Molecular biology of autoinflammatory diseases

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Abstract

The long battle between humans and various physical, chemical, and biological insults that cause cell injury (e.g., products of tissue damage, metabolites, and/or infections) have led to the evolution of various adaptive responses. These responses are triggered by recognition of damage-associated molecular patterns (DAMPs) and/or pathogen-associated molecular patterns (PAMPs), usually by cells of the innate immune system. DAMPs and PAMPs are recognized by pattern recognition receptors (PRRs) expressed by innate immune cells; this recognition triggers inflammation. Autoinflammatory diseases are strongly associated with dysregulation of PRR interactomes, which include inflammasomes, NF-kB-activating signalosomes, type I interferon-inducing signalosomes, and immuno-proteasome; disruptions of regulation of these interactomes leads to inflammasomopathies, relopathies, interferonopathies, and proteasome-associated autoinflammatory syndromes, respectively. In this review, we discuss the currently accepted molecular mechanisms underlying several autoinflammatory diseases.

Keywords: Interleukin-1, NF-kB, Type I interferon, Autoinflammatory diseases

Background

The human body has evolved various adaptive responses that protect against cell and tissue damage caused by physical, chemical, and biological factors. Such factors include molecules released by damaged tissues, metabolites, and/or infection (e.g., by bacteria, viruses, and parasites) [1–4]. Inflammation, an adaptive response to cell injury, generates damage-associated molecular patterns (DAMPs) and/or pathogen-associated molecular patterns (PAMPs), which are then recognized by pattern recognition receptors (PRRs) expressed mainly by innate immune cells [5]. PRRs include Toll-like receptors (TLRs), Nod-like receptors (NLRs), C-type lectin receptors (CLRs), and RIG-I-like receptors (RLRs) that recognize DAMPs and PAMPs to initiate immune responses. These receptors are also called innate immune receptors [6] (Fig. 1).

Autoinflammatory diseases are strongly associated with dysregulation of these PRR-containing interactomes, which include inflammasomes, nuclear factor (NF)-kB-activating signalosomes, type I interferon-inducing signalosomes, and immuno-proteasomes; dysfunction of these interactomes results in inflammasomopathies, relopathies, interferonopathies, and proteasome-associated autoinflammatory syndromes (PRAAS), respectively [7–11]. This explains the pathogenesis of autoinflammatory diseases involving recurrent inflammatory flare-ups in the absence of autoantibodies or antigen-specific T lymphocytes [12]. Knowledge of the molecular mechanism(s) underlying the functions of these innate immune receptors is useful for the treatment and management of individuals with autoinflammatory diseases (Fig. 1).

Interleukin-1β-mediated autoinflammatory diseases (inflammasomopathies)

When NOD-like receptors harboring a PYRIN domain (PYD) (e.g., NLRP1, NLRP2, NLRP3, NLRP6, NLRP9, and NLRP12) and other pyrin domain-containing PRRs (e.g., pyrin, AIM2, and IFI-16) sense DAMPs, PAMPs, or intracellular microenvironmental changes (e.g., potassium efflux), they interact with an adaptor protein...
apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) via PYD, and pro-caspase-1 via a caspase-recruitment domain (CARD). This interaction activates caspase-1, a process accompanied by pyroptotic cell death [13–29]. NOD-like receptors carrying a CARD domain or CARD including proteins alternatively interact with caspase-1 via CARD with ASC and pro-caspase-1 such as NLRP1, NLRC4, CARD8, and caspase-11 [30–32]. The resulting complexes act as a sensor of cell injury; this sensor is referred to as the inflammasome, an interleukin (IL)-1β- and IL-18-processing platform that plays a crucial role in the maturation and secretion of these cytokines from cells. The process is accompanied by a type of cell death, named pyroptosis, which is triggered by cleavage of gasdermin D (GSDMD) [33, 34] (Fig. 2). Below, we discuss specific inflammasomopathies.

**Cryopyrin-associated periodic syndrome**

Cryopyrin is the same protein as NLRP3 which was named by the nomenclature committee. Gain-of-function mutations in NLRP3 lead to cryopyrin-associated periodic syndrome (CAPS), a spectrum of diseases that includes familial cold autoinflammatory syndrome (FCAS, formerly termed familial cold urticaria (FCU)), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID; also called chronic infantile neurologic cutaneous and articular syndrome (CINCA)). Currently, 248 variants of the CIAS1 gene have been reported by “INFEVERS” (https://infevers.umai-montpellier.fr/web/search.php?n=4) [35]. The NLRP3 mutations in CAPS result in constitutive activation of the NLRP3 inflammasome (i.e., the threshold for stimulation is extremely low). Activation of the inflammasome leads to excess pyroptosis of cells expressing components of the NLRP3 inflammasome; these cells secrete excessive amounts of activated IL-1β upon autoinflammatory attack [36–41] (Fig. 2). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**NLRP1-associated autoinflammation with arthritis and dyskeratosis**

The NLRP1 inflammasome was the first “inflammasome” to be identified [14]. NLRP1 interacts with ASC through its PYD domain. ASC then interacts with procaspase-1 via its CARD domain, resulting in activation of IL-1β secretion; also, NLRP1 interacts with caspase-1
through its CARD domain to activate IL-1β secretion [96]. Currently, several mutations (A54T, A59P, A66V, M77T, R726W, T755N, F787_R843del, and P1214R) in the gene encoding NLRP1 have been identified ([https://infevers.umai-montpellier.fr/web/search.php?n=31](https://infevers.umai-montpellier.fr/web/search.php?n=31)). Patients harboring these mutations exhibit dyskeratosis, oligo/polyarthritis, and recurrent fever, along with immunological dysfunction and vitamin A deficiency [97–99]. The mutations may trigger proteasome-dependent functional degradation of NLRP1, and degraded CARD-FIIND-containing-NLRP1 fragments act as a scaffold like ASC for inflammasome activation [100] (Fig. 2).

### Corresponding common diseases caused by the similar signaling

Common diseases caused by the gain of function mutations of NLRP1, NLRP12, or other NLRP mutations are thought to be basically caused by the same mechanisms. Mutated TNFRSF1A (TNFR) in patients with TRAPS is misfolded and accumulated in the endoplasmic reticulum (ER), causing ER stress and increased generation of mitochondrial reactive oxygen species (ROS) that activates the NLRP3 inflammasome. PLCγ2 mutation in patients with APLAID (e.g., S707Y) leads to calcium influx from the ER and increased cytoplasmic Ca2+ levels promote activation of NLRP3 inflammasome.

### NLRP12 autoinflammatory syndrome

NLRP12 inhibits the activation of NF-κB. Mutations in NLRP12 are found in patients with hereditary periodic fever syndrome, the clinical signs of which are consistent with a diagnosis of CAPS [101]. Currently, 79 variants of the gene encoding NLRP12 have been reported ([https://infevers.umai-montpellier.fr/web/search.php?n=9](https://infevers.umai-montpellier.fr/web/search.php?n=9)). Since some patients with gain-of-function mutations in NLRP12 exhibit symptoms similar to those of CAPS, the
Table 1: The corresponding diseases caused by the similar signaling of autoinflammatory diseases

| Type of autoinflammatory diseases | Responding proteins | Functions                          | Corresponding diseases with the similar signaling                                                                 |
|----------------------------------|---------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Inflammasomopathies              |                     |                                   |                                                                                                                  |
| CAPS                             | Cryopyrin/NLRP3     | PRR for ROS, K+ efflux, cathepsin & B detection | Metabolic syndrome:  
Gout [42]  
Atherosclerosis [43]  
Type 2 diabetes [44]  
Neurodegenerative disease:  
Alzheimer’s disease [45, 46]  
Parkinson’s disease [47]  
Amyotrophic lateral sclerosis [48]  
Multiple sclerosis [49]  
Infections and aberrant inflammatory responses:  
Septic shock syndrome [50, 51]  
Ischemic diseases:  
Myocardial infarction [52]  
Stroke [53] |
| NAIAD                            | NLRP1               | PRR against Anthrax toxin detection | Infections and aberrant inflammatory responses:  
Anthrax lethal toxin [54]  
Neurodegenerative disease:  
Alzheimer’s disease [46]  
Ischemic diseases:  
Stroke [53] |
| NLRP12-AD                        | NLRP12              | PRR for Yersinia pestis detection | Infections and aberrant inflammatory responses:  
Yersinia pestis [55]  
Plasmodium chabaudi [56]  
NF-κB inhibition  
Regulation of inflammation:  
Salmonella typhimurium [57]  
Brucella abortus [58] |
| TRAPS                            | TNFRSF1A            | TNF receptor                      | Infections and aberrant inflammatory responses:  
Tumor necrosis factor [59] |
| APLAID                           | PLCγ2               | Cleavage PIP to DAG               | Immunodeficiency:  
Common variable immunodeficiency [60]  
PLCγ2-associated antibody deficiency and immune dysregulation syndrome (PLAID) [60]  
Familial cold autoinflammatory syndrome 3 [60]  
Neurodegenerative disease:  
Alzheimer’s disease [61, 62]  
Lewy body dementia [62]  
Frontotemporal dementia [62] |
| FMF                              | Pyrin               | Virulence sensor                  | Infections and aberrant inflammatory responses:  
Yersinia pestis infection [63] |
| PFIT                             | WDR1                | Actin assembly, leukocyte migration | Infections and aberrant inflammatory responses:  
Listeria monocytogenes dissemination [64] |
| PAAND                            | Pyrin               | Virulence sensor                  | Infections and aberrant inflammatory responses:  
Yersinia pestis infection [63] |
### Table 1 The corresponding diseases caused by the similar signaling of autoinflammatory diseases (Continued)

| Type of autoinflammatory diseases | Responding proteins | Functions Corresponding diseases with the similar signaling |
|----------------------------------|---------------------|-------------------------------------------------------------|
| PAPA syndrome                    | PSTPIP1/CD2BP1      | Pyrin regulation Immunodeficiency: Common variable immunodeficiency [65] |
| MKD                              | MVK                 | Lipid metabolism Metabolic syndrome: Atherosclerosis [66] |
| NLRC4 inflammasomopathies        | NLRC4               | PRR for flagellin detection Infections and aberrant inflammatory responses: *Pseudomonas aeruginosa* infection [67] Macrophage activation syndrome (MAS) [68] |
| Relopathies                      |                     |                                                             |
| BS/EOS                           | NOD2                | PRR for MDP Infections and aberrant inflammatory responses: *Mycobacterium tuberculosis* infection [69] |
| HA20                             | A20/TNF-AIP3A       | Deubiquitinating for NF-κB regulation Infections and aberrant inflammatory responses: Systemic lupus erythematosus (SLE) [70] Rheumatoid arthritis [71] |
| IAALUCD                          | LUBAC               | Ubiquitinating for NF-κB regulation Infections and aberrant inflammatory responses: *Salmonella enterica* infection [72] *Legionella pneumophila* infection [72] *Shigella flexneri* infection [72] |
| ORAS                             | OTULIN              | Deubiquitinating for NF-κB regulation Infections and aberrant inflammatory responses: *Salmonella Typhimurium* infection [73] |
| IL-1 receptor-related autoinflammatory diseases: |                     |                                                             |
| DIRA                             | IL1RN               | IL-1 receptor inhibitor Infections and aberrant inflammatory responses: Inflammasomopathies [74] |
| Interferonopathies               |                     |                                                             |
| AGS                              | RNASEH2             | RNase activity against viral RNA Infections and aberrant inflammatory responses: SLE and other autoimmune diseases [75, 76] Cervical cancer via human papilloma virus [77] |
| SAMHD1                           | dNTPase activity against viral RNA/DNA Epstein-Barr virus infection [78] Human immunodeficiency virus infection [79] Hepatitis B virus infection [80] Marburg and Ebola virus [81] |
| ADAR1                            | Viral RNA processing |                                                             |
| MDAS/IFIH1                       | PRR for viral RNA detection Paramyxovirus infection [82] Picornavirus infection [83] |
| SAVI                             | STING/TMEM173       | PRR for viral DNA/RNA detection Infections and aberrant inflammatory responses: SLE and other autoimmune diseases [76] ANCA-associated vasculitis [84] Herpes simplex virus infection [85] |
| COPA syndrome                    | αCOP                | Transport vesicles between Golgi to ER Infections and aberrant inflammatory responses: Interstitial lung disease [86] Capillaritis [87] |
| PRAAS/NNS/CANDLE                 | PSMB3,4,8,9         | Proteasome for antigen processing Infections and aberrant inflammatory responses: SLE and other autoimmune disease [87, 88] Cytomegalovirus infection [89] Hepatitis B virus infection [90] Influenza virus infection [91] |
disease was named FCAS2 [102] and patients with NALP12 periodic fever syndrome respond to canakinumab (an anti-human IL-1β monoclonal antibody) and/or etanercept (a tumor necrosis factor (TNF) receptor-IgG heavy chain chimeric protein that acts as a bivalent antag-2000

functions of the NLRP12 inflammasome by a similar mechanism of the NLRP3 inflammasome (Fig. 2). Corresponding common diseases caused by the similar signaling are shown in Table 1.

Autoinflammation and phospholipase Cγ2-associated antibody deficiency and immune dysregulation

Autoinflammation and phospholipase Cγ2 (PLCγ2)-associated antibody deficiency and immune dysregulation (APLAID) responds to PLCγ2 which encodes for a constitutively repressed phospholipase. The S707Y PLCγ2 mutation disrupts the autoinhibition of PLCγ2, thereby increasing PLCγ2 activity and calcium influx from the ER in the leukocytes of patients with APLAID [106, 107]. Increased cytoplasmic Ca2+ levels promote the assembly of the NLRP3 inflammasome [108] (Fig. 2). Corresponding common diseases caused by the similar signaling are shown in Table 1.

Familial Mediterranean fever

The causative gene of familial Mediterranean fever (FMF), MEFV, encodes pyrin (also named marenostrin) [109, 110]. Currently, 389 variants of MEFV have been reported (https://infevers.umai-montpellier.fr/web/search.php?n=1). FMF was reported to be autosomal recessive; mutations in pyrin are thought to result in loss of its ability to inhibit inflammasomes. Nowadays, pyrin assembles with ASC and pro-caspase-1 to form the pyrin inflammasome, as well as the NLRP3 inflammasome [111]. Usually, pyrin is phosphorylated by serine/threonine-protein kinases PKN1 and PKN2, and inhibited by 14-3-3 proteins. When virulence factors expressed or secreted by bacteria and/or viruses inhibit RhoA GTPase, the pyrin inflammasome triggers activation and secretion of IL-1β [112] (Fig. 3). Yersinia pestis-like bacteria have a YopM protein which interacts with pyrin to inhibit inflammatory responses for avoiding further anti-bacterial responses [113]. In patients with FMF, pyrin harboring mutant human B30.2 domains defects such kind of ability, thereby preventing binding to ASC; this makes prolonged inflammasome activation and IL-1β secretion [114] (Fig. 3). Corresponding common diseases caused by the similar signaling are shown in Table 1.

Periodic fever immunodeficiency and thrombocytopenia

The causative gene product of periodic fever immunodeficiency and thrombocytopenia (PFIT) is WDR1 [115, 116], which interacts with cofillin to promote cleavage and depolymerization of F-actin [117, 118]. The L293F mutation in WDR1 disrupts intramolecular hydrophobic

| Type of autoinflammatory diseases | Responding proteins | Functions | Corresponding diseases with the similar signaling |
|----------------------------------|---------------------|-----------|-----------------------------------------------|
| POMP                             | Proteasome chaperone| Infections and aberrant inflammatory responses: Psoriasis [92] Human papilloma virus infection [93] |
| SMS                              | MDAS/IFIH           | PRR for viral RNA detection | Infections and aberrant inflammatory responses: SLE and other autoimmune diseases [75, 76, 94] Paramyxovirus infection [82] Picornavirus infection [83] |
| RIG-I                            | PRR for viral RNA detection | Infections and aberrant inflammatory responses: SLE and other autoimmune diseases [95] Paramyxovirus infection [83] |
interactions, which are important for maintaining actin protein structure. This disruption leads to actin accumulation and aggregates with pyrin resulting in pyrin activation and release of IL-18 [119] (Fig. 4). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**Pyrin-associated autoinflammation with neutrophilic dermatosis**

The *MEFV* mutations in patients with pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) harbor S242R and E244K mutations in pyrin; these mutations are located in the 14-3-3 binding motif, which interferes with binding of pyrin to 14-3-3, thereby allowing assembly of the pyrin inflammasome and excessive release of IL-1β [120–123] (Fig. 5). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome**

The causative gene product of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) (also called CD2-binding protein 1 (CD2BP1)) [124, 125]. Currently, 66 variants of the *PSTPIP1* gene have been reported (https://infevers.umai-montpellier.fr/web/search.php?n=5). In patients with PAPA syndrome, mutations in PSTPIP1 result in hyperphosphorylation of PSTPIP1, which strengthens its interaction with pyrin via the B-box domain to activate the pyrin inflammasome. This leads to increased secretion of IL-1β...
1β [125] (Fig. 6). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**Mevalonate kinase deficiency/hyper-IgD syndrome**
The causative gene product of mevalonate kinase deficiency/hyper-IgD syndrome (MKD) (also known as hyper-IgD syndrome (HIDS)) is mevalonate kinase (MVK) [126]. Currently, 264 variants of this gene have been reported (https://infevers.umai-montpellier.fr/web/search.php?n=3). Geranylgeranyl pyrophosphate, the substrate of geranylgeranylation, is a product of the mevalonate pathway. Deficiency of MVK leads to depletion of geranylgeranyl pyrophosphate, resulting in the inactivation of RhoA [127, 128]. Since the inactivation of RhoA activates the pyrin inflammasome, MKD leads to an inflammasomopathy. Indeed, canakinumab, an anti-IL-1β monoclonal antibody, is an effective treatment for MKD, suggesting that IL-1β is a common mediator of these diseases [129] (Fig. 7). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**NLRC4 inflammasomopathies**
Gain-of-function mutations in NLRC4 result in early-onset recurrent fever and macrophage activation syndrome (MAS), neonatal-onset enterocolitis with periodic fever, fatal or near-fatal episodes of autoinflammation, or symptoms resembling those of FCAS [68, 130, 131]. So far, more than 31 genetic variants of NLRC4 have been reported (https://infevers.umai-montpellier.fr/web/search.php?n=25). The NLRC4 inflammasome activates caspase-1 either with or without an adaptor ASC, which
in turn activates IL-1β and IL-18. NLRC4 inflammasomeopathies are linked more closely with hypersecretion of IL-18 rather than of IL-1β; however, the precise mechanism remains to be elucidated [132] (Fig. 8). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**NF-κB-related autoinflammatory diseases (relopathies)**

Dysregulations of NF-κB signaling are closely linking to the ubiquitination system. In addition to constitutive activation of NF-κB, loss-of-function mutations in the ubiquitin-mediated NF-κB regulatory system cause autoinflammatory diseases [10] (Fig. 9).

**Blau syndrome/early-onset sarcoidosis**

The gene responsible for Blau syndrome (BS)/early-onset sarcoidosis (EOS) is *IBD1*, and its causative gene product is NOD2 [133]. Usually, NOD2 recognizes muramyl dipeptide (MDP), leading to activation of NF-κB. Currently, 185 variants of NOD2 have been reported (https://infevers.umai-montpellier.fr/web/search.php?n=6). Gain-of-function mutations in NOD2 increase signaling via NOD2-RIPK2-associated activation of NF-κB [134, 135] (Fig. 10). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**A20 protein haploinsufficiency**

A20 (also called TNF-α-induced protein (TNFAIP) 3, is an intracellular deubiquitinase. A20 plays a role in
deubiquitination of several proteins, including NF-κB. A20 protein haploinsufficiency (HA20) is caused by heterozygous mutation or deletion of A20, resulting in insufficient deubiquitination of TRAF6 downstream of the TNF-α pathway, RIPK1 downstream of the TLR pathway, and RIPK2 downstream of the NOD1 or NOD2 pathways. Loss of A20 function leads to constitutive activation of NF-κB signaling [136, 137]. A20 also regulates the activity of the NLRP3 inflammasome in macrophages [138]. So far, 55 variants of A20 have been reported (https://infevers.umai-montpellier.fr/web/search.php?n=26). Haplodeficient mutations severely reduce A20 function, leading to prolonged activation of NF-κB [139] (Fig. 11). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**Immunodeficiency, autoinflammation, and amylopectinosis with inherited linear ubiquitin chain assembly complex deficiency**

Loss-of-function mutation in linear ubiquitin chain assembly complex (LUBAC), a protein complex comprising heme-oxidized IRP2 ubiquitin ligase 1 (HOIL-1) (also called RBCK1), HOIL-1 interaction protein (HOIP, also called RNF31), and SHANK-associated RH domain-interacting protein (SHARPIN) is associated with autoinflammation [140–145]. The L72P mutation in the HOIP protein affects its interaction with OTU deubiquitinase with linear linkage specificity (OTULIN) and lysine 63 deubiquitinase (CYLD); however, the most common disease-causing phenomenon is loss of expression of the L72P allele of HOIP. Combined heteromutations
comprise L41fsX7 and Q185X, which result in deficient HOIL-1 expression. Lack of HOIL-1 expression by fibroblasts impairs phosphorylation of IKK kinase, slower degradation of IκBα, and decreased ubiquitination of NEMO in response to stimulation with either TNF-α or IL-1β. LUBAC deficiency in fibroblasts downregulates NF-κB activation in response to IL-1β or TNF-α, whereas deficient monocytes release more IL-6 but less IL-10 in response to IL-1β [146–148] (Fig. 12). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**OTULIN-related autoinflammatory syndrome**

OTULIN is a deubiquitination enzyme that hydrolyzes methionine-1 (M1), which links to linear ubiquitin chains to regulate the activity of NF-κB [149]. Homozygous loss-of-function mutations in OTULIN cause OTULIN-related autoinflammatory syndrome (ORAS) [150]. The L272P mutation is located in a helix of the catalytic OTU domain, which forms part of the binding pocket for M1-linked distal ubiquitin; this mutation disrupts the binding of OTULIN and ubiquitin to its substrate [151, 152] (Fig. 13). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**IL-1 receptor-related autoinflammatory diseases**

IL-1 receptor-related autosomal recessive autoinflammatory diseases are caused by mutations in IL1RN (interleukin-1 receptor antagonist), resulting in a condition called deficiency of interleukin-1 receptor antagonist (DIRA) [153–155]. So far, 22 variants of this gene have been reported (https://infevers.umai-montpellier.fr/web/
search.php?n=10). IL-1RA deficiency results in uncontrolled IL-1α, IL-1β and NF-κB signaling [156] (Fig. 9). Corresponding common diseases caused by the similar signaling are shown in Table 1.

**Interferonopathies**

Anti-viral first-line defense is dependent on innate immune receptors (e.g., cGAS, MDA5, and RIG-I) that are detecting intracellular viral, bacterial, or own nucleic acid, linking to type I interferon signaling. Interferonopathies are closely linked to dysfunction of these innate immune receptors and type I interferon signaling. Immunoproteasome dysfunction is also linked to the interferonopathies [157] (Fig. 14).

**Aicardi–Goutières syndrome**

Aicardi–Goutières syndrome (AGS) is an inherited encephalopathy that affects newborn infants and usually results in severe neuro-physical disability. AGS is caused by loss-of-function mutations in the genes encoding the three prime repair exonuclease 1 (TREX1), the ribonuclease H2 subunit (RNASEH2)A, RNASEH2B, RNASEH2C, the phosphohydrolase SAM domain and HD
domain-containing protein 1 (SAMHD1), or the dsRNA-specific adenosine deaminases acting on RNA1 (ADAR1) [158, 159]. In addition, gain-of-function mutations in the dsRNA sensor MDA5 (also called IFIH1) have been identified in AGS patients [157]. AGS pathology seems to be caused by the accumulation of nucleic acids, which can cause neurological and liver abnormalities that resemble congenital viral infection (Fig. 15). Corresponding common diseases caused by the similar signaling are shown in Table 1.

Stimulator of interferon gene-associated vasculopathy with onset in infancy

Stimulator of interferon gene (STING)-associated vasculopathy with onset in infancy (SAVI) is caused by gain-of-function mutations in STING (also called TMEM173). Mutation of the STING amplifies the function of STING, which is an adaptor molecule involved in signal transduction through cGAS, leading to hyperactivation of type I IFN pathways [160]. Corresponding common diseases caused by the similar signaling are shown in Table 1.
Coatomer protein alpha syndromes

Coatomer protein alpha (COPA) syndrome, characterized by high-titer autoantibodies, interstitial lung disease, and inflammatory arthritis, was found to be deleterious mutations in the COPA gene (encoding coatomer subunit α). Mutant COPA causes defective intracellular transport via coat protein complex I which leads to ER stress and the upregulation of the levels of transcripts encoding IL-1β, IL-6, and IL-23 [161]. COPA is a critical regulator of STING transport ER and retrieval of STING from the Golgi. Mutant COPA retention of STING on the Golgi resulting in STING activation leads to prolonged type I interferon signaling [86] (Fig. 16). Corresponding common diseases caused by the similar signaling are shown in Table 1.

Proteasome-associated autoinflammatory syndromes

Nakajo–Nishimura syndrome (NNS) and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE) were the first
PRAAS to be described. Loss-of-function mutation in immunoproteasome components such as proteasome subunit beta type (PSMB)8, PSMB4, PSMA3, PSMB9, or proteasome maturation protein (POMP) leads to increased secretion of type I IFN by immune cells [162, 163] (Fig. 17). Corresponding common diseases caused by the similar signaling are shown in Table 1.

Singleton–Merten syndrome
Singleton–Merten syndrome (SMS) is caused by gain-of-function mutations in the RNA sensor MDA5 or RIG-I. Typical SMS is caused by a mutation in MDA5, whereas atypical SMS is caused by a mutation in RIG-I; both mutations cause constitutive activation of IFN signaling pathways [164, 165]. Notably, mutations in the MDA5 are also associated with AGS, so that both SMS and AGS share a common molecular mechanism [164] (Fig. 18). Corresponding common diseases caused by the similar signaling are shown in Table 1.

Conclusions
Here, we describe briefly the molecular mechanisms underlying autoinflammatory diseases caused by dysregulation of IL-1β or IL-18 processing, NF-κB activation,
Fig. 12 Loss-of-function mutation in linear ubiquitin chain assembly complex (LUBAC) is associated with autoinflammation. Loss-of-function mutations in the HOIP (e.g., L72P) affects its interaction with OTU deubiquitinase with linear linkage specificity (OTULIN) and lysine 63 deubiquitinase (CYLD), leading to prolonged NF-κB activation.
Fig. 13 Homozygous loss-of-function mutations in OTULIN in patients with OTULIN-related autoinflammatory syndrome (ORAS). OTULIN is a deubiquitination enzyme that hydrolyzes methionine-1 (M1), which links to linear ubiquitin chains to regulate the activity of NF-κB. The L272P mutation of OTULIN disrupts the binding of OTULIN and ubiquitin to its substrate, leading to prolonged NF-κB activation.
Type I interferon signaling in interferonopathies. Type I interferon signaling is closely linked to innate immune receptors such as cGAS, MDA5, and RIG-I that are sensing viral, bacterial, or own DNA or RNA. Interferon-stimulated genes (ISGs) are induced by interferon regulatory factors (IRFs) downstream of cGAS, MDA5, and RIG-I. Immunoproteasome dysfunction is also linked to interferonopathies.

Fig. 15 Loss-of-function mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, or ADAR1 in patients with Alciddi-Goutières syndrome (AGS). Loss-of-function mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, or ADAR1 results in the accumulation of nucleic acids which leads to the induction of IRF transcription.
Fig. 16 Mutations in αCOP in patients with COPA syndrome. Mutations in αCOP (e.g., K230N) impair ER-Golgi transport resulting in ER stress-induced NF-κB activation and the mutant αCOP retention of STING on the Golgi resulting in STING activation leads to prolonged type I interferon signaling.
Fig. 17 Loss-of-function mutations in immunoproteasome components PSMB8, PSMB4, PSMA3, PSMB9, or proteasome maturation protein (POMP) in patients with PRAAS/NNS/CANDLE. Loss-of-function mutation in immunoproteasome components such as PSMB8, PSMB4, PSMA3, PSMB9, or proteasome maturation protein (POMP) leads to increased secretion of type I IFN by immune cells.
and IFN secretion. Disruption of the fine balance within these signaling pathways contributes to the pathogenesis of autoinflammatory diseases. Increasing our knowledge of the molecular biology underlying autoinflammatory diseases will facilitate the development of disease-targeting biologics. Therefore, future studies should elucidate the autoinflammatory disease-specific signalosome in detail.

Abbreviations

DAMP: Damage-associated molecular pattern; PAMP: Pathogen-associated molecular pattern; PRR: Pattern recognition receptor; TLR: Toll-like receptor; NLR: NOD-like receptor; CLR: C-type lectin receptor; RLR: RIG-I-like receptor; NF: Nuclear factor; PRAAS: Proteasome-associated autoinflammatory syndromes; IL: Interleukin; PYD: Pyrin domain; AIM2: Absent in melanoma 2; ASC: Apoptosis-associated speck-like protein containing a caspase-recruitment domain; CARD: Caspase-recruitment domain; GSDMD: Gaspdermin D; CAPS: Cryopyrin-associated periodic syndrome; FCAS: Familial cold autoinflammatory syndrome; FCU: Familial cold urticaria; MWS: Muckle–Wells syndrome; NOMID: Neonatal-onset multisystem inflammatory disease; CINCA: Chronic infantile neurologic, cutaneous, and arthritis; NAIAD: NLRP1-associated autoinflammation with arthritis and dyskeratosis; NLRP12-AD: NLRP12 autoinflammatory syndrome; TNF: Tumor necrosis factor; TRAPS: TNF receptor-associated periodic fever syndrome; TNFRSF: TNF receptor superfamily member; APLAID: Autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation; FMF: Familial Mediterranean fever; PFIT: Periodic fever immunodeficiency and thrombocytopenia; PAAND: Pyrin-associated autoinflammation with neutrophilic dermatosis; PAPA: Pyogenic arthritis, pyoderma gangrenosum, and acne; PSTPIP1: Proline-serine-threonine phosphatase-interacting protein 1; CD28P1: CD2-binding protein 1; MKD: Mevalonate kinase deficiency; HIDS: Hyperimmunoglobulinemia D and periodic fever syndrome; MK: Mevalonate kinase; MAS: Macrophage activation syndrome; B5: Blau syndrome; EOS: Early-onset sarcoidosis; MDP: Muramyl dipeptide; HA20: A20 protein haploinsufficiency; TNFAIP: Tumor necrosis factor alpha-induced protein; IAALUCD: Immunodeficiency, autoinflammation, and amylopectinosis with inherited linear ubiquitin chain assembly complex deficiency; LUBAC: Linear ubiquitin chain assembly complex; HOIL-1: Heme-oxidized IRP2 ubiquitin ligase 1; HOIP: HOIL-1 interaction protein; SHARPIN: SHANK-associated RH domain-interacting protein; OTULIN: OTU deubiquitinase with linear linkage specificity; CYLD: CYLD lysine 63 deubiquitinase; ORAS: OTULIN-related autoinflammatory syndrome; DIRA: Deficiency of the IL-1-receptor antagonist; AGS: Aicardi–Goutières syndrome; TREX: Three prime repair exonuclease; RNASEH2: Ribonuclease H2 subunit; SAMHD: SAM domain and HD domain-containing protein; ADAR1: dsRNA-specific adenosine deaminase acting on RNA 1; STING: Stimulator of interferon genes; SAVI: STING-associated vasculopathy with onset in infancy; COPA: Coatomer protein alpha; NNS: Nakajo–Nishimura syndrome; CANDLE: Chronic atypical neutrophilic dermatosis with lipodystrophy and
elevated temperature syndrome; PSMB: Proteasome subunit beta type; POMP: Proteasome maturation protein; SMS: Singleton–Merten syndrome

Acknowledgements
We greatly appreciate Dr. Isabelle Toutou, chief editor of "TNFEVERS" database, and its contributors.

Authors’ contributions
The manuscript was written by NK and JM. All authors read and approved the final manuscript.

Funding
This work was supported by Grants-in-Aid for Scientific Research (B) (JSPS KAKENHI Grant Number: 20H01085 to NK). This work was supported by Grants-in-Aid for Scientific Research (B) (JSPS KAKENHI Grant Number: 20H03719 to JM) and Grant-in-Aid for Encourage-
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