

Recent Advances in Autoinflammatory Diseases and Animal Models

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Abstract

Autoinflammatory disorders are a fast growing group of human diseases which have provided unique insights into key mechanisms of inflammatory pathways. With the recognition of inflammasomes as an important factor in causing ongoing inflammatory responses, the innate immune system experienced a renaissance in the field of immunological research. Here we summarize recent advances in the understanding of the pathogenesis of autoinflammatory diseases and review selected mouse models available to study such diseases.

Introduction

The concept of “autoinflammation” and “autoinflammatory diseases” dates back to 1999, when McDermott et al. [1] initiated this term for a family of disorders characterized by episodes of “seemingly unprovoked” inflammation without the appearance of autoantibodies or antigen-specific T cells. During the last decade the list of autoinflammatory diseases has been growing fast ([2], Table 1), and has been extended to a number of clinical entities with a more complex (polygenic) mode of inheritance. Autoinflammatory conditions now encompass a broader spectrum of clinical symptoms, such as serositis, pyogenic or crystalline arthritis, pyoderma gangrenosum, granulomatous uveitis, and certain forms of vasculitis. Therefore, the distinction between autoinflammatory and autoimmune disorders is sometimes difficult. The pathogenesis of *autoimmune diseases* like systemic lupus erythematoses (SLE) is characterized by the involvement of lymphocytes and antigen-receptors, and therefore driven by the adaptive immune system. In contrast, *autoinflammatory disorders* are defined by their relative lack of the involvement of adaptive immune mechanisms [2]. The innate immune system predominates the pathogenesis of these diseases. Myeloid cells in combination with pathogen- (PAMPs) and danger-associated molecular patterns (DAMPs) are initiators of autoinflammation. In addition, it has been elucidated that there are frequent triggers like cold exposure, physical trauma, mechanical skin trauma, childhood immunization, psychological stress, or hormonal triggers like menstruation or pregnancy. The lack of autoantibodies as criterion for autoinflammatory diseases is also not consistently valid. Therefore, Kastner and colleagues [2] proposed a revised definition, which includes hereditary factors as well as gene-environment interactions, and recognizes the clinical continuum of autoimmune and autoinflammatory diseases recommended by McGonagle and McDermott in 2006 [3]. “The *autoinflammatory diseases* are clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition” [2].

One milestone to elucidate the pathomechanism of autoinflammatory diseases was the recognition of disease-associated mutations in the NLRP3/CIAS1 gene [4-6]. Different classifications of autoinflammatory diseases exist. Dependent on the point of view there are more clinically based [2,7-9] or more molecular biology based classifications like IL-1 β -mediated disorders or inflammasomopathies [7].

This review summarizes recent progress in the understanding of the pathogenesis of the growing spectrum of autoinflammatory diseases and emphasizes selected mouse models available to study such diseases.

Monogenic autoinflammatory syndromes are rare diseases of hereditary recurrent fevers. They comprise FMF (Familial mediterranean fever), TRAPS (TNF receptor-associated periodic syndrome), CAPS (Cryopyrin-associated periodic syndrome), HIDS (Hyperimmunoglobulinemia D) and PAPA (Pyogenic arthritis, pyoderma gangrenosum, and acne) (Figure 1) [2,9]. Patients with tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), an autosomal dominantly inherited disorder, are characterized by long periods of fever (>7 days up to months) with abdominal pain, arthritis, pleurisy, sterile peritonitis, migratory erythema, periorbital edema, myositis and in some cases amyloidosis. TRAPS is caused by mutations in the *TNFRSF1A* gene [1].

Familial mediterranean fever (FMF) is the first-recognized (International FMF Consortium [10], FMF Consortium 1997 [11]) and most common hereditary recurrent fever syndrome. FMF patients show shorter fever periods (1-3 days) associated with serositis, synovitis, and cutaneous inflammation, often complicated by the development of amyloidosis. FMF has been shown to be caused by mutations in the *MEFV* gene [1,10,11].

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is an autosomal recessively inherited disease and manifests with fever, erysipelas-like skin rash, aphthous ulcers, abdominal pain and lymphadenopathy. The fever lasts about 4-6 days and recurs every 4-8 weeks. Vaccinations are a known trigger of this disease. Serum immunoglobulin D levels may be elevated, but they may also be normal, and are therefore not useful as diagnostic tool. The underlying mutations are located in the mevalonate kinase gene (*MVK*).

In PAPA (Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) the fever episodes are shorter between 1-3 days recurring every 28 days. It is caused by mutations in *PSTPIP1* (or CD2-binding protein 1; CD2BP1).

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Cryopyrin associated periodic syndromes (CAPS) comprising on their milder end the familial cold autoinflammatory syndrome (FCAS), the Muckle-Wells syndrome (MWS), and as the most severe phenotype the neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous and articular syndrome, or CINCA. FCAS is characterized by cold induced fever episodes, urticarial rash or hives, arthralgias and conjunctivitis. MWS patients suffer from periodic fever episodes, urticarial rash and deafness, as well as arthralgias, conjunctivitis and in some cases amyloidosis. NOMID manifests very early in life, often during the neonatal period, with sometimes continuous fevers, rash, epiphyseal overgrowth of

the long bones, chronic aseptic meningitis with sometimes blindness, progressive hearing loss, and mental retardation.

DIRA (deficiency of IL-1 receptor antagonist, IL-1ra) is the most recently described disease entity [7,12] and is characterized by neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis. The lack of the negative regulator IL-1ra leads to uncontrolled signalling of IL-1 β with increased activation of pro-inflammatory cytokines.

Early-onset enterocolitis (IBD, inflammatory bowel disease) due to lack of a functional IL-10 receptor has also been firstly described in 2009 [13]. It is a new autosomal recessive disorder caused by mutations

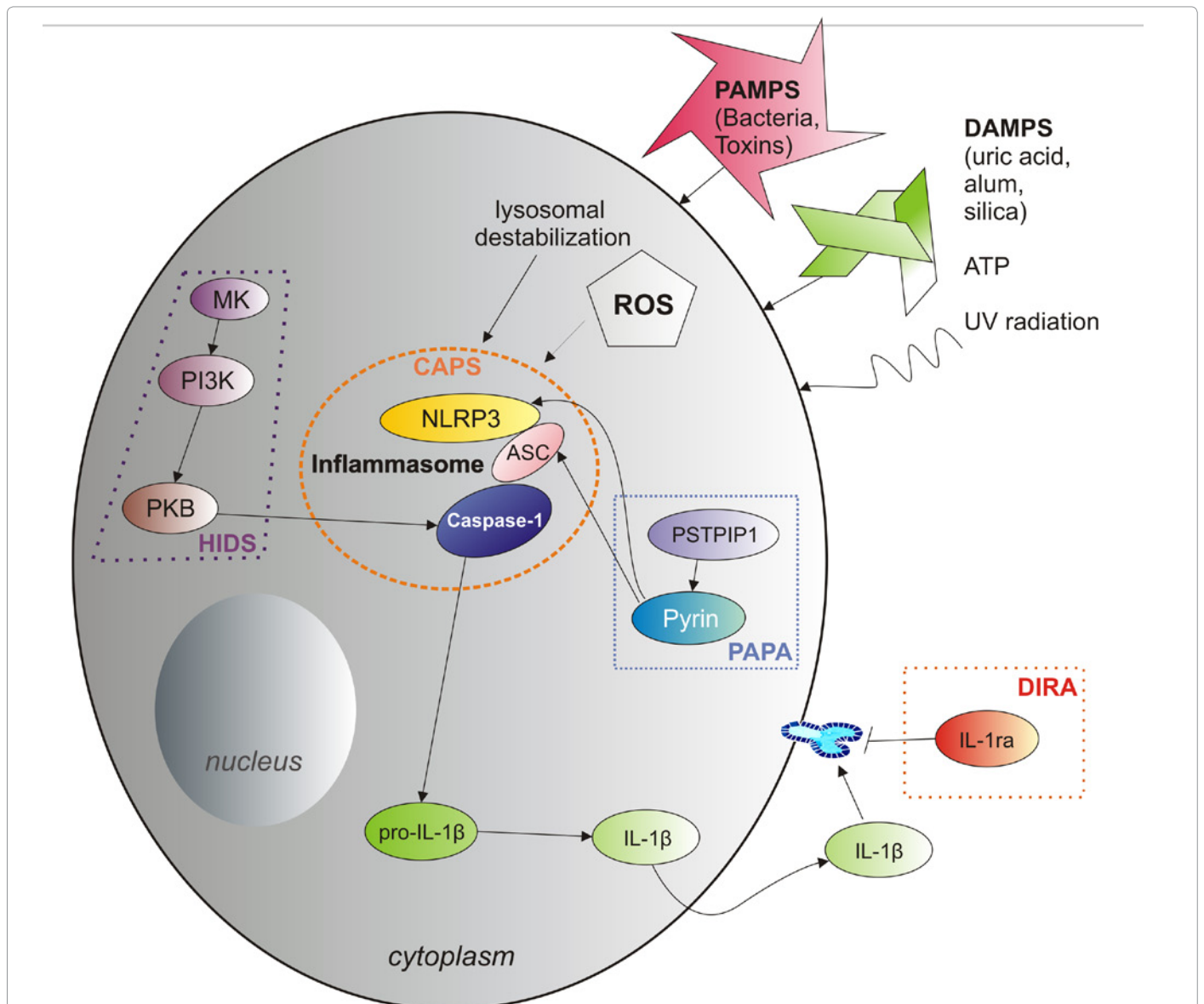


Figure 1: NLRP3 inflammasome and selected monogenic autoinflammatory diseases. Several endogenous and exogenous danger signals, such as urate crystals, asbestos, alum, silica, ATP, amyloid β , as well as bacteria, toxins, fungi and a variety of others, activate the NLRP3 inflammasome. The exact pathway, how these stimuli lead to NLRP3 activation is not known yet. However, reactive oxygen species (ROS) and lysosomal destabilization seem to be involved. The selected monogenic autoinflammatory syndromes result in activation, of the caspase-1 complex. In CAPS, mutations in *NLRP3* result in increased assembly of the NLRP3 inflammasome and active caspase-1 through interactions with ASC and procaspase-1. In PAPA, mutations in *PSTPIP1* lead to prolonged binding of *PSTPIP1* to pyrin and impairment of pyrin function. In FMF, mutant pyrin is pro-inflammatory in some conditions and results in caspase-1 activation. Active caspase-1 then cleaves pro-IL-1 β into its biological active form. Secreted IL-1 β can act through binding to the IL-1RI. IL-1 receptor antagonist (IL-1ra) is a naturally occurring IL-1 β antagonist. Mevalonate kinase may modulate inflammasome activity through Rac1/PI3K and PKB pathway.

in the IL-10 receptor genes (*IL10RA* and *IL10RB*), encoding the IL-10R1 and IL-10R2 proteins. These mutations result in the functional loss of IL-10 signalling by deficient STAT3 phosphorylation. Therefore, the loss of IL-10 as an anti-inflammatory cytokine directly leads to a pro-inflammatory condition, presenting already in the neonatal period with severe inflammatory bowel disease and folliculitis.

PRRs and Inflammasome activation

Inflammation is one defence mechanism of our body against endogenous and exogenous danger signals such as tissue damage, infection or tissue stress. Sensing of danger signals to the host is mediated by the innate immune system and depends on a variety of receptors (pattern recognition receptors, PRRs). The membrane associated Toll-like receptors (TLRs) and the predominantly cytoplasmic localized NOD-like receptors (NLRs) are the best-characterized of these. After recognition of danger signals by TLRs or NLRs, multiprotein complexes called inflammasomes are activated. *Inflammasomes* are macromolecular complexes by which IL-1 and IL-18 are activated in monocytes and macrophages. The NLRP3 inflammasome is the most studied so far, and comprises NLRP3, ASC and procaspase-1 (Figure 1). By inflammasome activation, caspase-1 cleaves pro-IL-1 β to active IL-1 β . In addition, other proteases, including caspase-8, proteinase 3 and granzyme A, have been shown to activate pro-IL-1 β . IL-1 β is, besides TNF and IL-6, one of the major mediators of fever and inflammation. It regulates the response to infections by generating fever, activating lymphocytes and recruiting leukocytes to the site of infection.

In contrast, IL-18 lacks this pyrogenic activity. It induces interferon- γ (IFN γ) production by activated T cells and natural killer cells. Its action depends on the presence or absence of IL-12 leading to a TH1 or TH2 response respectively. Furthermore, IL-18 has been implicated in driving TH17 cell response synergizing with IL-23.

Inflammasomes

To date there are six different known macromolecular inflammasomes, named by their scaffolding proteins: NLRP1 (NOD-like receptor family, pyrin domain containing 1), NLRP3, NLRC4 (NLR family CARD (Caspase activation and recruitment domain), AIM2 (Absent in melanoma 2), RIG-I (Retinoic acid inducible gene

I) and IFI16 (interferon gamma inducible protein [16]). The NLRP1 inflammasome is activated by muramyl dipeptide (MDP), a component of the bacterial cell wall, and the anthrax lethal toxin. Activation of the NLRC4 inflammasome is mainly induced by flagellin, whereas the AIM2 inflammasome is activated by cytoplasmic dsDNA RIG-I, as one of the RNA-sensing RIG-like receptors (RLRs), recognizes RNA-viruses, whereas IFI-16 might be responsible for sensing viral DNA in the nucleus. In contrast, the NLRP3 inflammasome has been shown to be activated by a wide range of pathogen-associated (PAMPs) or danger-associated molecular patterns (DAMPs) [14,15]. Besides the mentioned scaffolding proteins, the small adapter ASC (Apoptosis-associated speck-like protein containing a caspase recruitment domain) and the pro-inflammatory enzyme caspase-1 are the other typical components of inflammasomes.

Mouse models

Besides disease entities allowing insights into the pathomechanisms of autoinflammatory disorders, there are different mouse models available to study such diseases. *Knockout animals*, characterized by the inactivation of the endogenous genes and replacement of it by a disrupted version or a selection cassette via homologous recombination, have the potential disadvantage of embryonic lethality. Using *conditional (tissue-specific) knockout mice*, generated under utilization of the Cre/loxP DNA recombination system, researchers may overcome this problem. In addition, there are *knock-in mouse models*, in which a specific gene was knocked out and replaced by a gene with a specific disease-associated mutation. Transgenic *mouse models* contain additional, artificially-introduced genetic material in every cell. This often confers a gain of function, but also a loss of function may occur if the integrated DNA interrupts another gene. Transgenic mice are used to model human diseases that involve the over- or misexpression of a particular protein. Selected murine autoinflammation models are shown in Table 1.

TNFR1

Tumor necrosis factor (TNF) is a proinflammatory and cytotoxic cytokine with critical functions in immune regulation and host defense. TNF mediates its activities via two cell surface receptors, TNFR1

Affected protein	Associated human disease	Genetic models	References
TNFR1	TRAPS	nonsheddable p55TNFRs (p55 Δ NS), TNFRSF1A ^{T50M} , TNFRSF1A ^{C33Y} .	Xanthoulea S (2004) [18], Simon (2010) [20], Lobito (2006) [19]
		TNFR1 ^{-/-}	Rothe (1993) [21], Pfeffer (1993) [22], Peschon (1998) [16]
Pyrin/Marenostrin	FMF	knock-in mouse with B30.2 mutations (M680I, M694V, and V726A)	Chae (2011) [28]
		targeted truncation of pyrin	Chae (2003) [23]
Mevalonate kinase	HIDS	MVK ^{+/-}	Hager (2007) [33], Hager (2011) [34]
NLRP3 (Cryopyrin)	FCAS, MWS, NOMID/CINCA	NLRP3 ^{-/-}	Martinon (2006) [38]
		NLRP3 ^{A350VneoR/+} and NLRP3 ^{I351PneoR/+} mice, NLRP3 ^{R258W}	Brydges (2009) [36], Meng (2009) [35]
IL-1ra	DIRA	IL-1ra ^{-/-}	Horai 2000 [42]
PSTPIP1	PAPA	n.d.	

Table 1: Selected murine autoinflammation models. TRAPS, TNF receptor associated periodic syndrome; FMF, Familial mediterranean fever; HIDS, Hyperimmunoglobulinemia D with periodic fever syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; CINCA, chronic infantile neurologic cutaneous and articular syndrome; DIRA, deficiency of IL-1 receptor antagonist; PAPA, Pyogenic arthritis, pyoderma gangrenosum, and acne; IL-1ra, IL-1 receptor antagonist; PSTPIP1, Proline-serine-threonine phosphatase-interacting protein 1; TNFR1, TNF receptor 1; NLRP3, NACHT, LRR and PYD domains-containing protein 3; NOD2, nucleotide-binding oligomerization domain containing 2; CD2BP1, CD2-binding protein 1; n.d., not described.

(p55TNFR, CD120a) and TNFR2 (p75TNFR, CD120b). Both TNFRs are ubiquitously expressed and show structural similarities concerning their extracellular domains but signal through distinct intracellular regions. The TNFR1 contains an intracellular death domain that is not present in TNFR2. The TNFR1 initiates an intracellular signalling cascade through its intracellular death domain and the TNFR-associated death domain adaptor (TRADD) protein, activating NF- κ B and (mitogen-activated protein kinases). These signalling pathways independently induce gene expression of inflammatory cytokines and chemokines. TNFRs are initially synthesized as membrane-anchored proteins, which can subsequently be released from the cell surface. The soluble molecules are also capable of binding the TNF ligand. Soluble TNFRs are constitutively released in the circulation [16] and increase under inflammatory conditions. The receptor shedding (ectodomain cleavage) and the resultant decrease in surface bound TNFR1 may serve as a mechanism to desensitize cells to the TNF action. In addition, the soluble forms could compete for ligand binding with the cell surface receptor.

Since defective TNFR1 shedding has been suggested to be involved in the pathogenesis of TRAPS [17], Xanthoulea and coworkers [18] used a knock-in approach to generate mutant mice expressing non-sheddable TNFR1 (p55^{ANS}) to investigate the role of TNFR1 shedding *in vivo*. They showed that defective TNFR1 shedding in mice leads to a persistent expression of the receptor on the cell surface and acts as a dominant genetic trait to provoke spontaneous autoinflammatory reactions. This defective shedding resulted in enhanced host defenses to bacterial infections and to sensitization against TNF and LPS [18]. However, impaired TNFR1 shedding from the cell surface may have less proinflammatory effects than a more recently described mechanism due to abnormal receptor folding and trafficking [19]. Most mutations in the TNFR1 occur in the extracellular domain and therefore affect receptor folding and trafficking, resulting in the retention of misfolded TNFR1 complexes in the endoplasmic reticulum (ER).

Knock-in mice of mutant *TNFRSF1A* in which the T50M or C33Y TRAPS-associated mutations were engineered into the endogenous *TNFRSF1A* locus (*TNFRSF1A*^{T50M}, *TNFRSF1A*^{C33Y}) exhibited normal growth, development, appearance, and life span under specific pathogen-free conditions. The mutated TNF receptor has a high affinity to TNF but does not signal properly. Mutant receptors accumulate intracellularly in the ER leading to an enhanced MAPK activation [20], but this activation is not sufficient to trigger spontaneous cytokine production. However, after LPS stimulation, signals generated through TLR4 synergized with the elevated MAPKs and generated excessive cytokine production, e.g. IL-6 in fibroblasts [20]. After LPS challenge the authors observed increased serum TNF concentrations in heterozygous T50M and C33Y TNFR1-mutant mice compared with WT controls. Homozygous T50M and C33Y TNFR1-mutant mice, similarly to TNFR1-deficient mice (*TNFR1*^{-/-}) [16,21,22], were completely resistant to LPS-induced lethality and lack germinal centers and follicular dendritic cell networks in the spleen [20]. These T50M and C33Y TNFR1-mutant TRAPS modelling mice share some similarities with mice engineered to delete the cleavage site of TNFR1 [18,19]. However, there are some differences. The most important one is that the cleavage-defective TNFR1 protein still functions as a surface receptor for TNF, whereas the TRAPS mutant TNFR1 does not. In addition, T50M or C33Y TNFR1-mutant mice do not develop chronic active hepatitis as seen in cleavage-defective mutant mice.

Pyrin

Pyrin (marenostrin) is a 781-aa protein (molecular weight 86,000

Da) predominantly expressed in peripheral blood cells such as neutrophils, monocytes, and dendritic cells, but not in lymphocytes. The detection in spleen, lung and muscle is probably the result of leukocyte infiltration in these tissues. The role of pyrin in IL-1 β activation is still discussed controversially. Chae and colleagues [23] provided evidence that pyrin can inhibit IL-1 β activation. These findings suggest that pyrin negatively regulates inflammasome activity by competing for ASC. In contrast, Yu and coworkers showed in a transfection model, that pyrin may also assemble an inflammasome complex with ASC and procaspase-1 leading to caspase-1 activation and IL-1 β processing, suggesting a pro-inflammatory role [24]. Whether pyrin inhibits or activates IL-1 β , neither formulation adequately explains the proinflammatory effects seen in FMF patients.

Pyrin is composed of at least five domains, of which the most notable are the c-terminal B30.2 domain and the N-terminal pyrin domain (PYD). Interestingly, the C-terminal B30.2 domain of pyrin is the most frequent site of FMF mutations. The B30.2 domain is also the domain that interacts directly with caspase-1 [25] to convert pro-IL-1 β to active IL-1 β . PYD is found in a large number of proteins implicated in the control of inflammation. It probably controls the inflammatory response in myelomonocytic cells at the level of the cytoskeleton organization [26,27].

In 2003 Chae and colleagues [23] reported a mouse model generated by targeted truncation of pyrin that, similar to FMF patients, retained the full functional PYD. However, these mice did not show an overt phenotype related to FMF, suggesting that FMF may be caused by a gain of function.

In 2006 Chae and colleagues [25] demonstrated by co-immunoprecipitation direct interaction between pyrin and caspase-1 that was independent of ASC. They also showed that the B30.2 domain of pyrin was necessary and also sufficient for binding procaspase-1.

To study the pathogenesis of FMF induced by mutations in the B30.2 domain *in vivo*, Chae and coworkers [28] generated various knock-in mouse models with frequent FMF-associated B30.2 mutations (M680I, M694V, and V726A). In contrast to the truncation model, these knock-in mice showed severe inflammation comparable to the FMF patients. They found, that the inflammatory phenotype of these mice is mediated by an ASC-dependent, NLRP3-independent production of IL-1 β by bone marrow derived cells.

Therefore, NLRP3 inflammasome has no role in the inflammation of FMF knock-in mice. In addition, there are no differences in IL-1 β secretion of wildtype, pyrin-deficient, and knock-in macrophages induced by double-stranded DNA or *S. typhimurium*, suggesting that the AIM2 or NLRC4 inflammasomes are not involved in the inflammation of these mice [28]. Furthermore, the involvement of ASC in inflammation of these knock-in mice excludes the NLRP1 inflammasome from the pathogenesis of FMF, since murine NLRP1 lacks a functional PYD and is therefore predicted to be unable to interact with ASC [29].

Mevalonatekinase

Mevalonate kinase (MVK) is a cytosolic enzyme involved in early cholesterol synthesis. The protein consists of 396 amino acids and has a molecular weight of 42,450 Da. Defects in the MVK gene have been associated with human diseases, such as mevalonic aciduria (MA) [30] and hyperimmunoglobulinaemia D (HIDS) [31,32].

To study the pathogenesis of HIDS in more detail, Hager and

coworkers [33,34] established a mouse model, where the deletion of one *MVK* allele (*Mvk*^{-/-}) yielded viable mice with significantly reduced liver *MVK* enzyme activity. The loss of a single *MVK* allele in the mouse is associated with significant accumulation of tissue mevalonate, notably in spleen, kidney and heart, but not in liver and brain. These mice showed increased serum levels of IgD, IgA, and TNF α , temperature dysregulation, hematological abnormalities, and splenomegaly, and thus demonstrating several phenotypic features of human HIDS. Previous reports on deletion of specific genes in cholesterol synthesis in the mouse model revealed a high degree of embryonic lethality. Concordantly, murine mevalonate kinase gene ablation was embryonic lethal for homozygous mutants [33].

NLRP3

NLRP3 (NOD-like receptor family, pyrin domain containing 3), also called cryopyrin or NALP3 (NACHT domain-containing, leucine-rich-repeat- and pyrin domain-containing protein 3) is the most studied NOD-like receptor (NLR) protein. It contains a pyrin-domain and is predominantly expressed in peripheral blood leukocytes and monocytes [6]. The NLRP3 protein consists of 920 amino acids containing several distinct motifs. It has a molecular weight of 105.7 kD. Besides the amino-terminal pyrin domain (amino acids 13 through 83) it contains a central nucleotide-binding site (NACHT domain, amino acids 217 to 533), and a carboxy-terminal leucine-rich repeat (LRR) domain (amino acids 697 through 920). However, there exist several alternative splice variants, of which the largest protein contains 1,034 amino acids with a size of 117.9 kD. NLRP3 functions as a danger-sensing protein that acts as a cytosolic counterpart to the membrane-associated TLRs.

Recently, two research groups developed *NLRP3* knock-in mouse models (*NLRP3*^{A350VneoR/+} and *NLRP3*^{L351PneoR/+} mice, *NLRP3*^{R258W}) to characterize inflammatory mediators [35,36].

The A352V and L353P mutations were chosen, since they are strongly related to MWS and FCAS [37]. These amino acids are conserved in mouse (A352 and L353) and human (A350 and L351) *NLRP3*. Brydges and colleagues [36] created conditional knock-in mice with the above mentioned mutations. They found that embryonic or myeloid-specific expression of A350V or L351P resulted in neonatal lethality with severe inflammatory signs. Multiple cytokines were upregulated in serum and skin of these *NLRP3*^{A350VneoR/+} mice. Contrasting to human disease in which epidermal involvement is absent mice showed massive infiltrates of granulocytes in dermis and epidermis.

Meng and colleagues [35] analyzed the immune response of mice carrying an R258W mutation in the *Nlrp3* gene, which is equivalent to the R260W mutation associated with Muckle-Wells syndrome and familial cold autoinflammatory syndrome. They reported high levels of IL-17, increased TH17 differentiation and the development of anti-DNA antibodies in *NLRP3*^{R258W} knock-in mice. The mutant mice exhibited skin inflammation characterized by neutrophil infiltration and an IL-1 β -dependent Th17 dominant cytokine response. The authors concluded that the R258W mutation mimics human Muckle-Wells syndrome and leads to inflammasome hyperactivation and Th17 cell-dominant immunopathology.

In *NLRP3* knockout mice (*NLRP3*^{-/-}) described by Martinon and colleagues [38] MSU-induced inflammation has been reduced. Murine *NLRP3*^{-/-} cells do not produce any detectable amount of IL-1 β in response to LPS and ATP *in vitro* [39]. In addition, macrophages exposed to gram-positive *Staphylococcus aureus* or *Listeria monocytogenes* required both ASC and *NLRP3* to activate caspase-1

and secrete IL-1 β . Therefore, the authors [39] concluded that *NLRP3* is essential for inflammasome activation in response to ATP, nigericin, maitotoxin, *S. aureus*, or *L. monocytogenes*. Gross and colleagues [40] showed that *NLRP3*-deficient mice are hypersusceptible to *C. albicans* infection.

IL-1ra

Interleukin (IL)-1 is a proinflammatory cytokine that plays important roles in host defence. After proteolytic cleavage of the 34 kDa pro-IL-1 β by activated caspase-1 the functionally active 17 kDa IL-1 β is secreted, mainly from innate immune cells. For the activation of caspase-1, the 45 kDa procaspase-1 must be cleaved into 20 (p20) and 10 kDa (p10) catalytic subunits. IL-1 α and IL-1 β bind to IL-1 receptor type I (IL-1RI) and type II (IL-1RII) respectively. The IL-1RI is responsible for specific signalling, while the IL-1RII functions as a non-signalling decoy receptor. To investigate IL-1 signalling and the involvement of its receptors in more detail, mice with a genetically disrupted IL-1RI gene have been generated [41]. Mice lacking IL-1RI are of normal vitality and exhibit no overt phenotype.

IL-1 receptor antagonist (IL-1ra) is the endogenous inhibitor of IL-1 and regulates IL-1 activity. IL-1ra binds to IL-1RI and inhibits the binding of IL-1 α and IL-1 β . As a consequence, the biologic activity of these two cytokines is neutralized. A mouse model of uncontrolled IL-1 signalling is available, the IL-1ra knockout mouse (*IL-1ra*^{-/-}) [42]. Interestingly, dependent on the genetic background, these mice spontaneously developed chronic inflammatory polyarthropathy, seen in BALB/cA but not in C57BL/6J. Moreover, elevated levels of antibodies against type II collagen, and double-stranded DNA were detected in these mice, suggesting development of autoimmunity. In addition, overexpression of IL-1 β , IL-6, and TNF were found in the joints, indicating regulatory roles of IL-1ra maintaining homeostasis of the immune system.

The same authors [42,43] found that transferring T cells of *IL-1ra*^{-/-} to T cell-deficient nude mice resulted in the development of autoimmune arthritis. Furthermore, *IL-1ra*^{-/-} SCID mice failed to develop arthritis, suggesting that combined deficiency of T and B cells completely suppresses arthritis development in *IL-1ra*^{-/-} mice. Examining TNF^{-/-} and *IL-1ra*^{-/-} double-knockout mice Horai and colleagues [42,43] found that TNF is crucial for the development of arthritis. Treatment with either anti-CD40L or anti-OX40L suppressed the disease. Therefore, the authors concluded that CD40-CD40L and OX40-OX40L interactions are important for the development of arthritis.

PSTPIP1

Proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) is a cytoskeleton-organizing protein, also known as CD2-binding protein 1 (CD2BP1). The full-length protein contains 417 amino acids (molecular weight 50-kD) and shows 88% homology to the mouse PSTPIP1. It contains a coiled-coil region, a PEST region, and a C-terminal SH3 domain. This protein has been associated to the pathogenesis of PAPA syndrome. PSTPIP1 binds to pyrin [43,43,44] resulting in the unmasking of its pyrin domain and recruitment of ASC, leading to a prolonged activation of caspase-1 and the inflammasome, resulting in the formation of active IL-1 β and inflammation. Additionally, Yu and coworkers [43] provided evidence that pyrin is a cytosolic receptor for PSTPIP1. They also showed that PAPA-associated *PSTPIP1* mutants prevent phosphorylation of the molecule and lead to prolonged binding to pyrin [43]. As until now there is no mouse model described yet.

In summary, the study of autoinflammatory disorders poses new questions regarding the molecular mechanisms leading to organ-specific inflammation. Since material from patients suffering from such diseases is limited, it is advantageous to have additional tools to examine the underlying pathological mechanisms. Animal models are one of these alternative options in studying disease related conditions. Through genetic manipulation of mice, much progress has been made in understanding the contribution of inflammasome-associated proteins during physiological and disease conditions. This review summarizes selected mouse models available to study autoinflammatory disease-related pathways *in vivo*. Current and future studies have the potential to shed further light on the effects of manipulating inflammatory pathways, which could lead to novel therapeutic approaches.

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