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Inflammasome biology, molecular pathology and therapeutic implications

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ABSTRACT

Inflammasomes are intracellular multiprotein signaling complexes, mainly present in myeloid cells. They commonly assemble around a cytoplasmic receptor of the nucleotide-binding leucine-rich repeat containing receptor (NLR) family, although other cytoplasmic receptors like pyrin have been shown to form inflammasomes. The nucleation of the multiprotein scaffolding platform occurs upon detection of a microbial, a danger or a homeostasis pattern by the receptor that will, most commonly, associate with the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) through homotypic domain interactions resulting in recruitment of procaspase-1. This will lead to the autoproteolytic activation of caspase-1, which regulates the secretion of proinflammatory IL1β and IL18 cytokines and pyroptosis, a caspase-1-mediated form of cell death. Pyroptosis occurs through cleavage of Gasdermin D, a membrane pore forming protein. Recently, non-canonical inflammasomes have been described, which directly sense intracellular pathogens through caspase-4 and -5 in humans, leading to pyroptosis.

Inflammasomes are important in host defense; however, a deregulated activity is associated with a number of inflammatory, immune and metabolic disorders. Furthermore, mutations in inflammasome receptor coding genes are causal for an increasing number of rare autoinflammatory diseases. Biotherapies targeting the products of inflammasome activation as well as molecules that directly or indirectly inhibit inflammasome nucleation and activation are promising therapeutic areas. This review discusses recent advances in inflammasome biology, the molecular pathology of several inflammasomes, and current therapeutic approaches in autoinflammatory diseases and in selected common multifactorial inflammasome-mediated disorders.

Contents

Abbreviations: AIM2, absent in melanoma-2; ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphate; CAPS, cryopyrin-associated periodic syndromes; CARD, caspase recruitment domain; DAMP, danger-associated molecular pattern; DNA, deoxyribonucleic acid; ER, endoplasmic reticulum; FMF, Familial Mediterranean fever; GWAS, genome-wide association studies; LPS, lipopolysaccharide; LRR, leucine-rich repeat; mRNA, messenger ribonucleic acid; NACHT/NOD, nucleotide-binding and oligomerization domain; NBD, nucleotide-binding domain; NF-κB, nuclear factor-κB; NLR, Nucleotide-binding leucine-rich repeat containing receptors; NLRP1, NLR sensor molecule containing pyrin domain 1; NLRP3, NLR sensor molecule containing pyrin domain 3; NLRP12, NLR sensor molecule containing pyrin domain 12; NLRX1, NLR family member X1; P2X7, purinergic receptor; PYD, pyrin domain; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRIM, TRIpartite motif;
Definitions Canonical inflammasome, NLRP3-mediated caspase-1 activation leading to IL1β and IL18 maturation and secretion and to pyroptosis; Non-canonical inflammasome, Intracellular LPS mediated caspase 4/5 induced pyroptosis; Pyroptosis, Caspase-dependant inflammatory cell death mediated through the membrane-pore-forming-protein Gasdermin D.

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1. Introduction

Inflammasomes are caspase-1-dependent and -independent multiprotein platforms which nucleate around an intracellular receptor that typically belongs to the family of Nucleotide-binding, Leucine-rich Repeat containing proteins (NLRs). Inflammasome components are principally expressed in innate immune cells such as monocytes and macrophages (Awad et al., 2017), but also in dendritic cells and neutrophils (Bakele et al., 2014; Sharp et al., 2009), as well as in certain non-immune cells, such as keratinocytes (Feldmeyer et al., 2007). Inflammasome association and activity is triggered upon detection of microbial products, sterile endogenous danger signals or upon the more recently described alterations in homeostasis, known under the names of pathogen- or danger-associated molecular patterns or homeostasis-altering molecular processes (PAMPs or DAMPs or HAMPs, respectively) (Liston & Masters, 2017; Martinon, 2008). Inflammasomes, play major roles in host defence against intracellular bacteria and viruses (Vanaja, Rathinam, & Fitzgerald, 2015) and in the regulation of inflammation (Próchnicki & Latz, 2017; Robbins, Wen, & Ting, 2014) through pro-inflammatory cytokine secretion. Mutations in inflammasome genes are causal for an increasing number of self-directed inflammatory diseases termed autoinflammatory diseases (McGonagle & McDermott, 2006). A deregulated inflammasome activity has also been reported in common metabolic, immune and inflammatory disorders (Davis, Wen, & Ting, 2011; de Zoete, Palm, Zhu, & Flavell, 2014; Guo, Callaway, & Ting, 2015; Lamkanfi, Walle, & Kanneganti, 2011; Robbins et al., 2014). Biotherapies targeting inflammasome-mediated cytokine release and pharmacological inhibitors that interfere with inflammasome nucleation and activation are promising therapeutic areas in inflammatory diseases. In the current review, we will discuss the biology, the molecular pathology and therapeutic implications of selected inflammasomes in autoinflammatory diseases, as well as in several common multifactorial inflammasome-mediated disorders.

2. The key inflammasome players

2.1. Nucleotide-binding, leucine-rich repeat containing receptors (NLRs)

NLRs are a group of germline-encoded innate immune receptors present in the cytoplasm of immune cells (Janeway & Medzhitov, 2002) which are involved in microbial recognition and host defence. In humans, 22 evolutionarily conserved NLRs are known today, several of which are implicated in inflammatory diseases (Zhong, Kinio, & Saleh, 2013). These proteins contain several domains: a central nucleotide-binding and oligomerisation domain, also known as NOD or NACHT — standing for NAIP (neuronal apoptosis inhibitor protein), CIITA (MHC class II transcription activator), HET-E (incompatibility locus protein from Podospora anserina) and TP1 (telomerase-associated protein) —, required for ATP-dependent self-oligomerization, a NACHT-associated domain (NAD) and a C-terminal leucine-rich repeat (LRR) domain potentially implicated in ligand detection. The N-terminal domain is variable and subdivides the family into at least 5 groups (Chen, Shaw, Kim, & Nuñez, 2009; Ting et al., 2008) (Fig. 1). The NLRA group is defined by the presence of an acidic transactivation domain, whereas the NLRB group contains baculovirus inhibitor repeats (BIRs). The NLRC group is defined by the presence of a caspase recruitment domain (CARD), whereas the presence of a pyrin (PYD) domain is specific to the largest group called NLRP. Finally, the NLRX group contains NLRX1, a protein that lacks both PYD and CARD domains, with an atypical N-terminal domain which contains a mitochondrial-targeting sequence (Arnoult et al., 2009; Moore et al., 2008). The N-terminal domain of NLRs mediates homotypic interactions with other proteins. In this regard, the presence of an N-terminal domain like a PYD or a CARD, which are members of the six-helix death domain-fold superfamily, is crucial to mediate inflammatory and apoptotic signalling pathways via the activation of caspases.

2.2. Inflammasome forming NLRs

Upon detection of a molecular pattern (PAMP, DAMP, or HAMP), NLRs associate in multiprotein complexes called inflammasomes that mediate caspase-1 activation and cytokine secretion (Fig. 2). An increasing number of NLR family members have been shown to form inflammasomes (Fig. 1). Inflammasome assembly is guided by homotypic interactions between the PYD domain of the receptor (commonly but not exclusively from the NLRP family) and the adaptor protein ASC (Apoptosis-associated Speck-like protein containing a CARD) which, through CARD-CARD domain interactions recruits pro-caspase-1 into the complex (see below). This leads to an active caspase-1 heterotetramer that proteolytically processes the zymogen forms of IL1β and IL18 pro-inflammatory cytokines, leading to their maturation and secretion (Martinon & Tschopp, 2004; Thornberry et al., 1992). In the case of NLRs that contain both a CARD and a PYD domains like NLRP1, or NLRs with a CARD domain like NLRC4, the interaction between the NLR and pro-caspase can, in some cases, occur in the absence of ASC (Broz, von Moltke, Jones, Vance, & Monack, 2010; Faustin et al., 2007; Mariathasan et al., 2004; Yu, Moecking, Geyer, & Masters, 2017). In this review, among the inflammasome forming NLRs, we will focus on the NLRP3 inflammasome, which is the best-characterized inflammasome nucleating around an NLR; we shall equally discuss the NLRP12 inflammasome whose existence remains controversial.

2.3. Non-NLR proteins forming inflammasomes

Inflammasomes can also nucleate around non-NLR proteins as first shown with AIM2 (Absent In Melanoma-2), a cytoplasmic protein not belonging to the NLR family. AIM2 contains an N-terminal PYD domain and in response to double stranded cytosolic DNA, is able to form an inflammasome (Fernandes-Alnemri, Yu, Datta, Wu, & Alnemri, 2009; Hornung & Latz, 2010a). This is also the case for three other non-NLR proteins, the interferon-inducible protein 16 (IFI-16) (Kerur et al., 2011), the retinoic acid inducible gene I (RIG-1) (Pothlichet et al., 2013) and pyrin (Xu et al., 2014). In this review, we will also discuss the inflammasome nucleating around the PYD domain of pyrin.

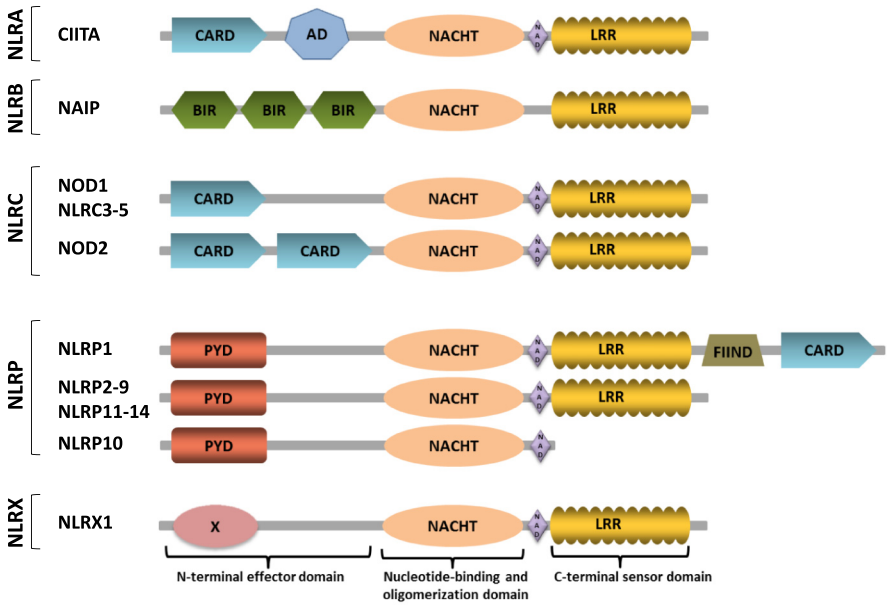

Fig. 1. The human NLR family. The NLR family is sub-divided into at least five subgroups (NLRA, NLRB, NLRC, NLRP and NLRX) based on the nature of the N-terminal effector domain. The NLRA group is defined by the presence of an acidic transactivation domain (AD), whereas the NLRB group contains baculovirus inhibitor repeats (BIRs). The NLRC group is defined by the presence of a caspase recruitment domain (CARD), whereas the largest group, termed NLRP, is characterized by the presence of a pyrin (PYD) domain. The NLRX group contains NLRX1, a protein that has an atypical N-terminal domain which contains a mitochondrial-targeting sequence. A central nucleotide-binding and oligomerization domain (called NACHT or NOD) and a C-terminal LRR (leucine-rich repeat) domain are common to all members with the exception of NLRP10 that lacks the LRR domain. NAD: (NACHT-associated domain); FIIND: (function to find domain).

2.4. Role of ASC in inflammasomes

ASC, also known as PYCARD, is a bipartite protein with two death-fold interaction domains, the N-terminal PYD and the C-terminal CARD domains. Its unique structure makes ASC an important adaptor protein bringing together PYD- and CARD-containing proteins (Gumucio et al., 2002). ASC was first identified in large cytosolic hollow-centred aggregates termed "specks" in the human promyelocytic cell line HL60 undergoing apoptosis (Masumoto et al., 1999). ASC specks are around 1 μm, visible under the microscope, and usually one speck per cell is seen upon inflammasome activation (Beilharz, De Nardo's, Latz, & Franklin, 2016; Fernandes-Alnemri et al., 2007; Stutz, Horvath, Monks, & Latz, 2013). ASC specks involve oligomerization of ASC through their PYD domains into filaments and cross-linking of these filaments by the CARD domains of ASC. These oligomers create caspase-1 activation sites, amplifying inflammasome-mediated signalling (Dick, Sborgi, Rühl, Hiller, & Broz, 2016). In this regard, speck formation is often used as a read-out for inflammasome activation (Jéru et al., 2010; Stutz et al., 2013). Interestingly, oligomeric ASC particles have also been found in the extracellular space and in the serum of patients with several autoinflammatory diseases suggesting that the particles *per se* may act as danger signals amplifying the inflammatory response (Baroja-Mazo et al., 2014; Franklin et al., 2014).

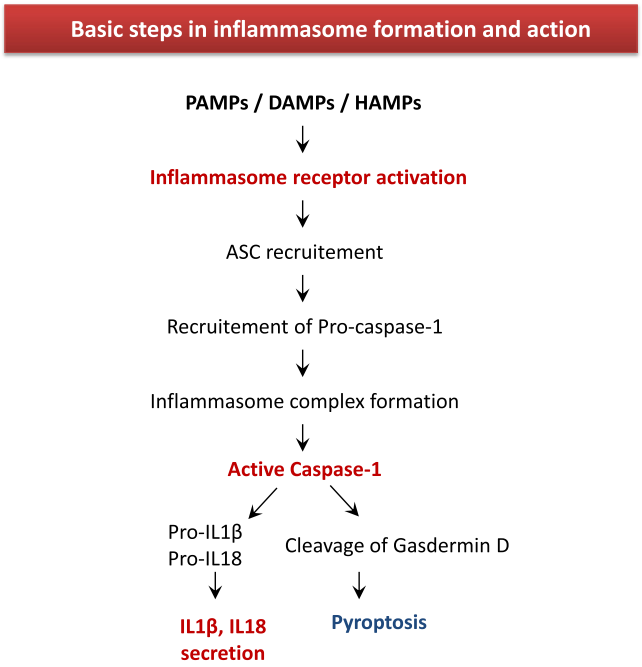

Fig. 2. Basic steps in inflammasome formation and action. DAMPs, PAMPs or HAMPs activate the inflammasome sensor usually from the NLR family. This leads to the adaptor protein ASC and pro-caspase-1 recruitment leading to the formation of the inflammasome complex. Inflammasome activates caspase-1 which then proteolytically maturates pro IL1β and pro-IL18 leading to their secretion. Caspase 1 can also cleave Gasdermin D leading to pyroptosis

2.5. Non-inflammasome forming NLRs involved in inflammation

As mentioned above, several NLRs form inflammasomes; however, some NLR members such as NOD1/NLRC1, NOD2/NLRC2 and NLRX1 activate downstream inflammatory signalling through engagement of nuclear factor-κB (NF-κB), mitogen-activated protein kinases (MAPKs) and interferon regulatory factors (IRFs) without being implicated in multiprotein complexes (Zhong et al., 2013). NLRX1 has a unique mitochondrial localization (Arnoult et al., 2009) and although the N-terminal domain is still not well characterized, it has been shown to regulate interferon and NF-κB signalling (Moore et al., 2008; Tattoli et al., 2008). In epithelial cells, *Chlamydia trachomatis* infection activates reactive oxygen species (ROS) production. Interestingly, ROS production is induced by NLRX1 and confers optimal growth conditions for *Chlamydia trachomatis* (Abdul-Sater et al., 2010). In another study, NLRX1, in interaction with TUFM (mitochondrial Tu translation elongation factor) another mitochondrial protein, stimulated autophagy

induction (Lei, Wen, & Ting, 2013) in response to viral infection. These results suggest that further studies are required in order to understand the function of non-inflammasome-forming NLRs in inflammation.

3. The canonical and non-canonical inflammasomes

In the so-called "canonical inflammasome", caspase-1 plays a central role (Fig. 3, **middle panel**). Proximity-induced oligomerization of caspase-1 in the inflammasome enables its activation and autoproteolysis leading to p20/p10 caspase-1 dimers that associate in tetramers in solution (Boatright et al., 2003; Elliott, Rouge, Wiesmann, & Scheer, 2009; Walker et al., 1994). The enzymatically active dimers subsequently cleave pro-IL1β and pro-IL18 to their biologically active forms. Both cytokines play an important role in systemic inflammation due to their ability to act on various target organs and to induce the expression of a large panel of pro-inflammatory genes thereby amplifying the inflammatory response (Cerretti et al., 1994; Dinarello, 1997; Garlanda, Dinarello, & Mantovani, 2013; Keller, Rüegg, Werner, & Beer, 2008; Martinon, Burns, & Tschopp, 2002; Okamura, Tsutsui, Kashiwamura, Yoshimoto, & Nakanishi, 1998; Schmitz et al., 2005). In addition, inflammasome activation leads to a distinct form of lytic death called pyroptosis. Pyroptosis induction was recently shown to be linked to gasdermin-D (GSDMD), a protein with membrane pore-forming activity (Kayagaki et al., 2015; Liu et al., 2016). Caspase-1-dependent cleavage of GSDMD liberates the pro-pyroptotic N-terminal domain from an inhibitory interaction with the C-terminal domain of the protein. Once generated, the N-terminal part of GSDMD targets the cytoplasmic face of the plasma membrane, due to its affinity for phospholipids like phosphorylated phosphatidylinositols and cardiolipin (Liu et al., 2016). Accumulation and oligomerization of the N-terminal part of GSDMD leads to pore formation (Aglietti et al., 2016; Ding et al., 2016; Sborgi et al., 2016). The subsequent loss of membrane integrity allows small intracellular molecules such as pro-inflammatory cytokines and different alarmins to be released

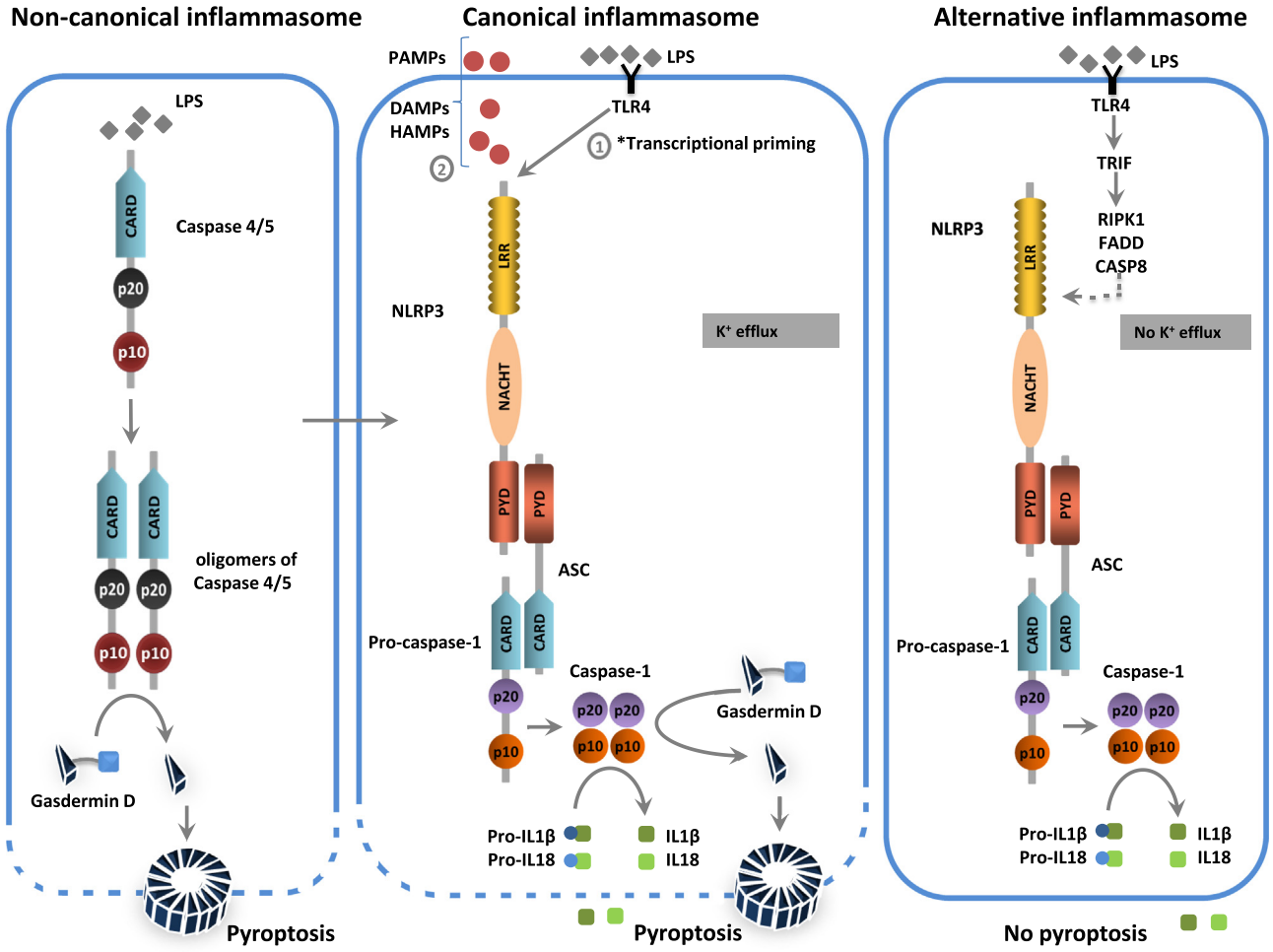

Fig. 3. Canonical, non-canonical and alternative inflammasomes. Left panel: non-canonical inflammasome. LPS enters the cytoplasm by unknown mechanisms. LPS is directly recognized by the CARD domain of caspase 4/5 in humans (the exact mechanism of interaction is still not understood) leading to caspase oligomerization and activation. Active caspase 4/5 cleaves gasdermin D, a membrane-pore-forming protein leading to cell swelling and membrane rupture accompanied by the release of alarmins in the extracellular space. Middle panel: canonical inflammasome. The canonical NLRP3 inflammasome is activated by a TLR signal (LPS is the most commonly used experimentally), which induces transcriptional activation of *NLRP3* and *IL1β*. *A post-transcriptional modification is also possible and involves deubiquitination of NLRP3. A second signal (DAMP, PAMP or HAMP) leads to NLRP3 oligomerization (not shown), with caspase-1 activation, followed by the maturation of pro-IL1β and pro-IL18 and the release of the mature forms of these pro-inflammatory cytokines. Caspase-1 activation also induces a lytic death called pyroptosis through the cleavage of gasdermin D, a membrane-pore-forming protein leading to cell swelling and membrane rupture accompanied by the release of alarmins and proinflammatory cytokines in the extracellular space. Common mechanisms which promote NLRP3 inflammasome activation include alteration in K^+ or Ca^{2+} concentrations, mitochondrial damage, lysosomal destabilization. DAMP: (Danger Associated Molecular Pattern); PAMP: (Pattern Associated Molecular Pattern); HAMP: (homeostasis-altering molecular processes). The arrow in grey indicates interactions between the non-canonical and the canonical inflammasome as the non-canonical inflammasome mediates NLRP3-dependent IL1β and IL18 secretion. Right panel: alternative inflammasome. The NLRP3 inflammasome is activated by LPS or other molecules that mimic LPS like OxPAPC (oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine) or N-acetylglycosamine leading to caspase-1 activation and release of IL1β and IL18 without K^+ efflux or pyroptosis.

(Aachoui, Sagulenko, Miao, & Stacey, 2013; Fink & Cookson, 2007; Lamkanfi et al., 2011). The liberation of the intracellular content on the one hand leads to pathogen clearance (Miao et al., 2010; Miao, Rajan, & Aderem, 2011), but excessive pyroptosis activation, on the other hand, can be detrimental for the host (Bergsbaken, Fink, & Cookson, 2009).

The observation that, in mouse macrophages, Gram-negative bacteria induce pyroptosis through caspase-11 without requiring the Nlrp3-Asc-caspase-1 pathway paved the route for the discovery of a non-canonical, caspase-11-dependent inflammasome (Hagar, Powell, Aachoui, Ernst, & Miao, 2013; Kayagaki et al., 2013) (Fig. 3, **left panel**). In humans, caspase-1-independent inflammasomes employ pro-inflammatory caspase-4 and -5, which are the closest homologues to murine caspase-11 (Lamkanfi, Declercq, Kalai, Saelens, & Vandenabeele, 2002). The discovery that caspase-4 and -5 are activated by direct binding to intracellular LPS without the requirement of an NLR or ASC suggested that pathogens may escape innate surveillance through receptors present in the plasma membrane and invade the host cell leading to infection (Shi et al., 2014). Intracellular LPS sensing in human monocytes and macrophages leads to caspase-4 mediated pyroptosis (Shi et al., 2014). Similar results have been found in endothelial and epithelial cells as well as in keratinocytes (Casson et al., 2015; Kayagaki et al., 2013; Knodler et al., 2014; Shi et al., 2014), suggesting the implication of non-myeloid cells in pathogen detection. Among the structural moieties of LPS, the conserved lipid A is the part considered responsible for non-canonical inflammasome activation through interaction with the CARD domain of caspase-4 and -5. Caspase-4 tissue expression is wider than that of caspase-5 (Lin, Choi, & Porter, 2000), potentially suggesting cell/tissue-specific roles for each caspase (Lin et al., 2000; Salskov-Iversen, Johansen, Kragballe, & Iversen, 2011). Whether or not both caspases are required for the intracellular detection of LPS is so far unknown. Caspase-4/-5 may also regulate the secretion of IL1α and other cytokines in certain cells types (Yang, Zhao, & Shao, 2015). Interestingly, active caspase-4 and -5 in humans or caspase-11 in mice also induce NLRP3-mediated IL1β secretion through a pyroptosis-mediated mechanism (Baker et al., 2015). In that situation, cell-intrinsic mechanisms like potassium efflux (Rühl & Broz, 2015; Schmid-Burgk et al., 2015) activate NLRP3, thereby unveiling interactions between the canonical and non-canonical inflammasomes (Lamkanfi & Dixit, 2014).

4. The NLRP3 inflammasome: activation and regulation

The inflammasome that nucleates around NLRP3 is the most studied. NLRP3 is primarily expressed in cells of the myelomonocytic lineage (Feldmann et al., 2002; Hoffman, Mueller, Broide, Wanderer, & Kolodner, 2001; Manji et al., 2002) and its mRNA and protein levels are up-regulated in monocytes and macrophages upon exposure to inflammatory stimuli (Awad et al., 2017; O'Connor, Harton, Zhu, Linhoff, & Ting, 2003). *NLRP3* expression has also been reported in B and T lymphocytes (Kummer et al., 2007), in epithelial cells lining the oral and genital tracts, in skin keratinocytes (weak expression) (Kummer et al., 2007), as well as in chondrocytes (Feldmann et al., 2002).

4.1. Classical activation of the NLRP3 inflammasome

For an active inflammasome, a two-step process is required (Fig. 3, **middle panel**). The first step/signal, which also is known as the priming signal, is usually a bacterial component like LPS that induces *NLRP3* and *IL1B* transcription. Basal expression of NLRP3 is not sufficient for inflammasome activation in resting cells. It has been shown that the amount of *NLRP3* mRNA is tightly regulated by the myeloid-specific microRNA-223 (miR-223), which is expressed in monocytes and leads to decreased NLRP3 protein levels, thus influencing the threshold of NLRP3 activation (Haneklaus et al., 2012). Post-translational modifications of NLRP3 such as ubiquitin modifications have also been reported to regulate NLRP3 (Juliana et al., 2012; Kattah, Malynn, & Ma, 2017; Py, Kim, Vakifahmetoglu-Norberg, & Yuan, 2013; Song et al., 2016). Juliana et al. showed that, in primary mouse macrophages, signalling through the Toll-like receptor results in Nlrp3 priming by stimulation of its deubiquitination, itself dependent on mitochondrial ROS (Juliana et al., 2012). ATP can also trigger NLRP3 deubiquitination but through a mitochondrial ROS-independent mechanism (Juliana et al., 2012). Subsequently, Py et al. identified Brcc3 as the mouse deubiquitinase that regulates Nlrp3 by specifically interacting with the ubiquitinated LRR domain of Nlrp3 (Py et al., 2013). In addition, as shown by Song et al., the E3 ubiquitin ligase Trim 31 attenuates Nlrp3 inflammasome activation by promoting proteasomal degradation of Nlrp3 in both resting and activated mouse macrophages (Song et al., 2016).

The second signal promotes the association of the inflammasome components to create a functional inflammasome with translation and secretion of the mature IL1β protein (Bryant & Fitzgerald, 2009). The second signal can be of variable nature (PAMPS, DAMPs or HAMPs). Various activators of the NLRP3 inflammasome have indeed been identified such as Gram-positive bacteria (like *Staphylococcus aureus* and Group B *Streptococcus),* Gram-negative bacteria (like *Citrobacter rodentium, Escherichia coli,* or *Vibrio cholerae*), viruses (like Influenza virus), the bacterial toxin nigericin, pore-forming toxins like hemolysin and pneumolysin, environmental nanoparticles like silica, asbestos or alum, and cellular damage molecules like ATP, β-amyloid aggregates, monosodium urate (MSU) and cholesterol crystals (Bauernfeind et al., 2009; Bryant & Fitzgerald, 2009; Costa et al., 2012; Duncan et al., 2009; Elliott & Sutterwala, 2015; Franchi, Muñoz-Planillo, & Núñez, 2012; Ichinohe, Pang, & Iwasaki, 2010; Kingsbury, Conaghan, & McDermott, 2011; Koizumi et al., 2012; Lupfer & Kanneganti, 2013; Mariathasan et al., 2006; Sutterwala, Ogura, & Flavell, 2007; Vanaja et al., 2015).

How exactly all these diverse danger signals trigger the same inflammasome sensor remains unclear. Their highly variable structures suggest that NLRP3 senses them indirectly. Cellular stress or altered homeostasis signals are considered as intermediate steps resulting in NLRP3 inflammasome activation (Latz, 2010; Liston & Masters, 2017). The most prevailing inflammasome activating mechanism involves changes in cytosolic K^+ concentration (Pétrilli et al., 2007; Yaron et al., 2015). In this line, DAMPs like ATP, which engage the purinergic receptor P2X7, or bacterial pore-forming toxins, induce cytosolic K^+ efflux (Di Virgilio, 2007, 2013; Muñoz-Planillo et al., 2013). The decreased intracellular K^+ levels trigger NLRP3 inflammasome activation. A second mechanism concerns crystalline or particulate structure DAMPs, (such as β-amyloid aggregates, MSU and cholesterol crystals) which, after being phagocytosed by immune cells induce lysosomal swelling and damage (Dostert et al., 2008; Halle et al., 2008; Hornung et al., 2008; Hornung & Latz, 2010b). The subsequent release of lysosomal proteases like cathepsin B activates NLRP3 inflammasome. A third mechanism suggests an important role for mitochondria in NLRP3 inflammasome activation (Nakahira et al., 2011; Shimada et al., 2012; Subramanian, Natarajan, Clatworthy, Wang, & Germain, 2013; Tschopp & Schroder, 2010; Zhou, Yazdi, Menu, & Tschopp, 2011). Mitochondrial ROS activate thioredoxin-interacting protein (TXNIP) that, in turn, binds to and activates the NLRP3 inflammasome (Zhou, Tardivel, Thorens, Choi, & Tschopp, 2010). Apart from ROS generation, mitochondrial movement along microtubules (Misawa et al., 2013), altered mitochondrial elongation and fission (Park et al., 2015) and defective mitophagy (Zhong et al., 2016) can also regulate NLRP3 inflammasome activation. A fourth mechanism links NLRP3 inflammasome activation to alterations in intracellular calcium concentration. The transcription factor C/EPB homologous protein (CHOP, also known as DDIT3), which modulates calcium mobilization from the endoplasmic reticulum (ER), amplifies inflammasome activation in LPS-primed mouse macrophages, linking ER stress to activation of the NLRP3 inflammasome (Murakami et al., 2012). Activation of the calcium-sensing receptor (CASR) activates the NLRP3 inflammasome through increased intracellular calcium or

decreased cellular cAMP concentrations; this activation involves phospholipase C which through production of inositol-1,4,5-trisphosphate (IP3) induces liberation of calcium from ER resulting in NLRP3 activation (Lee et al., 2012). Intracellular calcium is important for spontaneous IL1β secretion in cells from patients with mutations in *NLRP3* (Lee et al., 2012). In addition, extracellular calcium can also act as a DAMP to induce NLRP3 activation (Rossol et al., 2012).

4.2. Alternative NLRP3 inflammasome pathway

Recently, work on human monocytes has identified an alternative pathway of NLRP3 inflammasome activation leading to IL1β secretion from living cells (Gaidt & Hornung, 2017). Although the alternative inflammasome activates NLRP3-ASC-Caspase-1, it does not display classical inflammasome characteristics like pyroptosis, and is not dependent on K+ efflux (Fig. 2, **right panel**). Rather, in the alternative pathway, the axis of Toll-like receptor (TLR) -4, (TLR4-TRIF-RIPK1-FADD-CASP8) which signals upstream of NLRP3, is important for IL1β responses in human monocytes (Gaidt et al., 2016). Additional studies have supported an alternative NLRP3 inflammasome (Wolf et al., 2016; Zanoni et al., 2016). Oxidized 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (oxPAPC), a common oxidized lipid in inflammation and a damage molecule that mimics LPS, can induce Il1β secretion in murine dendritic cells through a caspase-11-dependent Nlrp3 inflammasome without inducing pyroptosis. N-acetylglucosamine (NAG), a sugar subunit of peptidoglycan present in Gram-positive bacteria, induces IL1β secretion independently of potassium efflux and pyroptosis, a pattern supporting the alternative NLRP3 inflammasome (Wolf et al., 2016). The presence of NAG in the cytoplasm is detected by the glycolytic enzyme hexokinase. Following NAG detection, hexokinase is inhibited and detaches from the outer mitochondrial membrane. The dissociation of hexokinase from the mitochondria is sufficient to stimulate NLRP3 inflammasome activation and IL1β secretion (Wolf et al., 2016). Hexokinase thus, acts as a pattern recognition receptor, alerting the cell to the presence of microbial products in phagosomes thereby suggesting interplay between metabolism and pathogen detection.

5. What about the NLRP12 inflammasome?

NLRP12 (also called MONARCH-1, PYPAF-7 or NALP12) is one of the first described NLR proteins. However, its physiological role remains controversial, since, by using different models and technical approaches, both pro- and anti-inflammatory properties of NLRP12 have been reported. Indeed, in 2002, Wang et al. performed transient expression studies in different cell lines and showed that NLRP12 activates NF-κB and caspase-1 (Wang et al., 2002). More specifically, co-expression of ASC with increasing amounts of NLRP12 in HEK293T cells resulted in a concentration-dependent increase in NF-κB activity. The expression of NLRP12 together with pro-caspase-1, pro-Il1β, and ASC in COS7L cells showed that NLRP12 and ASC synergistically activate pro-caspase-1. These *in vitro* studies also revealed that NLRP12 co-localizes with ASC punctate structures in the cytoplasm; however, no interaction between NLRP12 and ASC could be shown by co-immunoprecipitation experiments (Wang et al., 2002). Several subsequent studies have argued for an anti-inflammatory role of NLRP12. A study performed in human PBMCs and in THP1 cells infected with *Mycobacterium tuberculosis*, showed that NLRP12 inhibits IRAK-1 phosphorylation, repressing TLR signalling, thus resulting in negative regulation of canonical NF-κB signalling (Arthur, Lich, Aziz, Kotb, & Ting, 2007; Lich et al., 2007; Williams et al., 2005). Two years later, the same team showed that NLRP12 also induces proteasome-mediated degradation of NF-κB Inducing Kinase (NIK) (Lich et al., 2007), thereby inhibiting "noncanonical" NF-κB signalling. Similarly, another *in vitro* study showed that NLRP12 strongly inhibits NF-κB activation induced by p65 (Jéru et al., 2008), whereas the study of *Nlrp12*−/− mice demonstrated that Nlrp12, on the one hand, suppresses colon inflammation and tumorigenesis through negative regulation of non-canonical NF-κB signalling (Allen et al., 2012; Zaki et al., 2011); Nlrp12 on the other hand exerted no effect on Il1β and Il18 production (Ulland et al., 2016). Whether or not NLRP12 acts as a part of an inflammasome component and its precise role requires further validation.

6. The Pyrin inflammasome

Inflammasomes can also assemble around proteins that contain PYD domains but do not belong to the NLRP family. The pyrin protein contains an N-terminal PYD domain, a basic leucine zipper domain (b-ZIP), a B-box domain that through multiple finger-like protrusions, makes tandem contacts with possible target molecules, and a coiled-coiled domain, which consists of α-helices wrapped around each other to form a supercoil and a C-terminal B30.2 domain (Gumucio et al., 2002) (Fig. 4A). Pyrin is part of a larger family of antiviral proteins termed TRIM (TRIpartite Motif) which are involved in innate immunity (reviewed in (Nisole, Stoye, & Saïb, 2005)). Pyrin is strongly expressed in neutrophils, and to varying degrees in monocytes, eosinophils and dendritic cells, but not in lymphocytes (Centola et al., 2000; Tidow et al., 2000). Pyrin is also expressed, but to a lesser degree, in fibroblasts from synovium, peritoneum and skin (Diaz et al., 2004; The International FMF Consortium, 1997). *In vitro* differentiation of human monocytes to macrophages down-regulates the expression of the gene coding for pyrin, *MEFV* (standing for MEditerranean FeVer because of its involvement in the autoinflammatory disease called familial Mediterranean fever or FMF — see below) (Seshadri, Duncan, Hart, Gavrilin, & Wewers, 2007). Various mediators like LPS, pro- and anti-inflammatory cytokines and colchicine (the drug of choice for FMF patients) have been shown to modulate *MEFV* expression. Their effect depends on the cell type and the experimental conditions used (Centola et al., 2000).

The involvement of *MEFV* in the pathogenesis of FMF was the first evidence suggesting that pyrin may play an important role in inflammation. Further indirect evidence supported this hypothesis: first of all, pyrin expression is restricted to cells of innate immunity (neutrophils and monocytes), which are the main cellular mediators of inflammation. Secondly, the PYD domain of pyrin is commonly found in other proteins implicated in inflammation and apoptosis (i.e. several NLRPs and ASC). In addition, using a yeast two-hybrid screen, pyrin was found to associate through PYD: PYD homotypic interactions with ASC (Masumoto et al., 1999; Richards et al., 2001). While contradictory hypotheses have been formulated concerning pyrin's role and its capacity to form an inflammasome, recent advances have shown the molecular interactions leading to a pyrin inflammasome (Xu et al., 2014). More than ten years ago, a two-hybrid screen identified the highly conserved 14-3-3τ and 14-3-3ε proteins as partners of pyrin. This was not the case -for a pyrin isoform lacking the domain encoded by exon 2 and generated by alternative splicing (Jéru et al., 2005; Papin et al., 2000). More precisely, it was shown that pyrin could be phosphorylated and that its interaction with 14-3-3 proteins depends on the phosphorylation status of 3 serine residues (i.e. Ser208, Ser209 and Ser242) clustered in a pyrin region encoded by exon 2 and located downstream of the PYD domain, with Ser242 being the major determinant for this interaction (Jéru et al., 2005). This data represents the missing link required to explain the observation made in 2014 by Xu et al. (2014) that bacterial toxins such as Clostridium difficile toxins A and B activate pyrin: these toxins inactivate the swhitch-1 region of the RhoA GTPase (Xu et al., 2014) whereas, as shown recently, RhoA activates the serine-threonine kinases PKN1 and PKN2 that bind and phosphorylate pyrin at residues 208 and 242 (Park, Wood, Kastner, & Chae, 2016).

The current model suggests that these toxins activate pyrin through dephosphorylation, thereby preventing the binding of 14-3-3 proteins to pyrin. As a consequence, such "free" pyrin is able to participate in a

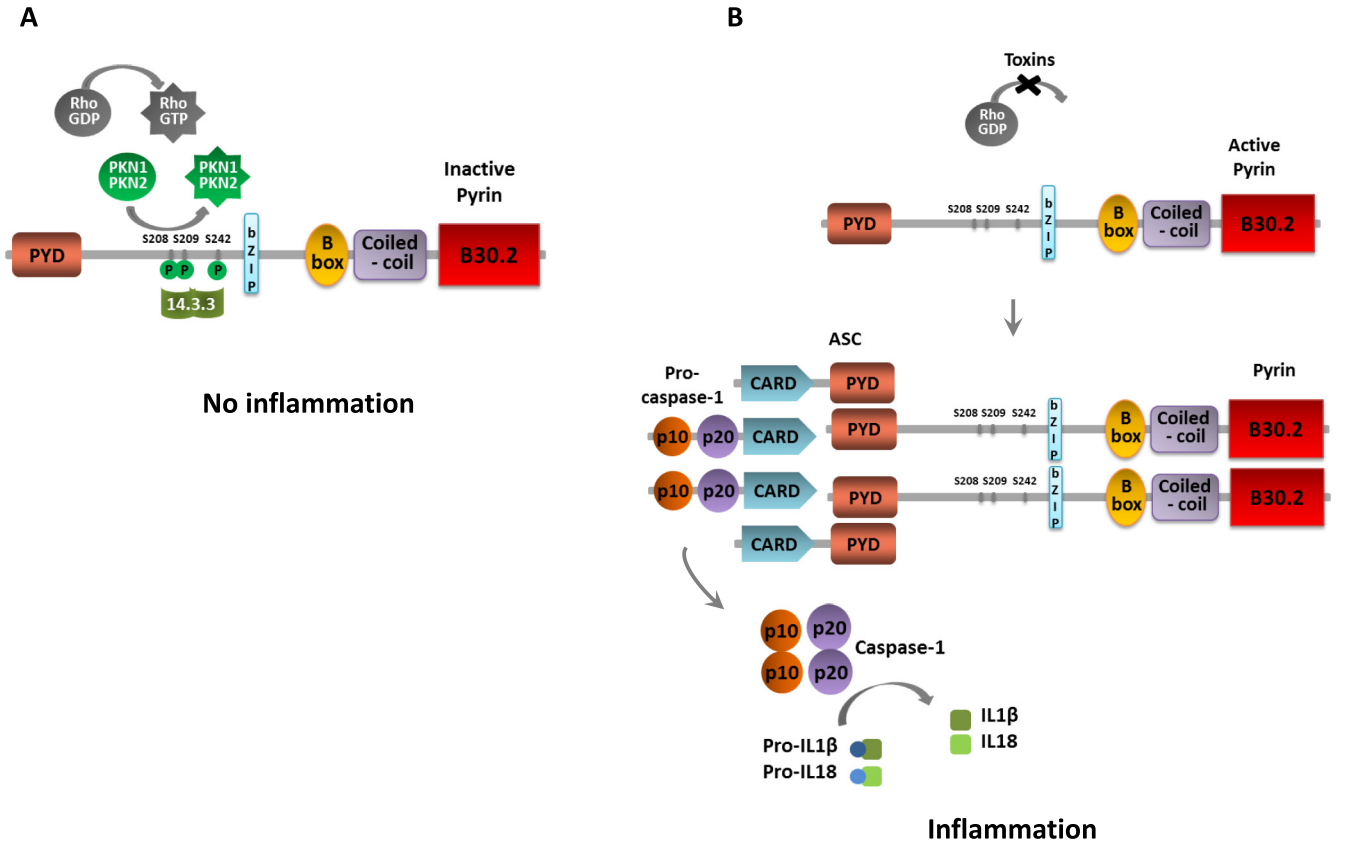

Fig. 4. A Model for pyrin activation. A. The serine residues Ser208, Ser209 and Ser242 in human pyrin are phosphorylated by the PKN1 and PKN2 kinases, which are RhoA effectors. 14-3-3 proteins interact with the phosphorylated serines and maintain pyrin in a resting/inactive state. B. Bacterial toxin-mediated modifications inactivate RhoA, preventing PKN1 and PKN2 activation. Consequently, the serine residues are not phosphorylated and 14-3-3 proteins fail to interact with pyrin leading to its activation. Activated pyrin interacts with ASC and pro-caspase-1, forming a pyrin inflammasome that activates caspase-1, leading to proteolytic cleavage of pro-IL1β and pro-IL18. The mature forms (IL1β and IL18) are then secreted and induce inflammation. PKN1 (protein kinase N1), PKN2 (protein kinase N2), RhoA (Ras homolog gene family, member A).

caspase-1-dependent inflammasome leading to IL1β release (Fig. 4B), whereas the binding of 14-3-3 proteins to phosphorylated pyrin locks pyrin into an inactive state. This model is strongly supported by the recent report on families with a dominantly inherited autoinflammarory disease due to a missense mutation involving Ser242 of pyrin (p.S242R). This severe condition, called PAAND (Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis, see below), in fact results from a constitutive loss of interaction of the mutant pyrin with 14-3-3 proteins (Masters et al., 2016). Other Rho-inactivating toxins, all of which modify a switch-I residue of members of the Rho subfamily and activate pyrin inflammasome, include the *Vibrio parahaemolyticus* VopS, *Histophilus somni* IbpA and *Clostridium botulinum* C3 toxins. Pyrin, therefore, senses bacterial virulence through the effect of Rho inactivation rather than through a bacterial-specific signal (Xu et al., 2014). Microtubule dynamics are also important in pyrin activation and microtubule-targeting drugs like colchicine inhibit pyrin inflammasome formation without affecting the pyrin phosphorylation status (Gao, Yang, Liu, Wang, & Shao, 2016). Interestingly, colocalisation of pyrin with actin has also been described, and recently, aberrant actin depolymerization was shown to trigger the activation of the pyrin inflammasome (Kim et al., 2015). These data strongly suggest that perturbations of the cytoskeleton structure may also impact the pyrin inflammasome.

7. Molecular pathology of the NLRP3 inflammasome

In the early 2000s, before the discovery of the role of NLRP3 in an inflammasome, germline mutations in *NLRP3* (also known as *PYPAF1* or *CIAS1*), coding for a protein called cryopyrin, have been implicated in two autosomal dominant disorders: Familial Cold Autoinflammatory Syndrome (FCAS; OMIM #120100) and Muckle-Wells Syndrome (MWS; OMIM #191900) (Hoffman et al., 2001). Secondarily, *NLRP3* mutations were also identified in Neonatal-Onset Multisystem Inflammatory Disease (NOMID), also known as Chronic Infantile Neurological Cutaneous and Articular syndrome (CINCA; OMIM #607115) (Aksentijevich et al., 2002; Feldmann et al., 2002). Previously described as distinct entities, all these disorders caused by *NLRP3* gain-of-function mutations are now named Cryopyrin-Associated Periodic Syndromes (CAPSs, also known as cryopyrinopathies) and are part of the spectrum of the same systemic autoinflammatory condition. Cardinal clinical signs are fever, urticaria-like rash, arthralgia, sensorineural deafness and possibly amyloid A amyloidosis. Usually, familial cases are observed in patients with FCAS and MWS, and sporadic cases (due to *de novo* *NLRP3* mutations) in NOMID patients. Most of the mutations identified in CAPS patients are missense variants located in the NACHT domain of NLRP3. However, mutations involving the same amino acid residue can be associated with either a severe form of the disease or a mild phenotype. Moreover, it has been shown that NOMID and MWS can be due to post-zygotic mosaic *NLRP3* mutations that were identified in circulating leukocytes (Nakagawa et al., 2015; Omoyinmi et al., 2014; Saito et al., 2005; Tanaka et al., 2011). Recently, somatic *NLRP3* mutations have been reported in few patients with late onset CAPS, probably reflecting the late occurrence of a mutational event in target cells of this disease (Mensa-Vilaro et al., 2016; Zhou et al., 2015).

Peripheral blood mononuclear cells (PBMCs) from CAPS patients are characterized by a constitutively active inflammasome, as revealed by

the high levels of IL1β present in their supernatants (Janssen, Verhard, Lankester, Ten Cate, & van Dissel, 2004). Noteworthy, monocytes harbouring the *NLRP3* mutations associated with CAPS secrete IL1β without prior stimulation. Adherent monocytes from healthy donors require 24h treatment with LPS for IL1β secretion, whereas the kinetics of IL1β secretion from CAPS-monocytes are faster even after a short 2h treatment (Agostini et al., 2004). The proposed underlying mechanism leading to inflammasome activation suggests that several mutations in the NACHT domain of the protein prevent the NLRP3 repression that is normally achieved by signals like intracytoplasmic cAMP (Lee et al., 2012). Indeed, high levels of cAMP have been shown to inhibit NLRP3 by at least two mechanisms: (i) through NLRP3 ubiquitination and subsequent degradation of the protein (Yan et al., 2015), and (ii) through activation of protein kinase A that, in turn, phosphorylates Ser295 located in the NACHT domain, thereby inhibiting the NLRP3 ATPase activity required for assembly of NLRP3-ASC complexes (Mortimer, Moreau, MacDonald, & Chadee, 2016). Although the potential impact of *NLRP3* mutations on the ubiquitination state of cryopyrin remains to be assessed, several CAPS mutations have indeed been shown to prevent phosphorylation of Ser295 (Mortimer et al., 2016). Recently NEK7, a member of the NIMA (Never In Mitosis gene A)-related kinases, has been shown to be an important factor mediating NLRP3 oligomerization and ASC speck formation downstream of potassium efflux (He, Zeng, Yang, Motro, & Núñez, 2016; Schmid-Burgk et al., 2016; Shi et al., 2016). In this regard, macrophages from mice harbouring the CAPS-associated p.R258W mutation (p.R260W in humans) with a Muckle-Wells phenotype do not require potassium efflux for inflammasome activation (Meng, Zhang, Fuss, Kitani, & Strober, 2009), but require NEK7 for caspase-1 activation, thereby suggesting that, in the presence of this mutation, NLRP3 associates with NEK7 in the absence of potassium efflux (He et al., 2016).

8. Molecular pathology of NLRP12

NLRP12 transcripts have been found in human peripheral blood leukocytes, mainly in eosinophils and in granulocytes, and to a much lesser extent in monocytes, whereas no transcript was detected in T or B cells (Wang et al., 2002). Extremely rare *NLRP12* mutations have been identified in a group of autoinflammatory diseases known as NLRP12-associated periodic fevers syndromes (NLRP12-APS), a disease condition transmitted in an autosomal dominant manner and characterized by the association of cold-induced urticarial rash, fever, arthralgia and myalgia (Borghini et al., 2011; Jéru et al., 2008; Jéru, Le Borgne, et al., 2011; Xia et al., 2016). Some rare mutations are loss-of-function mutations (nonsense and frameshift mutations) present in the heterozygous state in patients (Jéru et al., 2008; Xia et al., 2016). In a similar manner to observations in CAPS patients, increased or accelerated IL1β secretion from monocytes of NLRP12-APS patients has also been reported (Borghini et al., 2011; Jéru, Hentgen, et al., 2011). These results are not in agreement with those obtained in mice carrying a homozygous inactivation of *Nlrp12*, in which, Il1β production was not found to be altered (Ulland et al., 2016). Taken together these data underline the necessity of additional molecular studies in order to further assess the implication of NLRP12 in human pathology.

9. Molecular pathology of the Pyrin inflammasome

MEFV (also known as *TRIM20*), the gene coding for pyrin, was identified as the gene involved in FMF (French FMF Consortium, 1997; The International FMF Consortium, 1997), the most prevalent autoinflammatory disease condition, transmitted as autosomal recessive trait among patients of Mediterranean extraction. The most common mutations (i.e., p.M680I, p.M694V, p.M694I and p.V726A) are clustered within exon 10 that encodes the C-terminal B30.2/SPRY domain of the protein, with the M694V/M694V homozygous genotype being associated with a high prevalence of renal amyloidosis (Cazeneuve et al., 1999, 2000; Dewalle et al., 1998).

One major question for many years was to understand whether FMF is a recessive disorder due to loss-of-function mutations in pyrin, a protein with, therefore, anti-inflammatory properties, or a dominant disorder with gain-of-function mutations (with gene-dosage effect) in the pyrin protein that would then have pro-inflammatory properties. Although the first FMF mutations were identified more than 20 years ago, it is only just recently that some answers have emerged. First of all, it is important to remember that the *MEFV* gene was successfully identified through linkage analysis and a positional cloning approach by two international consortia in 1997 (French FMF Consortium, 1997; The International FMF Consortium, 1997), based on a transmission model assuming that FMF is an autosomal recessive condition. Several lines of evidence - including of course those deduced from the disease phenotype of FMF patients, but also the tissue-specific expression of *MEFV*, as well as results from *in vitro* studies (Centola et al., 2000) - strongly suggested that pyrin is implicated in the regulation of inflammatory processes. However, the mechanisms by which this protein may regulate such processes were poorly understood until recently. Depending on experimental conditions, data have been accumulated in favor of either an anti-inflammatory or a pro-inflammatory role for pyrin. For instance, anti-inflammatory properties were first deduced from the phenotype of mice carrying a targeted disruption of pyrin (Chae et al., 2003). As murine pyrin lacks the C-terminal B30.2 domain found in humans which contains the main FMF mutations, additional studies have been performed using the human pyrin (Chae et al., 2006, 2008, 2011; Yu et al., 2007). In addition, the fact that FMF was first classically considered as a recessive disorder has raised other important questions with regard to the underlying pathophysiological mechanisms. First, it is striking to note that, except in extremely rare instances, the FMF-associated sequence variants are missense mutations, most of them being conservative (i.e. replacing an amino acid by another one with similar biochemical properties in terms of charge, hydrophobicity and size). In other words, there is virtually no obvious loss-of-function mutation in FMF, like for instance splicing defects, deletions, frameshift or nonsense mutations, which are expected to occur in recessive conditions. Second, a significant number of patients with a clinical diagnosis of FMF carry only a single mutated *MEFV* allele. Third, although several studies showed that peripheral blood leukocytes from FMF patients have reduced *MEFV* mRNA levels as compared to controls (Notarnicola et al., 2002; Ustek et al., 2007), a higher expression of the pyrin protein in neutrophils of FMF patients carrying one or two mutated *MEFV* alleles was found in another study, as compared to controls and to non-FMF patients with active inflammation (Booty et al., 2009). This latter study also showed a trend toward higher expression levels of *MEFV* transcripts in FMF patients (as compared to controls). Taken together, these data raise the question as to whether the pyrin mutations found in FMF patients would be gain-of-function mutations with a gene-dosage effect consistent with a semi-dominant mode of transmission of the disease. In fact, additional studies strongly support such hypothesis of gain-of-function mutations in pyrin. This is the case for the data obtained from the generation of knock-in mice harboring mutant human B30.2 domains (Chae et al., 2011). The report of an FMF patient, homozygous for the p.M694V mutation, and who developed a chronic myelomonocytic leukemia leading to an uncontrolled inflammatory syndrome, also strongly argues for a pro-inflammatory role of the wild-type protein, with the p.M694V mutation acting as a gain-of-function mutation (Awad et al., 2015).

With the recent discovery of the pyrin inflammasome, questions regarding the causality of the identified *MEFV* sequence variations have become even more important as toxins can activate the pyrin inflammasome in both humans and mice, thereby suggesting that the B30.2 domain (absent in mice) is not required for activation (Gao et al., 2016; Van Gorp et al., 2016). The pyrin inflammasome requires microtubules for its function, although their exact role remains to be

identified (Van Gorp et al., 2016). Colchicine, a microtubule inhibitor which is also the drug of choice for FMF, has been shown to abolish pyrin-mediated IL1β secretion from *C. difficile*-infected mouse macrophages or PBMCs from healthy donors, from CAPS patients or from other patients with an autoinflammatory disease (Van Gorp et al., 2016). Surprisingly however, PBMCs from FMF patients in the presence of colchicine continued to secrete significant levels of IL1β and IL18 in response to *C. difficile* toxin A, thereby suggesting that the FMF mutations remove the dependency of pyrin for microtubules. As several pathogens use microtubule dynamics to their advantage, the authors speculate that FMF mutations may confer protection to endemic pathogens (Van Gorp et al., 2016). Along similar lines, Jamilloux et al showed that monocytes from FMF patients have an increased ability to respond to low doses of a pyrin-activating stimulus as compared to monocytes from healthy donors (Jamilloux et al., 2017).

More recently, another phenotype distinct from FMF and transmitted in an autosomal dominant manner was found to be associated with novel *MEFV* mutations located within exon 2 and present in the heterozygous state in the patients (Masters et al., 2016). This disease, named PAAND for Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis, was first described in a large family with the p.S242R mutation (see above, paragraph 6). This mutation concerns one of the amino acids that are phosphorylated and critical for 14-3-3 binding (Jéru et al., 2005; Masters et al., 2016). A second family with PAAND was subsequently reported. The patients were shown to carry the c.730G>A (p.E244K) mutation also located in *MEFV* exon 2. Similarly to the p.S242R mutation, the p.E244K mutation displays a reduced phosphorylation of the 14-3-3 binding site and a reduced 14-3-3 binding (Moghaddas et al., 2017). These two observations further support the pro-inflammatory role of pyrin.

10. NLRP3, NLRP12 and pyrin in common diseases with an inflammatory component

10.1. NLRP3 in common diseases and inflammatory disease susceptibility

10.1.1. NLRP3 in common diseases

A number of metabolic DAMPs have been shown to activate the NLRP3 inflammasome in common multifactorial chronic inflammatory diseases (Abderrazak, Syrovets, et al., 2015; Freeman & Ting, 2016; Grant & Dixit, 2013; Haneklaus & O'Neill, 2015; Hoseini et al., 2017; Ralston, Lyons, Kennedy, Kirwan, & Roche, 2017; Rheinheimer, de Souza, Cardoso, Bauer, & Crispim, 2017; Sepehri et al., 2017; So & Martinon, 2017). Among them, we will focus on Alzheimer, Type 2 diabetes (T2D), obesity, gout and atherosclerosis.

Alzheimer's disease is a neurodegenerative disease associated with the presence of insoluble amyloid β (Aβ) aggregates that lead to neuronal death. It has been shown that Aβ particles activate the NLRP3 inflammasome in resident microglia cells, leading to caspase-1 activation and IL1β secretion through lysosomal damage (Gold & El Khoury, 2015). The release of pro-inflammatory cytokines from microglia cells surrounding Aβ-containing senile plaques activate additional microglia cells as well as astrocytes, leading to neurotoxic factors and pro-inflammatory cytokine production, which in turn contribute to neuronal dysfunction and cell death (Edison et al., 2008; Halle et al., 2008; Heppner, Ransohoff, & Becher, 2015; Liu & Chan, 2014; Rossi & Bianchini, 1996; Rubio-Perez & Morillas-Ruiz, 2012).

T2D, is characterized by progressive dysfunction of pancreatic islet beta-cells leading to insulin resistance and high plasma glucose concentrations. Islet amyloid polypeptide (IAPP), a hormone secreted in parallel with insulin, causes amyloid deposits in the islets and thus further induces beta cell damage. As shown by Masters et al., IAPP activates the Nlrp3 inflammasome in mouse macrophages and dendritic cells, resulting in Il1β secretion, providing a mechanistic link for Il1β activation in T2D (Masters et al., 2010). Accordingly, transgenic mice overexpressing the human IAPP show increased Il1β expression in the pancreas, which colocalises with amyloid deposits . High concentrations of glucose alone are not able to prime the NLRP3 inflammasome, although in monocyte-like THP1 cells, high glucose concentrations have been shown to induce the mRNA expression of pro-inflammatory cytokines (Shanmugam, Reddy, Guha, & Natarajan, 2003). A D-glucose analogue, 2-deoxy-D-glucose, which blocks glycolysis, is known to prevent the induction of Il1β expression in LPS-primed mouse macrophages, suggesting that metabolism of glucose is required for inflammasome activation (Masters et al., 2010). Consistent with these data, in diabetic rats, silencing of Nlrp3 has been shown to improve diabetic cardiomyopathy and inflammatory status (Luo et al., 2014).

Obesity is a multifactorial condition characterized by fat accumulation and hypertrophy of adipose tissue due to impaired metabolism, genetic and environmental factors. In most cases, fat accumulation is also present in the liver, skeletal muscle, and pancreas leading to chronic low-grade inflammation. Increased glucose and free fatty acid levels in the plasma of obese people links obesity to insulin resistance and metabolic syndrome (Hotamisligil, 2006; Odegaard & Chawla, 2008). High glucose levels increase *IL1B* expression and secretion in human and murine adipose tissue through activation of TXNIP, a protein linking oxidative stress with the activation of inflammasome (Koenen et al., 2011; Zhou et al., 2010). Palmitate and stearate, both saturated fatty acids, activate the NLRP3 inflammasome in primed murine and human macrophages (L'homme et al., 2013; Wen et al., 2011). Conversely, the unsaturated oleate and linoleate block NLRP3-mediated IL1β secretion and prevent NLRP3 activation induced by saturated fatty acids in human monocytes/macrophages (L'homme et al., 2013; Wen et al., 2011). Interestingly, it has been shown that palmitate, but not the unsaturated palmitoleate, activates caspase 4/5 -mediated pyroptosis in monocytes from obese-diabetic patients, thereby contributing to the release of IL1β and IL18 (Pillon et al., 2016). Ceramides, also present at high concentrations in obese adipose tissue, can also activate NLRP3. In obese individuals with T2D, calorie restriction and exercise-mediated weight loss reduce *NLRP3* and *IL1B* expression in adipose tissue, lower glycemia and decrease inflammation, further supporting links between lipotoxicity and the NLRP3 inflammasome (Rheinheimer et al., 2017; Vandanmagsar et al., 2011).

Gout, another common inflammatory disease, is characterized by increased levels of uric acid and deposition of monosodium urate crystals in the joints. Deposition of crystals is accompanied by a strong pro-inflammatory response characterized mainly by IL1β secretion. Internalization of MSU crystals by resident macrophages activates NLRP3 inflammasome, with neutrophil recruitment in the joint area (Martinon, Petrilli, Mayor, Tardivel, & Tschopp, 2006).

Atherosclerosis, the underlying cause of several cardiovascular diseases, is another common chronic condition characterized by chronic low-grade inflammation, in which the NLRP3 inflammasome has been implicated (Duewell et al., 2010). Interactions between lipids and arterial wall cells lead to plaque formation. Lipid-loaded macrophages — known as foam cells— resulting from uptake of modified low-density lipoproteins is a hallmark of atherosclerosis. Oxidized lipids present in the local environment, hypoxia, necrosis and inflammatory cytokine secretion lead to lesion development and vessel stenosis. Plaque rupture can be responsible for tissue ischemia and major events including myocardial infarction or stroke. An experimental *ApoE*−/− mouse model, which develops hypercholesterolemia and spontaneous atherosclerosis, crossed with *Nlrp3*−/−, *Asc*−/− or *caspase-1*−/− mice did not support the implication of Nlrp3 in the pathophysiology of atherosclerosis (Menu et al., 2011). However, it has been shown that cholesterol crystals, which are present in early atherosclerotic lesions, activate the Nlrp3 inflammasome by inducing lysosomal damage in LPS-primed mouse macrophages. Similarly, cholesterol crystals injected intraperitoneally induced an acute inflammation that was impaired in mice deficient in inflammasome components (Duewell et al., 2010). These results were supported by the attenuated early atherosclerosis in mice deficient in the low-density lipoprotein receptor (*Ldlr*−/−)

transplanted with *Nlrp3* −/−, *Asc* −/−, or *IL1α/β*-deficient bone marrow cells (Duewell et al., 2010). Activation of complement has been suggested as a possible link between cholesterol crystals and NLRP3 activation (Samstad et al., 2014). Furthermore, the local acidic environment in atherosclerotic areas is now recognized as a novel endogenous DAMP for NLRP3 inflammasome activation in immune cells (Rajamäki et al., 2013). Necrosis, also present in atherosclerotic lesions, activates the NLRP3 inflammasome through the release of DAMPs from necrotic cells (Li, Ambade, & Re, 2009).

10.1.2. NLRP3 in inflammatory disease susceptibility

An intronic 42 base-pair variable number tandem repeat polymorphism (rs74163773) of *NLRP3* has been shown to be associated with susceptibility to essential hypertension in a Japanese study (Omi et al., 2006). In healthy adults carrying this genotype, the transcript levels of *NLRP3* were higher, suggesting that this tandem repeat is a functional polymorphism for hypertension. However, in the same study, a replicate panel from a random population (268 men and 162 women) showed significant association of this polymorphism with mean systolic blood pressure, which was slightly elevated in men, but not in women (Omi et al., 2006). A GWAS meta-analysis performed in order to identify genetic variants associated with plasma levels of C-reactive protein (CRP, a marker of chronic inflammation) in 82725 subjects of European ancestry, including incident cases with cardiovascular events, identified 18 significant loci. An *NLRP3* polymorphism (rs12239046) was part of them, but neither the *NLRP3* locus nor 11 other loci were confirmed in a replication panel of the study (Dehghan et al., 2011).

Several *NLRP3* polymorphisms were analysed in targeted association studies of common diseases. These studies performed in subjects from the Chinese Han-population suggested an association of *NLRP3* SNPs with occurrence of coronary artery disease (for the rs10754558) (Zhou et al., 2016), with a risk of late onset of Alzheimer's disease (for the rs2027432) (Tan et al., 2013), and with ischemic stroke susceptibility (for the rs10754558) (Zhu et al., 2016). However, a recent study of atherosclerotic plaque from the carotid artery performed in Swedish patients with ischemic cerebrovascular disease compared to healthy controls failed to find significant associations between the *NLRP3* SNPs (rs6672995 and rs10733113) and NLRP3 expression in atherosclerotic plaque (Paramel Varghese et al., 2016). In summary, although the involvement of *NLRP3* mutations in autoinflammatory diseases is established, association between frequent *NLRP3* polymorphisms and susceptibility to common diseases failed to be clearly demonstrated.

10.2. NLRP12 in common diseases and inflammatory disease susceptibility

In mice, Nlrp12 maintains intestinal homeostasis, attenuates colon inflammation and tumorigenesis, through negative regulation of NF-κB and MAPK pathways (Allen et al., 2012). Mice lacking *Nlrp12* are highly susceptible to colitis and colitis-associated colorectal cancer (Allen et al., 2012; Zaki et al., 2011), and hyper-resistant to *Salmonella typhimurium* infection (Zaki, Man, Vogel, Lamkanfi, & Kanneganti, 2014) suggesting that Nlrp12 is a negative regulator of innate immunity. Nlrp12-deficient mice present a dysbiotic microbiome and increased colonic basal inflammation, which were reversed by antibodies targeting Tnf and the Il6 receptor or by administration of Lachnospiraceae strains (Chen et al., 2017). Nlrp12 has also been shown to play a role in host defences against bacterial pathogens. Nlrp12 is indeed able to detect *Yersinia pestis* (causal for plague). *Yersinia pestis* infection induces Nlrp12 inflammasome activation, leading to Il18 production and clearance of the infection. Following infection, Nlrp12-deficient mice showed higher mortality rates and lower secretion of Il18, Il1β and Ifn-γ (Vladimer et al., 2012). In humans, NLRP12 expression was shown to be significantly down-regulated in patients with active ulcerative colitis, as compared to patients with inactive ulcerative colitis or healthy controls (Chen et al., 2017). In malaria infected-patients, both NLRP12 and NLRP3 inflammasomes were detected, suggesting that NLRP12 may play a role in the regulation of IL1β production and in the hypersensitivity to secondary bacterial infection during malaria (Ataide et al., 2014). Of note, increased *NLRP12* mRNA and protein expression was found to be associated with prostate cancer (Karan, Tawfik, & Dubey, 2017).

10.3. Pyrin in common diseases and inflammatory disease susceptibility

The fact that FMF-associated mutations are more frequent in Mediterranean populations has led to the hypothesis that mutations may confer a selective advantage, possibly a defence mechanism against endemic bacterial or viral infections (Aksentijevich et al., 1999; Jamilloux et al., 2017). Interestingly, recent studies have shown that *Yersinia pestis* prevents innate immune responses by inhibiting the pyrin inflammasome (Chung et al., 2016; Ratner et al., 2016). These studies, however, did not implicate the NLRP12 inflammasome in *Yersinia pestis* recognition (Ratner et al., 2016; Vladimer et al., 2012). *Yersinia pestis* harbors a sophisticated virulence system in which the GAP effector YopE is detected by immune cells; however, YopM blocks the response by inhibiting the pyrin-mediated inflammasome (Ratner et al., 2016); indeed, YopM activates the host kinases PKN1 and PKN2 that phosphorylate pyrin, and as a result *Yersinia pestis* escapes antibacterial responses (Chung et al., 2016).

GWAS studies failed to identify disease-associated common variants in *MEFV*. Nevertheless, targeted analyses of *MEFV* in the Turkish population in which FMF mutations are common suggested that the p.M694V mutation may be a risk factor for ankylosing spondylitis (Zhong, Song, Wang, Li, & Ma, 2017), inflammatory bowel disease (Akyuz et al., 2013) and Behcet disease (Kirino et al., 2013).

11. Current therapeutic approaches in inflammasome-related pathologies

11.1. Pharmacological inhibitors of NLRP3 inflammasome activation

Several molecules have been shown to inhibit NLRP3 inflammasome activation (Di Virgilio, 2013; Shao, Xu, Han, Su, & Liu, 2015) but there is no evidence that they directly inhibit NLRP3. Molecules like sulforaphane and isoliquiritigenin can also inhibit other inflammasomes in addition to NLRP3, or inhibit also general inflammatory pathways such as that of NF-κB (Greaney, Maier, Leppla, & Moayeri, 2016; Heiss, Herhaus, Klimo, Bartsch, & Gerhäuser, 2001; Honda et al., 2012). The fenamate class of non-steroidal anti-inflammatory drugs (Daniels et al., 2016) and the β-hydroxybutyrate (Youm et al., 2015) inhibit ion fluxes. Other inhibitors like Parthenolide, BAY 11-7082, INF39, (Cocco et al., 2017; He et al., 2014; Juliana et al., 2010) or the 3,4-methylenedioxy-β-nitrostyrene that inhibits the activity of Src and Syk kinases (Wang, Wu, & Wu, 2006), have broad anti-inflammatory activities and equally suppress NF-κB activation (Cocco et al., 2017; Strickson et al., 2013; Yip et al., 2004). Arglabin, a guaianolide sesquiterpene lactone with both anti-inflammatory and antitumor activity has been shown to inhibit the NLRP3 inflammasome and atherosclerotic lesion formation in high-fat fed ApoE2Ki mice (Abderrazak, Couchie, et al., 2015). MCC950 a diarylsulfonylurea-containing compound which inhibits caspase-1 (Perregaux et al., 2001) specifically inhibits NLRP3 inflammasome activation in a mouse model of CAPS and in cells of patients with Muckle-Wells syndrome (Coll et al., 2015; Dempsey et al., 2017). It was also shown to be effective in reducing caspase-1-activation in microglia cells and in atherosclerotic mice models (Dempsey et al., 2017; van der Heijden et al., 2017); however, its direct target remains unknown. Recently, the CY-09 compound was shown to inhibit NLRP3 inflammasome assembly and activation through binding to the NACHT domain of NLRP3 (Jiang et al., 2017). Treatment of mice with CAPS with CY-09 led to an impressive improvement of the disease phenotype (Jiang et al., 2017). Furthermore, CY-09 has also been shown to be successful in blocking the NLRP3 inflammasome *ex vivo* in

monocytes from healthy individuals and in synovial fluid cells from patients with gout (Jiang et al., 2017). It was also successful in reversing metabolic disorders in diabetic mice, strongly supporting the role of NLRP3 in chronic inflammation (Jiang et al., 2017). MicroRNA mir-9, which targets specifically NLRP3 has shown promising results *in vitro* atherosclerosis models (Wang et al., 2017). Mir-223 (Bauernfeind et al., 2012) which regulates NLRP3 inflammasome activity and is implicated in cholesterol metabolism (Vickers et al., 2014) is another interesting target.

11.2. From colchicine to biotherapies

Colchicine, an alkaloid extract from *Colchicum autumnale*, is the first line of treatment for FMF patients. The anti-inflammatory action of colchicine is attributed to its capacity to inhibit microtubule polymerization and thus to alter the adhesion and mobility of leukocytes (Niel & Scherrmann, 2006). Most patients respond well to colchicine, which prevents acute symptoms, reoccurrence of episodes and amyloid A amyloidosis, the major long-term FMF complication (Dinarello, Wolfe, Goldfinger, Dale, & Alling, 1974; Goldfinger, 1972; Saatçi et al., 1997; Zemer et al., 1974; Zemer et al., 1986). Colchicine is a daily lifelong treatment, which should be started as soon as the diagnosis is established (Grattagliano et al., 2014). A small percentage of FMF patients do not respond to colchicine or are intolerant due to side effects, particularly at the gastrointestinal level.

Colchicine is not efficient in CAPS, neither in other autoinflammatory diseases. As a common characteristic of all these diseases concerns the increased secretion of cytokine members of the proinflammatory IL1 family by myelo-monocytic cells, biological treatments targeting IL1 have been tested. These biotherapies include Anakinra (a recombinant nonglycosylated IL1 receptor antagonist (IL1Ra) that blocks both IL1α and IL1β), Canakinumab (a fully humanized IgG1 monoclonal antibody with a high-affinity specifically to IL1β which does not cross-react with IL1α or IL1Ra) (Hacihamdioglu & Ozen, 2012; Ozen, Bilginer, Aktay Ayaz, & Calguneri, 2011; Stankovic Stojanovic et al., 2012) and Rilonacept (a fusion protein consisting of the extracellular domains of humanized IL1 type 1 receptor and IL1 receptor accessory protein fused with the FC protein of IgG1, which can bind both IL1β and IL1α) (Chae, Aksentijevich, & Kastner, 2009; Meinzer et al., 2011; Soriano, Verecchia, Afeltra, Landolfi, & Manna, 2013). Gevokizumab is another humanized IgG2 monoclonal antibody against IL1β which is authorized for the treatment of rare conditions like pyoderma gangrenosum, Schnitzler syndrome, chronic non-infectious uveitis or congenital hyperinsulinism (Peiró, Lorenzo, Carraro, & Sánchez-Ferrer, 2017).

Since the first publication on the efficacy of Anakinra in CAPS, which changed completely the prognosis of the disease (Hawkins, Lachmann, & McDermott, 2003), additional randomized trials have confirmed the clinical efficacy of Anakinra as well as that of Rilonacept and Canakinumab; the latter have a longer half-life (Goldbach-Mansky et al., 2006; Hoffman et al., 2008; Lachmann et al., 2009). Several studies reinforced these phase III results, often with follow-ups of several years, thereby confirming their safety and efficacy (Goldbach-Mansky et al., 2008; Imagawa et al., 2013; Koné-Paut et al., 2011; Kuemmerle-Deschner, Hachulla, et al., 2011; Kuemmerle-Deschner, Tyrrell, et al., 2011; Kuemmerle-Deschner et al., 2016; Neven et al., 2010; Yokota et al., 2016). In NLRP12-associated inflammation, Anakinra was also found to be useful, at least transiently (Jéru, Hentgen, et al., 2011). In addition, FMF patients who do not respond to colchicine, respond to IL1 inhibition (Ben-Zvi et al., 2017; Hashkes et al., 2012; Koga, Migita, & Kawakami, 2016; Ozen, Kone-Paut, & Gül, 2017).

11.3. Biotherapies in inflammasome mediated-inflammatory diseases

The role of the NLRP3 inflammasome in common inflammatory diseases has paved the way for the use of anti-IL1 molecules in clinical trials related to these diseases (https://clinicaltrials.gov/). Several studies have reported a beneficial effect of Anakinra in acute coronary syndromes (Abbate et al., 2010, 2013; Morton et al., 2015). Recently the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) study, which aimed to test the efficacy of canakinumab at reducing cardiovascular events in 10 061 atherosclerotic patients after a myocardial infarction, showed that canakinumab at a dose of 150 mg every 3 months leads to a significantly lower rate of recurrent cardiovascular events than the placebo, independent of lipid lowering (Ridker, Everett, et al., 2017). The clinical use of this drug in the treatment of atherosclerosis is thus promising. However, Canakinumab administration was associated with a higher incidence of fatal infections as compared to placebo. Canakinumab was also efficient in reducing the incidence of lung cancer and lung cancer mortality, in the same group of atherosclerotic patients who had no previously diagnosed cancer (Ridker, MacFadyen, et al., 2017).

IL1 inhibitors have been shown to be efficient in crystal-induced arthritis and gout (Aouba et al., 2015; Chakraborty et al., 2013; Mitha et al., 2013; Ottaviani et al., 2013; Pascart & Richette, 2017).

Beta-hydroxybutyrate treatment in mice attenuated both behavioural and inflammatory responses (Yamanashi et al., 2017) strongly suggesting that the use of IL1 inhibitors may be beneficial in neurologic diseases and neuroinflammation in which NLRP3 has been shown to be implicated (Heneka, 2017; Kaufmann et al., 2017; Pennisi et al., 2017; Saresella et al., 2016; Song, Pei, Yao, Wu, & Shang, 2017; White, Lawrence, Brough, & Rivers-Auty, 2017).

12. Conclusion

Danger and pathogen patterns lead to changes in cell homeostasis which alert the cell to trigger inflammasome activation. The complexity of the mechanisms involved in pathogen detection has further been underlined by the discovery of the non-canonical inflammasomes. Despite the important insights in the field many questions still remain. For example, how do pathogens escape innate immune surveillance to enter the cells and activate caspases? What is the role of the cytoskeleton in inflammasome activation? How do inflammasomes secrete proinflammatory cytokines in the absence of pyroptosis, do various inflammasomes in the same cell regulate the activity of each other, and many others.

A major outcome of research on rare disorders is the better understanding of the pathophysiology of common diseases, as rare disorders often represent “models of dysfunction” severely affecting a limited number of biological pathways. This was clearly exemplified by the study of CAPS, which led to the discovery of NLRP3, the first inflammasome that turned out to be a major deregulated pathway in several common multifactorial disorders with an inflammatory component. Mutations in inflammasome receptors lead to autoinflammatory diseases and a deregulation in inflammasome activity is associated with the pathology. And finally, therapies used in rare autoinflammatory diseases are now successful in common diseases.

Conflict of interest statement

The authors declare there are no conflicts of interest

Author contribution

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