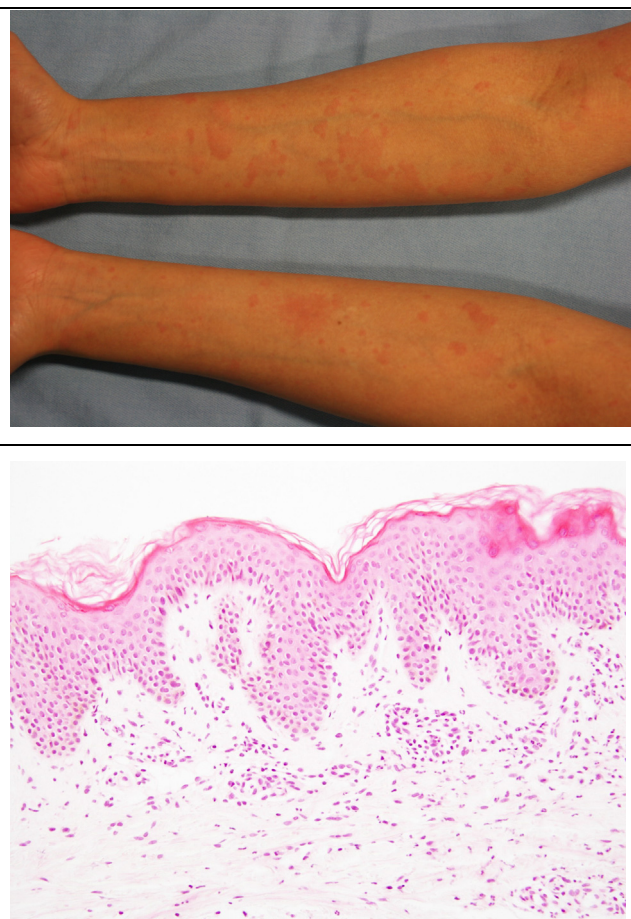
biological effects via conformational changes of misfolded TNFR1 proteins that result in the up-regulation of multiple pro-inflammatory genes<sup>9</sup>). Despite an initial expectation of responses to TNF antagonists, such as etanercept, the treatment of TRAPS remains challenging; acute attacks might typically respond to high-dose corticosteroids and an IL-1Ra, anakinra<sup>10</sup>).

Hyper IgD syndrome (HIDS) is an autosomal recessive disease. Acute attacks triggered by physical stress or vaccination can last for 3 to 7 days and can recur after 4 to 6 weeks. Most patients experience their first symptoms in the first year of life. Fever is usually associated with painful neck lymphadenopathy, hepatosplenomegaly, abdominal pain, vomiting, and diarrhea. About half of these patients show aphthous oral or genital ulcers. Maculopapular skin rashes, nodules, and urticarial or measles-like rashes can also occur.

High IgD levels (>100 UI/ml) during these attacks were considered to be the main feature of HIDS, although their specificity was quite low. HIDS is linked to mutations in the *MVK* gene, which encodes for mevalonate kinase. This enzyme converts mevalonic acid into 5-phosphomevalonic acid that is essential for the production of cholesterol, steroid hormones, vitamin D, bile salts, and isoprenoids. In HIDS, reduced *MVK* enzyme activity results in lower serum cholesterol levels, higher urinary excretion of mevalonic acid, and increased activity of hydroxymethylglutaryl CoA (HMGCoA) reductase, which promotes the synthesis of pro-inflammatory isoprenoids<sup>11</sup>). This metabolic shunt could explain the efficacy of statins in reducing HIDS symptoms<sup>12</sup>). Variable responses to etanercept in HIDS patients have been reported, while at the same time anakinra has proven to be more effective for reducing duration of symptoms<sup>13</sup>).

An urticarial rash (Fig. 1) that develops in the neonatal or early infantile period is one of the clinical manifestations characteristic of CAPS. CAPS comprises 3 phenotypically overlapping, but relatively distinct syndromes: familial cold autoinflammatory syndrome (FCAS; MIM #120100), Muckle-Wells syndrome (MWS; MIM #191900), and chronic infantile neurological cutaneous and articular syndrome (CINCA; MIM #607115), also known as neonatal-onset multisystem in-

flammatory disease or NOMID. FCAS and MWS are characterized by periodic attacks of urticarial rash, fever, and arthralgia. Patients with CINCA, the most severe form of CAPS, exhibit chronic urticaria, as well as fever, arthropathy, chronic meningitis, papilledema, growth and mental retardation, and hearing loss<sup>14</sup>).



**Figure 1. Eruption of cryopyrin-associated periodic syndrome.** a. Clinical manifestations observed for a 26-year-old woman with a E567K mutation in *NLRP3*. b. Histopathology (HE staining). Edema is observed in the dermis accompanied by inflammatory cell infiltration, predominantly neutrophils.

A susceptibility gene for CAPS (previously designated *CIAS1* after cold-induced autoinflammatory syndrome, and now termed *NLRP3*) was identified by Hoffman et al. in 2001. The mutations found in CAPS, usually detected in the centrally located nucleotide-binding oligomerization domain (NOD) of *NLRP3*, induce caspase-1 activation with subsequent IL-18 secretion. Although caspase-1 activation via inflammasome formation is also required for processing IL-18,





IL-33, and several other non-traditionally secreted proteins<sup>15</sup>), most research has focused on how *NLRP3* mutations affect IL-1 $\beta$  production<sup>16-17</sup>. This was because the IL-1Ra anakinra showed dramatic effects not only on rash and acute-phase proteins, but also on the aseptic meningitis and cochlear inflammation associated with the most severe cases of CAPS<sup>18</sup>. Currently, improved therapy that targets IL-1 for CAPS patients focuses on new biologics with more favorable treatment schedules, such as rilonacept (once per week) and canakinumab (once every two months)<sup>19-20</sup>.

Blau syndrome (MIM #186580) is characterized by granulomatous inflammation of the skin, eyes, and joints<sup>21</sup>. The genetic locus of this systemic granulomatous syndrome was mapped to the 16q12.1-13 chromosomal region, which also contains one of the susceptibility loci for inflammatory bowel disease, *IBD1*. In addition with Crohn's disease (MIM #266600), *NOD2* (previously designated *CARD15*) was identified as the gene responsible for this second of the granulomatous disorders<sup>22</sup>. Blau syndrome exhibits a phenotypic overlap with sporadic early-onset sarcoidosis (EOS; MIM #609464) and we have reported that EOS was also associated with mutations in *NOD2*<sup>23</sup>.

Interestingly, amino acid residues of the disease-associated mutations of R334W in *NOD2* and R260W in *NLRP3* were at analogous sequence positions in each of the NOD domains, suggesting a common molecular mechanism for the development of autoinflammatory diseases<sup>24</sup>. Through interactions with their own carboxyl-terminal leucine-rich repeats (LRRs), cryopyrin and *NOD2* are maintained in inactive conformations, which are mitigated by ligand recognition, probably through their LRRs. These autoinflammatory disease-associated mutations are thought to mimic active conformational changes induced by a microbial ligand. In the case of *NOD2*, Blau syndrome/EOS-associated mutations lead to increased constitutive NF- $\kappa$ B activity in the absence of muramyl dipeptide (MDP), a component of bacterial cell wall peptidoglycans<sup>23</sup>. Although activation of NF- $\kappa$ B leads to transcription of the pro-IL-1 $\beta$  gene, the levels of IL-1 $\beta$  secreted into the peripheral blood in Blau syndrome are comparable to the levels of healthy controls<sup>25-26</sup>. In addition, Martin et al. presented 2 case reports for

which anakinra was not effective for treating Blau syndrome<sup>25</sup>.

Children with recurrent development of multiple sterile abscesses in the joints and bones can now be studied by genetic analysis for other autoinflammatory diseases. These include pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome (PAPA; MIM #604416), chronic recurrent multifocal osteomyelitis (CRMO; MIM 259680), and Majeed syndrome (MIM #609628). PAPA is primarily characterized by a destructive pyoarthrititis with a pauciarticular onset and elevated leukocyte activity in inflammatory exudates, pyoderma gangrenosus (sometimes induced by trauma or worsening with puberty), and cystic acne. Clinical appearance results from mutations in *PSTPIP1* resulting in abnormal pyrin ligation and persistent caspase-1 activation. Indeed, PAPA can be successfully controlled by IL-1 blockade<sup>27</sup>.

CRMO is characterized by antibiotic-resistant, multiple chronic osteomyelitis foci, which appear as a mixture of osteolysis/sclerosis on X-ray, and is associated with recurrent fever. Currently, the gene responsible for CRMO and the pathogenesis of CRMO are unknown; consequently, a targeted therapy is not available.

Majeed syndrome has only been reported in Jordan and is caused by mutations in *LPIN2*<sup>28-29</sup>. This rare disease is defined by an association of CRMO with congenital dyserythropoietic anemia and neutrophilic dermatosis, although the role of lipin 2 in bone and skin-localized inflammation remains unknown. Multifocal osteomyelitis associated with pustulosis has also been described as deficiency of an IL-1Ra (DIRA; MIM #612852)<sup>30-31</sup>. This newly described member of the autoinflammatory diseases showed dramatically improved clinical symptoms after the administration of an IL-1Ra.

## Autoinflammatory diseases and inflammasome regulation

Based upon the underlying molecular mechanisms, Kastner et al recently proposed a new classification scheme for autoinflammatory diseases (Table 1)<sup>2</sup>. With the exceptions of Blau syndrome and EOS that are classified as Type 2 NF- $\kappa$ B activation disorders, based on the accumulating evidence for the efficacy of anti-IL-1 therapy for autoinflammatory diseases, the major types of



these hereditary recurrent fever syndromes are defined as IL-1 $\beta$  activating disorders or inflammasomopathies. These type 1 inflammasomopathies are further divided into intrinsic CAPS disorders with NLRP3 in common and extrinsic conditions that take into account a number of related proteins, including FMF, PAPA, HIDS and DIRA, which are the disorders associated with upstream or downstream regulatory elements of the inflammasome.

NLRP3, one of the major players of the in-

flammasome, is a member of the NOD-LRR containing (NLR) family that is a mammalian homologue of plant resistance (R) genes. Plants, which do not have circulating white blood cells, cannot escape from undesirable locations by their own locomotion. Once plant cells become infected, they activate R genes to induce local cell death and inflammation. NLRP3 also operates as an intracellular pattern recognition receptor to induce programmed cell death <sup>32)</sup> and inflammation.

**Table 1**

Disease	Gene
<b>Type I: IL-1<math>\beta</math> activation disorders (inflammasomopathies)</b>	
<i>Intrinsic</i>	
CAPS (FCAS, MWS, CINCA/NOMID)	<i>NLRP3</i>
<i>Extrinsic</i>	
FMF	<i>MEFV</i>
PAPA	<i>PSTPIP1</i>
CRMO	?
Majeed syndrome	<i>LPIN2</i>
HIDS	<i>MVK</i>
DIRA	<i>IL1RN</i>
<b>Type 2: NF-<math>\kappa</math>B activation disorders</b>	
Blau syndrome/EOS	<i>NOD2</i>
<b>Type 3: Protein folding disorders of the innate immune system</b>	
TRAPS	<i>TNFRSF1A</i>
CAPS: cryopyrin-associated periodic syndrome, FCAS: familial cold antoinflammatory syndrome, MWS: Muckle-Wells syndrome, CINCA: chronic infantile neurological cutaneous and articular syndrome, NOMID: neonatal-onset multisystem inflammatory disease, FMF: familial Mediterranean fever, PAPA: pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome, CRMO: chronic recurrent multifocal osteomyelitis, HIDS: hyper IgD syndrome, DIRA: deficiency of interleukin-1 receptor antagonist, EOS: early-onset sarcoidosis, TRAPS: tumor necrosis factor receptor-associated periodic syndrome	

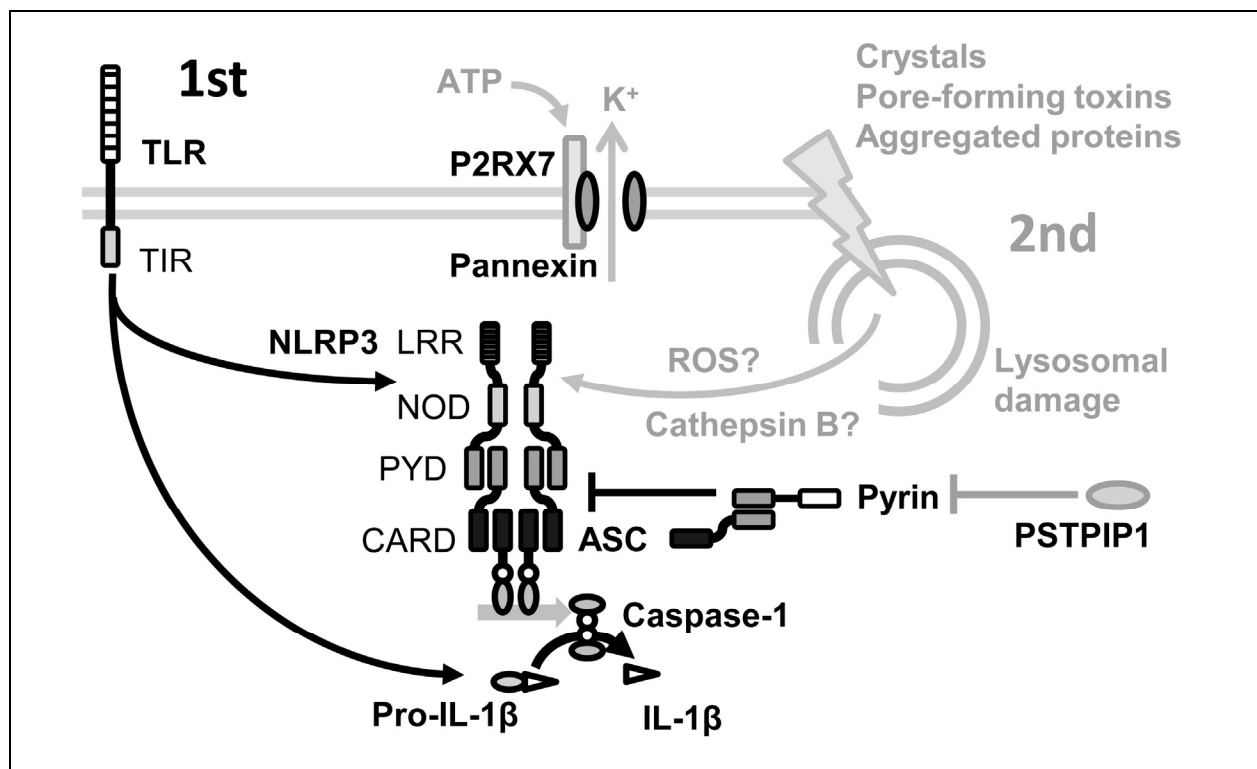
Indeed, in vitro studies suggest that *NLRP3* mutations observed in CAPS show gain-of-function effects to induce ASC-dependent NF- $\kappa$ B activation, which depend on the severity of clinical symptoms. Activation of NF- $\kappa$ B then induces inflammatory cytokine production, including the accumulation of pro-IL-1 $\beta$ . At the same time, pro-caspase-1 is recruited to ASC via each caspase-activating and recruitment domain (CARD), and

NLRP3 forms a multiple-protein complex, termed the inflammasome (Fig. 2). Formation of the inflammasome results in the self-cleavage of pro-caspase-1. Then, activated caspase-1 cleaves its target molecule, pro-IL-1 $\beta$ , into a biologically active form to induce inflammation. In fact, purified monocytes from CAPS patients showed constitutive release of IL-1 $\beta$ , in contrast to those from healthy controls that required LPS stimula-

tion<sup>17)</sup>.

The role of pyrin encoded by *MEFV* during IL-1 $\beta$  activation is controversial. Transfection of full-length mouse pyrin into monocytic cells suppressed IL-1 $\beta$  secretion and GST pull-down experiments showed that ASC preferentially bound to pyrin in comparison to caspase-1, suggesting that pyrin negatively regulated inflammasome activation by competing for ASC via each pyrin domain<sup>33)</sup>. Chae et al. also reported an ASC-indepen-

dent pathway by which pyrin regulated caspase-1 activation. In this report, they showed that the carboxyl-terminal B30.2 domain of pyrin bound to and inhibited the catalytic activity of caspase-1 and 3, and that common FMF-associated mutations attenuated this suppressive effect<sup>34)</sup>. However, using a transfection system with human embryonic kidney 293T cells, another report showed that pyrin may activate caspase-1 and IL-1 $\beta$ <sup>35)</sup>.



**Figure 2. IL-1 $\beta$  activation of the inflammasome mediated by NLRP3.** The production and release of mature IL-1 $\beta$  requires two stimuli. The 1st promotes gene transcription and the accumulation of pro-IL-1 $\beta$ . Microbial ligands, such as LPS, with signals mediated by Toll-like receptors (TLR) trigger the synthesis of IL-1 $\beta$  precursors. The second signal is a toxin that induces pore formation in the cell wall and ATP that mediates K<sup>+</sup> efflux mediated by P2RX7. This ATP-receptor complex rapidly transforms to a pore-like structure by recruiting a pannexin-1 pore that allows passage of molecules as large as 900 Da. Other 2nd signals that can activate the inflammasome are crystals, such as monosodium urate and aggregated proteins, which probably induce lysosomal damage and release reactive oxygen species (ROS) and cathepsin B. Activation of NLRP3, induced either by pathogen-associated or danger-associated molecules probably recognized by leucine-rich repeats (LRR), or a CAPS-associated mutation typically recognized in the centrally located nucleotide-binding oligomerization domain (NOD) of NLRP3, induce ASC-dependent NF- $\kappa$ B activation. At the same time, pro-caspase-1 is recruited to ASC via each caspase-activating and recruitment domain (CARD), and NLRP3 forms the multiple-protein complex called the inflammasome. Formation of the inflammasome results in self-cleavage of pro-caspase-1, after which activated caspase-1 cleaves its target molecule, pro-IL-1 $\beta$ , into a biologically active form to induce inflammation. Pyrin encoded by *MEFV* negatively regulates inflammasome formation by competing for ASC via each pyrin domain (PYD). A mutation in *PSTPIP1* associated with PAPA produces a hyperphosphorylated product that binds more avidly to pyrin and suppresses the regulatory effects of pyrin to induce IL-1 mediated inflammation.

Another accessory molecule for the inflammasome that is associated with autoimmune disease is PSTPIP1. PSTPIP1 co-localizes with pyrin in neutrophils. Mutations in the encoding gene produce a hyper-

phosphorylated product. The hyperphosphorylated PSTPIP1 binds more avidly to pyrin. As a result, the suppressive regulation of the inflammasome mediated by pyrin is abrogated.



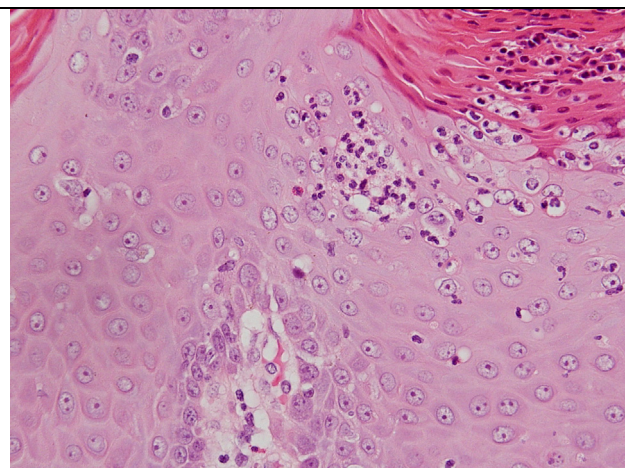
## Inflammasome and skin diseases associated with neutrophil recruitment

In addition to their molecular functions, knowledge obtained from analyzing these inflammasome-activating disorders is relevant to the pathogenesis of a number of common diseases. For example, the characteristic clinical manifestation of CAPS is a urticarial skin rash<sup>36</sup>. Skin samples from CAPS patients show edema in the dermis accompanied by inflammatory cell infiltrations, predominantly neutrophils (Fig. 1b). Because anti-IL-1 treatment, but not anti-histamines, relieved the skin eruptions, IL-1 $\beta$  producing cells in the skin were postulated to play essential roles in these eruptions, and we found that dermal mast cells in CAPS patients constitutively expressed active IL-1 $\beta$  without any treatment<sup>37</sup>.

In a mouse model, mast cells with a stably expressed gain-of-function mutation in Nlrp3 could secrete IL-1 $\beta$  without an inflammasome activator and induced vascular leakage when injected into the skin. For these conditions, these mast cells did not show any degranulation. Histopathology revealed the presence of neutrophils and edema in the dermis in a pattern that was similar to that observed in the involved skin of human CAPS<sup>37</sup>. Thus, disease-associated NLRP3 promoted neutrophil recruitment and vascular leakage in the skin, two histological hallmarks of urticarial rash associated with CAPS, which was independent of histamine. In contrast, ordinary non-CAPS-associated urticaria is sometimes unresponsive to anti-histamines. It is possible that skin rash associated with histamine resistance is mediated by inflammasome activation in mast cells through activation of the inflammasome via pathogen-associated molecular patterns or danger-associated molecular patterns that can activate NLRP3.

Of potential interest is the neutrophil migration observed in skin samples from CAPS patients. In the field of dermatology, sterile pustules or aseptic abscesses containing neutrophils are one of the characteristic phenomena seen in inflammatory keratoses, as represented by psoriasis (Fig. 3) and more evident in palmoplantar pustulosis, probably a kind of localized pustular psoriasis. Interestingly, in these skin disorders, focal bacterial infections involving tonsillitis or dental

caries frequently worsened the clinical symptoms, which suggested innate immune response mechanisms. In addition, recent advanced therapy targeting IL-23 (IL-12 p40) suggested the importance of IL-17 producing helper T cells (Th17) in psoriasis, because the development and maintenance of Th17 cells have been linked to IL-23 comprised of the hetero-dimer of IL-12 p40 and specific IL-23 p19<sup>38</sup>.



**Figure 3.** Histopathology of a skin sample from a psoriasis patient (HE staining). Neutrophil infiltration is seen under the honey cell layer (so-called Munro's micro-abscess) and among the epidermal layer.

From observations using gene-targeted mice with disease-associated Nlrp3 mutation knock-in, the pathogenesis of CAPS was also suggested to be mediated by Th17 cells<sup>39-40</sup>. Antigen presenting cells from knock-in mice acted upon CD4<sup>+</sup> T cells and favored Th17 cell differentiation via IL-1 $\beta$ . IL-1 $\beta$  has been shown to up-regulate factors that induce and enhance IL-17 transcription, such as ROR $\gamma$ t and IRF-4.<sup>41-42</sup> Thus, neutrophil migration mediated by Th17 cells in CAPS and psoriasis is induced by the microenvironment promoted by the influence of IL-1 signaling, even though neutrophil migration in CAPS is observed in the dermis, whereas that in psoriasis is found in the epidermis.

Characterizing these autoinflammatory syndromes has also led to new insights into how the corresponding genes play roles in regulating inflammatory responses and in evoking clinical manifestations. NLRP3 is activated by "danger signals," like monosodium urate, calcium pyrophosphate dihydrate, amyloid-beta, glucose, or silica and





asbestos, and for these reasons the activation of NLRP3 has been proposed as a key molecular mechanism in gout, pseudogout, Alzheimer's disease, pulmonary fibrosis, or even type 2 diabetes mellitus<sup>2)</sup>. However, we still cannot answer all of the questions regarding the roles of the inflammasome. In order to determine what happens in humans when the inflammasome is activated, we must look carefully at the clinical manifestations of autoinflammatory syndromes.

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