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# The burgeoning field of innate immune-mediated disease and autoinflammation.

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# The burgeoning field of innate immune-mediated disease and autoinflammation.

(short title **"Innate immune-mediated disease and autoinflammation"**

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## Abstract

Immune-mediated autoinflammatory diseases are occupying an increasingly prominent position among the pantheon of debilitating conditions that afflict mankind. This review focuses on some of the key developments which have occurred since the original description of autoinflammatory disease, in 1999, and focuses on underlying mechanisms that trigger autoinflammation. The monogenic

autoinflammatory disease range has expanded considerably during that time, and now includes a broad spectrum of disorders, including relatively common conditions such as cystic fibrosis and subsets of systemic lupus erythematosus. The innate immune system also plays a key role in the pathogenesis of complex inflammatory disorders. We have proposed a new nomenclature to accommodate the rapidly increasing number of monogenic disorders, which predispose to either autoinflammation or autoimmunity or, indeed, combinations of both. This new terminology also encompasses a wide spectrum of genetically determined autoinflammatory diseases, with variable clinical manifestations of immunodeficiency and immune dysregulation/autoimmunity. We also explore some of the ramifications of the breakthrough discovery of the physiologic role of pyrin and the search for identifiable factors that may serve to trigger attacks of autoinflammation. The evidence that pyrin, as part of the pyrin inflammasome, acts as a sensor of different inactivating bacterial modification Rho GTPases, rather than directly interacting with these microbial products, sets the stage for a better understanding of the role of micro-organisms and infections in the autoinflammatory disorders. Finally, we discuss some of the triggers of autoinflammation as well as potential therapeutic interventions aimed at enhancing autophagy and proteasome degradation pathways.

## Introduction

“La fixité du milieu intérieur est la condition de la vie libre et indépendante” Claude Bernard in “Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux”. Paris, Paris, Baillière, 1878-1879, 2 vols; 404 p. and 564

“*The constancy of the internal environment is the condition for a free and independent life*” in (*Lessons on the physiological properties and pathological changes of body fluids)*

Since the discovery of mutations in the pyrin protein as the cause of familial Mediterranean fever (FMF), in 1997 [1,2], a veritable treasure trove of susceptibility genes, with associated signalling pathways and potential disease mechanisms have been unearthed, which, in turn, has provided some essential guidelines on the most effective therapies for these debilitating conditions [3,4]. The term “autoinflammation” was first proposed by Dan Kastner, in 1999, [5] to differentiate between the pathogenesis of various hereditary periodic fever syndromes (HPFs), which are uncommon causes of recurrent fevers in clinical practice, and that of autoimmune diseases, characterized by the presence of autoantibodies and autoantigen-specific T and B cells. In particular, autoinflammation describes the type of inflammation mediated by the innate immune system [6], and the expression of pyrin in key cells of this system, including neutrophils, monocytes, dendritic cells, and serosal fibroblasts reflects this. Mutations in other central regulators of the innate immune system, as described below, have subsequently been found to underlie a range of other monogenic conditions as well as polygenic autoinflammatory diseases [7], such as Behcet’s and Crohn’s disease [8,9] (Figs. 1).

With relatively recent advances in massively parallel sequencing and wider use of this technology, we have witnessed the discovery of a succession of monogenic disorders, predisposing to either autoinflammation or autoimmunity or, indeed, combinations of both, further revealing the complex functioning of the human immune system [3,9,10]. These novel monogenic diseases may be of limited clinical impact, in the overall scheme of things, but they do represent true experiments of nature that continue to provide unique pathogenic insights into the hierarchy and levels of regulation of organ-specific immune defence responses. To quote directly from DJ Weatherall *"if the severity of their phenotypes can be reduced by genetic or even environmental factors, it may be possible to reproduce these effe*cts *pharmacologically"* [11].

Furthermore, functional studies of these disorders have generated many new and surprising biological concepts; for example, the discovery that autosomal recessive mutations of the mevalonate kinase gene (MVK), a key step in the cholesterol pathway, caused hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) [12,13], has prompted closer examination of the broader interactions between inflammation and overall lipid signalling. The expanding list of novel autoinflammatory diseases and associated susceptibility genes has already been extensively covered [3,14]; in this review we propose to describe a selection of these diseases in order to illustrate some of the many unanticipated developments in this field, which have arisen as a result of the study of genetic causes of autoinflammation, often in quite rare conditions.

## Interleukin 1 (IL-1)/NLRP3-mediated autoinflammatory diseases

In 2002, the late Jurg Tschopp's laboratory reported reported on the identification of an intracellular complex called the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome that triggered activation of inflammatory caspases, with pro-interleukin 1β (pro-IL-1β) processing and subsequent secretion of pro-inflammatory IL-1β [15] (Fig. 2). The genetic basis of familial cold autoinflammatory syndrome (FCAS) [16], Muckle-Wells syndrome (MWS) [17,18] and chronic infantile neurologic, cutaneous, articular syndrome/ neonatal-onset multisystem inflammatory disease (CINCA/NOMID) [19,20], were all found to be associated with mutations in the *NLRP3/CIAS1* gene, and evidence that release of IL-1β was central to the pathogenesis of MWS came with the demonstrated efficacy of interleukin-1 receptor antagonist (IL-1Ra), anakinra, in 2 patients with MWS [21]. Collectively, the spectrum of these conditions soon became known as cryopyrin associated periodic syndrome (CAPS), reflecting a shared aetiopathogenesis (Table 1). Furthermore, as it quickly became apparent that this collection of conditions responded exquisitely to IL-1 blockade [21-23], so too it gradually emerged that IL-1 inhibition was also effective in other HPFs, like TNF receptor-associated periodic syndrome (TRAPS) [24], HIDS and FMF [25], although the response was less predictable in some cases. So it was proposed that caspase-1 activation with release of IL-1β was a pathway common to many autoinflammatory conditions; the mutated NLRP3 produces a gain of function, with lack of feedback inhibition, that results in constitutive activation of the NLRP3 inflammasome with IL-1β and IL-18 release [3,26]. The interleukin-1 receptor antagonist (IL-1Ra) provides a "biological brake" on inflammation driven by either endogenous IL-1α or IL-1β; deficiency of IL-1Ra (DIRA) [27] and deficiency of IL-36 receptor antagonist (IL-

36Ra) (DITRA) lead to unopposed IL-36 signalling and pustular psoriasis [28,29] (Table 1).

A broad range of autoinflammatory diseases is currently being treated with IL-1 cytokine blockade, with marked attenuation of symptoms and disease progression. Canakinumab is a high affinity fully human monoclonal anti-human interleukin 1β antibody and rilonacept (IL-1 Trap) is a long-acting dimeric fusion protein IL-1 blocker. Clinical trials have been undertaken in CAPS, gouty arthritis, and systemic juvenile idiopathic arthritis (sJIA) [30-33]. There is a growing literature supporting the use of these agents in a wide spectrum of autoinflammatory conditions, including gout, Schnitzler syndrome, and Blau syndrome [34]. While multiple studies are ongoing, these agents have already been approved by for the treatment of CAPS and sJIA by a number of drug regulatory bodies.

Finally, somatic mosaicism has been reported in a number of autoinflammatory conditions. Since the first ever report of somatic mosaicism, in a Japanese patient with CINCA/NOMID in 2005 [35], it has subsequently been reported in several cases of CAPS, as well as FMF [36] and TRAPS [37].

## Interferon (IFN) mediated autoinflammatory diseases

Aicardi-Goutières syndromes (AGS) constitute a collection of rare inflammatory disorders, associated with aberrant sensing of DNA/RNA, and usually affecting the brain and skin with clinical onset, most often, in early childhood. Since the initial description, of mutations in genes encoding the 3′→5′ exonuclease TREX1 in patients with AGS1 [38,39], in 2006, a total of seven AGS susceptibility genes have been identified to date, and this wide range of genetic mutations all lead to excessive interferon (IFN)-producing responses, known as type I interferonopathies

[40]. A variety of disease mechanisms are involved: AGS 1-6 are of autosomal recessive inheritance and the AGS 7 patients have autosomal dominant gain-of-function mutations in the interferon induced with helicase C domain 1 *(IFIH1)* gene.

TREX1 is induced as part of the IFN-stimulatory DNA (ISD) response, an antiviral pathway that detects DNA, triggering immune activation through IRF3 [41]. Both TREX1 and SAMHD1 (AGS5) act as a negative regulators of the ISD response [42]. The genotype-phenotype spectrum of TREX1 is remarkably broad and complex [43]. Familial chilblain lupus, systemic lupus erythematosus (SLE) and retinal vasculopathy with cerebral leukodystrophy have all been associated with mutations in TREX1 [44], in addition to the AGS1 phenotype, which, in its more severe form, is characterized by intracranial calcifications, cerebral atrophy, leukodystrophy, chronic cerebrospinal fluid (CSF) lymphocytosis, increased CSF alpha-interferon (IFN$\alpha$) and negative serologic investigations for prenatal infections.

Individuals with AGS7 also have severe neurologic impairment and immunological disease, particularly SLE [45]. However, clinical variability and non-penetrance are notable features of some AGS7 patients, despite the presence of IFN up-regulation (increased expression of type I IFN regulated genes, referred at as an IFN signature).

A variety of therapies have been used to treat the chronic excessive IFN production in AGS patients. Anti-inflammatory therapies, including Janus kinase (JAK) inhibitors, such as baricitinib and tofacitinib, and IFN pathway-blocking drugs, such as sifalimumab, have all been been used in AGS [46,47]. If AGS progresses to antibody-mediated disease then anti-B cell therapy, such as rituximab may be of benefit. Reverse transcriptase inhibitors (RTIs) are also being used to treat severely affected AGS patients and results are awaited with interest.

Apart from AGS there is a growing list of interferonopathies, due to gain-of-function mutations in genes such as the *PSMB8*, present in most patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/ proteasome-associated autoinflammatory syndrome (CANDLE/PRAAS) syndrome [48]. Liu et al. have demonstrated that mutations in the stimulator of interferon genes (STING) lead to constitutive STING–IFN-β pathway activation in patients with STING-associated vasculopathy with onset in infancy (SAVI) (STING is also known as transmembrane protein 173) [49]. A clinical trial aiming to assess the effect of JAK inhibitors, in SAVI and other related autoinflammatory syndromes, is currently ongoing (ClinicalTrials.gov number, NCT01724580).

It has been proposed that IL-1β and type I IFN are the main drivers, respectively, of autoinflammation and autoimmunity, acting as counterregulators of each other by activating specific metabolic signalling pathways to limit either innate or adaptive immune responses [50]. However, the fine details of such regulatory networks remain to be established.

## Autophagy in autoinflammation.

Autophagy is emerging as a major pathway involved in the pathogenesis of autoinflammatory disease. The MVK mutation, and the subsequent depletion in isoprenoid synthesis, reduces functional autophagy in HIDS. However, this is not the only autoinflammatory disease where defective autophagy contributes to disease pathogenesis. Autophagy is a cellular process that maintains homeostasis by the clearance of redundant or damaged cellular components. There is a close relationship between autophagy and the inflammasomes, with evidence that autophagy has a role in inhibiting the inflammasomes. This evidence not only suggests that autophagy clears inflammasome activators, such as ROS [51,52], mtDNA [53], HMGB1-DNA [54] and β-amyloid plaques in Alzheimer's disease [55], but also clearance of the inflammasome itself [56]. Studies inhibiting autophagy observe increased NLRP3 inflammasome activation due to ROS accumulation [57].

The autophagy mechanism is a regulated process of 'self-eating' where the contents of entire organelles are recycled for other biological functions. Mutations in proteins such as NLRP3 or TNFR1, can overcome normal protein homeostatic mechanisms, resulting in autoinflammatory diseases, such as CAPS and TRAPS [58]. The inflammasomes are at the centre of the pathogenesis of autoinflammatory diseases and so the involvement of autophagy in these conditions may uncover new therapeutic targets. TRAPS is known to have inflammasome activation and individuals with TRAPS respond well to anakinra. Defective autophagy within TRAPS contributes to NF-κB signalling, ROS production and defective TNF-induced apoptosis [59,60]. Autophagy deficiency can be considered as a causal link between a pathological mutation and subsequent protein accumulation, inflammasome activation and cytokine secretion [59,60]. This is particularly relevant in inflammatory diseases with known protein misfolding and ER stress. One such example is cystic fibrosis (CF), which has been shown to have defective autophagy [61-63] and common infections of *Burkholderia cepacia complex (B. cenocepacia)*, which is able to inhibit autophagy as part of its infection machinery [64,65]. Autophagy and the inflammasomes go hand-in-hand, so in order to expose new disease mechanisms of innate immune driven diseases, both should be considered in tandem. On the other hand, genetic defects in the proteasome cause protein accumulation and proteasome dysfunction, which can trigger IFN-dependent autoinflammation. Loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients also promote type I IFN production [48,66].

## The unfolded protein response (UPR)

Many different factors trigger activation of NLRP3; this is a 2-stage process requiring priming, usually via toll-like receptor (TLR) signalling, with a 2nd signal, typically intracellular calcium ($Ca^{2+}$) ion release, potassium ($K^{+}$) flux or intracellular reactive oxygen species (ROS). An ever-increasing number of molecules, in the form of whole pathogens, toxins, pathogen-associated molecular patterns (PAMPs), and DAMPs, are being found to trigger activation of the different inflammasomes, in particular the NLRP3 inflammasome (Fig. 3). It is most unlikely that these diverse agents bring about the activation by direct interactions with the intracellular NLRP3 receptor; instead, it is probable that NLRP3 is responding to generic cellular stress-signals induced by this variety of triggers. Among the cellular mechanisms that have evolved to maintain protein homeostasis include proteasome-mediated degradation of ubiquitinated proteins and the unfolded protein response (UPR). The UPR prevents protein overload in the secretory pathway and also prevents the spread of inflammation by degrading pro-inflammatory protein complexes, such as the NLRP3 inflammasome [58].

## Cystic Fibrosis (CF) as an autoinflammatory disease

Cystic Fibrosis (CF) is a life-threatening autosomal recessive disorder of the lungs and digestive system [67,68]. The defective gene CFTR results in abnormalities in production and function of the CFTR protein, causing dysregulation of epithelial fluid transport and inflammation [69-72] and a predisposition to recurrent pulmonary infections due to pathogens such as *Pseudomonas aeruginosa (P. aeruginosa)* and *B. cenocepacia.* Alterations in function and localisation of CFTR within leukocytes and epithelial tissues results in an exaggerated inflammatory response, with production of a wide spectrum of proinflammatory and chemotactic cytokines such as IL-17, IL-8, IL-6, IL-1β, IL-18, TNF, upregulation of TLRs and lipopolysaccharide (LPS) response [73]. The neutrophil is the predominant cell type infiltrating the CF lung, like a primary inflammatory response seen in acute infection, with inflammation in CF airways being driven by local environmental cells (macrophages and bronchial epithelial cells), rather than T cell derived lymphokines, as a systemic immune response. CF exhibits many hallmarks of an autoinflammatory condition [10], with infiltration by innate immune cells (neutrophils and macrophages) at target sites, and a paucity of autoantibodies or autoreactive T cells.

The physiological drive to autoinflammation in CF is due to CFTR dysfunction, which results in abnormal airway surface liquid (ASL) dehydration, reduced airway luminal pH, increased ASL glucose and hyperuricaemia [74-76]. These changes provide a milieu for activation of the NLRP3 inflammasome [77-79]. In human macrophages, IL-1β secretion and caspase-1 activation occurs following extracelluar acidification, which is abolished following knockout of mRNA expression of NLRP3 receptor [79].

As well the physiological changes in epithelial ion transport, abnormal CFTR production, function and trafficking results in a state of hyperinflammation, associated with expansion of the endoplasmic reticulum (ER), located within the cytoplasm of cells, that inhibits ROS-mediated autophagy [61,80,81]. The most common mutation F508 results in a misfolded protein which is retained intracellularly and results in defective autophagy due to transglutaminase (TG2)-mediated depletion of Beclin 1 and overactivation of protein kinase CK2 [81]. Normal autophagy activity suppresses activation of AIM2 and NLRP3 inflammasomes and helps regulate inflammation[82]. Reduced autophagy induces aberrant activation of the inflammasomes with accumulation of bacterial containing phagosomes [82,83]. In CF murine airways and human macrophages, defective CFTR results in reduce levels of scaffold protein, CAV1, reduced inhibition of TLR4 signalling and hyperinflammation [84,85]. Similarly, studies in human CF broncho-epithelial cells show evidence of increased NLRP3 activation and defective NLRC4 activity, which can be inhibited by IL-1Ra (Fig. 3) [86]. Increased levels of ceramide appear to trigger the inflammasome protein complex, with upregulation of ASC protein, caspase-1 and increased production of IL-1β and IL-18 cytokines in the lungs of a CF mouse model [69].

## Autoinflammation and Infection

The UPR, is activated in airways of patients by recurrent bacterial infections [30]. The ER stress responses involve atypical UPR induction, with lack of PERK-eIF2α response to *P.* aeruginosa [87]. This atypical UPR fails to resolve ER stress in CF and sensitises innate immunity to respond vigorously to microbial challenge. This persistent autoinflammatory response is associated with CF arthropathy in 9% of adults, which in some cases is associated with a fever and rash [88]. The complex relationship between inflammation, CFTR, innate immunity and infection is poorly understood and may be related to macrophage dysfunction, abnormal phagocytic killing of *P aeruginosa* [89] and impaired degranulation of antimicrobial proteins through defective activation of GTP-binding protein, Rab27a [90]. In addition, CFTR dysfunction results in an increase sensitivity to LPS (a major constituent of the outer membrane of Gram-negative bacteria) stimulation, altered inflammatory signaling due to abnormal neutrophil extracellular trap formation [89,91,92] and activation of micro-RNAs (miRNAs) [93] and NF-κB. These bacteriae trigger the NLRP3 inflammasome through cytosolic receptors resulting in increased caspase 1 protease (CASP-1) and IL1B and IL18 production (Fig. 3). Triggers of NLRP3 inflammasome include the common CF lung pathogens *Staphylococus aureus*, *Haemophilus influenza*, *P. aeruginosa*, *B cepacia complex*, *rhinovirus*, *influenza* and *Aspergillus fumigatus* [94-99].

Viruses activate inflammasome-mediated innate immunity through recognition of viral RNA [100] by TLR7 and other triggers including altered ion flux with activation of NLRP3 and NLRC5. *P. aeruginosa* and *Burkholderia cenocepacia (B. cenocepacia)* are two major pathogens which when isolated in sputum of patients with CF are associated with clinical deterioration. *B. cenocepacia* is particularly pathogenic and can result in acute clinical deterioration with uncontrolled inflammation, necrotizing pneumonia and bacteraemia. B. cenocepacia accentuates inflammation via upregulation of mononuclear cell IL-1β processing and inhibition of autophagy [101,102]. Stimulation of autophagy with rapamycin in the CF lungs mouse model reduces both inflammation and infection induced by *B. cepacia* [102]. LPS, L-Ala-γ -D-Glu-m-diaminopimelic acid (m-DAP), muramyl dipeptide (MDP) present in gram-negative and some gram-positive bacteria are also involved inactivation of the innate immune systems, though TLR and Nod-like receptor (NLR) proteins. Furthermore, a number of chemicals can induce structural changes in LPS, and subsequently modify the inflammatory response [103]. CF-associated ER stress responses involve atypical UPR induction, with lack of PERK-eIF2α response to the *P. aeruginosa* organism [87]. This shows that the atypical UPR fails to resolve ER stress in CF and sensitises innate immunity to respond vigorously to microbial challenge.

A key component of the UPR is the IRE1 enzyme, activated by ER stress. IRE1 induces conversion of the transcription factor XBP1u mRNA (unspliced) to spliced XBP1 (XBP1s), the active form. Martinon et al. proposed a pro-inflammatory role for IRE1, with TLR2 and TLR4 activating IRE1 to induce sXBP1 [104]. In macrophages, IRE1 activation exacerbates secretion of proinflammatory cytokines such as IL-6, TNF and IFNβ [105]. Furthermore, the effects of defective XBP1 functioning in autoinflammatory diseases may be augmented by concomitant defects that heighten cellular stress, including mitochondrial ROS or dysregulated microRNA regulation of XBP1 mediated inflammatory processes in TRAPS [106,107]. Thus, via both direct and indirect mechanisms, XBP1 dysregulation may be an important step in the cascade of intracellular events contributing to the pathogenesis of a number of autoinflammatory diseases. Indeed, there is also evidence of a UPR mediated by the XBP1s isoform in the airway epithelium of CF patients [108]. On the other hand, an in-vitro study from Italy shows that the degree of P. aeruginosa-dependent mitochondrial dysfunction is strictly dependent on defective expression of the CFTR channel and on a flagellin-activated TLR5-dependent pathway [109].

The NLRP3 inflammasome complex also senses mitochondrial dysfunction [110] and intracellular ROS is a crucial element for inflammasome activation. Anakinra reduced endotoxin-induced airway inflammation in healthy volunteers [111], so we postulate that spontaneous NLRP3 inflammasome activation occurs in in CF patients [112]. Recent studies have linked IRE1 to NLRP3 activation [113] and have also shown that XBP1 modulates innate immune responses of alveolar macrophages in CF patients [114]. IL-1 and the NLRP3 inflammasome activation cause arthropathy and the IRE1/XBP1 axis has been implicated in synovial macrophages and fibroblasts of RA patients [107,115].

One of the unique features of CF as an autoinflammatory disease is that it is the only such condition to have a “laboratory proven” association with bacterial infections, including *P. aeruginosa* and *B.cenocepacia*. The NLRP3 and NLRC4 inflammasomes serve different functions in regulating inflammatory responses in mice and humans with CF (Fig. 4). While both NLRP3 and NLRC4 inflammasomes contribute to pathogen clearance, NLRP3 contributes to a greater extent than NLRC4 to deleterious inflammatory responses in CF and correlates with defective NLRC4-dependent IL-1Ra production. Also IL-1 blockade markedly reduces inflammasome-dependent inflammation in murine and human CF [116].

## Metabolic/mitochondrial mechanisms of autoinflammation.

The relationship between inflammation and metabolism constitutes a delicate balance, with pathways from both systems converging to preserve the “milieu interieur” of the cell. This balance in maintained by short-term adaptive measures to keep these systems in check, but there may be a detrimental outcome when one arm becomes overactive and suppresses the other in the longer term. HIDS is a classic example of a monogenic autoinflammatory disease, with a metabolic defect at its core. This disease is caused by two mutations in the mevalonate kinase (MVK) gene [12,13,117] and presents with increased excretion of urinary mevalonic acid and raised immunoglobulin (Ig)-D and IgA levels in the serum [118]. Symptoms are often neurological in nature with increased mental retardation, ataxia, seizures and ocular problems. Fevers usually last around 5 days and are often triggered by traumas, illnesses or vaccine reactions. Although not consistently successful IL-1 antagonists are the most effective treatment for HIDS, with steroids having limited efficacy [118,119]. The mutated MVK gene translates into reduced levels of the enzyme mevalonate kinase, which normally converts mevalonic acid into mevalonate -5-phosphate, an intermediate in isoprenoid and sterol synthesis. The exact pathogenic molecular mechanism in HIDS is not clear but recent publications, describing the pyrin inflammasome and its detection of bacterial modifications of Rho GTPases, are promising avenues of exploration, as the causal biochemical deficiency of isoprenoid synthesis in HIDS reduces RhoA prenylation [120]. As IL-1 antagonists, such as anakinra and canakinumab, are able to reduce fever frequency and severity, the NLRP3 inflammasome is a key pathway of interest although it is not the only possible source of IL-1β [121]. Research advances into how the inflammasomes are controlled by ROS and autophagy, and their links to Rho GTPase prenylation, also offer significant insights into the precise metabolic and mitochondrial mechanisms of autoinflammatory disease.

Recently, Celsi *et al.* described an increase in NLRP3 activity in a HIDS mouse cell model, using siRNA *mvk* silencing, when cells are treated with LPS and lovastatin, a statin drug used to lower cholesterol [122]. However, complete knockdown of *mvk* did not induce an increase in NLRP3 activity. This lead to the conclusion that increased mutated mvk protein levels may trigger NLRP3 activity by initiating the UPR due to protein accumulation. This hypothesis is supported by a HIDS THP-1 macrophage cell line model [123]. This cell model produced increased IL-1β and IL-18 levels, as well as an altered redox state. An important role for this altered redox state was revealed as it was associated with increased mitochondrial membrane potential, increased mitochondrial damage and increased mtDNA in the cytosol, all linked to a defective autophagy pathway. Autophagy would ordinarily be activated in the situation of an altered redox state to clear defective mitochondria and reduce ROS-dependent damage; however, in this cell model, autophagy was found to be defective. The mutations in MVK, with subsequent reduction in isoprenoid synthesis, causes reduced prenylation of small GTPases, which are key upstream proteins involved in autophagosome formation [123]. The authors suggest a model whereby defective autophagy, due to reduced prenylation of small GTPases, occurs upstream of increased mitochondrial damage and the increased ROS, in turn, activates the NLRP3 inflammasome [124]. Interestingly, when these small GTPases, specifically the Rho family, become modified they trigger the pyrin inflammasome [125]. The link between HIDS and reduced prenylation of Rho GTPases activating the pyrin inflammasome has been suggested to offer an effective therapeutic target [120]. RhoA activates PKN1 and PKN2 serine threonine kinases, which in turn phosphorylate pyrin. Phosphorylated pyrin is bound to 14-3-3 proteins that restrict pyrin from forming its inflammasome. Arachidonic acid is a known activator of PKN kinases and is a potential future therapeutic option for innate immune-mediated inflammation. Therefore, changes in post-translational modifications of Rho GTPases, in diseases such as HIDS or FMF, produce a reduced pyrin inhibitory capacity as well as defects in autophagy. In addition, autophagy has been shown to not only degrade ROS and mitochondrial debris in the cytosol, but also targets the NLRP3 inflammasome and pro-IL-1$\beta$ for autophagosomal degradation [126,127]. Further evidence for disruption in metabolic pathways triggering the inflammasomes exists with hexokinase. Hexokinase is a glycolytic enzyme located on mitochondrial membranes. When inhibited, hexokinase dissociates from the membrane and allows release of mitochondrial DNA, activating the NLRP3 inflamamsome [128]. Metabolic conditions in which hexokinase function is impaired cause NLRP3 activation.

Bacterial peptidoglycan-derived N-acetylglucosamine is detected by mitochondrial membrane-bound hexokinase, causing membrane dissociation and NLRP3 activation [129].

## The UPR, metabolic pathways and associated therapies

The interplay between various metabolic pathways and the UPR has raised the possibility that key points in specific metabolic pathways could be targeted in autoinflammatory diseases. XBP1s acts a transcriptional activator of the hexosamine biosynthetic (HBP) pathway [130]; the UPR-HBP axis is triggered in a variety of stress conditions, including ischemia-reperfusion (I/R) injury, where stimulation of Xbp1s induces cardio-protection by induction of HBP. Ischemic accumulation of succinate has been shown to control reperfusion injury through mtROS [131]. Therefore the prevention of succinate accumulation could be a therapeutic goal in a range of autoinflammatory diseases that are resistant to standard therapies.

The rapid advances in the pathogenesis of autoinflammatory diseases and recognition that altered protein homeostasis contribute an innate immune component to many common diseases, underlines the unmet need for novel therapies for these conditions. For such therapies to be effective they would need to prevent protein accumulation, suppress ROS generation, and enhance of clearance mechanisms thereby preventing the development of (auto)inflammation. Therapies that succeed in augmenting the UPR could prove to be highly beneficial, as protein misfolding within the ER leads to activation of the UPR, with associated inflammation and increased disease severity. Anti-oxidants could be prescribed as adjunct therapies for diseases with aberrant ROS production and oxidative stress, like TRAPS [131].

Since both autophagy and proteasome degradation have anti-inflammatory properties, possible therapeutic interventions will be directed towards enhancing these pathways to effectively reduce NLRP3 activation [132]. Small molecules that block the NLRP3 inflammasome and related signalling pathways have recently shown promise in pre-clinical studies [133-135]. Clinical trials of agents that modulate proteotoxic stress and deactivate the inflammasome(s), combined with traditional therapies, such as IL-1 antagonists, will provide new insights into the connections between protein homeostasis and autoinflammation. https://clinicaltrials.gov/ct2/show/NCT01724580?term=NCT01724580&rank=1 [135]

## The physiologic role of pyrin

The discovery of the physiologic role of pyrin by Feng Shao's group represents a major advance in the field of autoinflammation [125,136]. The raison d'etre of the innate immune system is to protect the population from infection (Fig. 2); however, mutations in these protective genes can also lead to autoinflammatory disease. Shao and colleagues presented evidence that pyrin, as part of the pyrin inflammasome, acts as a sensor of different inactivating bacterial modification RHO GTPases, rather than directly interacting with these microbial products. This guard mechanism of pathogen detection has previously reported for pathogen recognition receptor (PRRs) in plants. Several Rho-inactivating bacterial toxins have been reported, including the TcdB toxin from *Clostridium difficile* the C3 toxin from *Clostridium botulinum* and the pertussis toxin from *Bordetella pertussis,* and, in the context of this review *B. cenocepacia* deamidates RhoA at Asn41 [125,136].

More recent developments in this field include the discovery that RhoA activates the serine-threonine kinases PKN1 and PKN2 that bind and phosphorylate pyrin

[120]. This activation of PKN1 and PKN2 was found to decrease IL-1β release from peripheral blood mononuclear cells (PBMCs) of patients with FMF or HIDS. Defective prenylation, as seen in HIDS, was associated with RhoA inactivation and pyrin inflammasome activation (Fig. 4). Thus, the authors propose a novel molecular connection between FMF and HIDS.

Masters et al. have described an autoinflammatory disease, labelled pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND), caused by a mutation in pyrin, which disrupts pyrin regulation and mimics the effect(s) of pathogen sensing by pyrin, leading to proinflammatory IL-1β production [137]; the disease resolved in one patient by targeting IL-1β. These data reveal a regulatory mechanism of pyrin activation and suggest that it is regulated through a guard-like mechanism, which prevents the development and progression of autoinflammation.

A number of fundamental questions arise from these fascinating discoveries, including the precise molecular mechanisms of pyrin inflammasome activation and whether specific environmental factors may trigger attacks in patients with autoinflammation.

## New diseases and mechanisms

Gain-of-function mutations in the NLRC4 gene a novel inflammasome disorder associated with predisposition to macrophage-activation syndrome (MAS) and highly elevated IL-18 levels [14] (Table 1). Aksentijevich and colleagues [138] found that *TNFAIP3* mutations cause haploinsufficiency of A20 (HA20), with reduction of NF-κB [139] and IL-1 signalling leading to A20 haploinsufficiency, in an early-onset autoinflammatory disease, where the phenotype resembles Behcet’s disease [140]. A paper in press by the same group describes another NF-κB mediated disease, caused by loss-of-function mutations in OTULIN/FAM105B gene, encoding a deubiquitinase with linear linkage specificity. These patients have a very severe phenotype, surprisingly resembling CANDLE, but clinically responsive to TNF inhibitors [141]. Together with HA20 these two diseases described a new category of autoinflammatory diseases, due to dysregulated ubiquitination. Thus the ubiquitination pathway has assumed greater important in the investigation of systemic autoinflammatory disorders of undefined etiology (SAIDs).

Mutations in the TNFRSF11A gene have been reported in patients with a disease that has clinical similarities to TRAPS [142]. A report of a novel digenic pattern of inheritance in CANDLE/PRAAS patients, has provided insights into proteasome dysfunction and associated IFN production [66].

## Triggers of autoinflammation

Autoinflammatory diseases are mainly driven by proinflammatory cytokines, usually generated as a result of cellular stress, and especially oxidative stress with associated mitochondrial DNA (mtDNA) damage. The resulting release of metabolic mediators such as mitochondrial ROS, which acts as a DAMP for the NLRP3 inflammasome activation [143]. The search for identifiable (exogenous) factors that might serve to trigger attacks of autoinflammation involves careful the patient's environment, diet, or lifestyle [110]. Some known triggers known to influence the effects of individual mutations include

1. Generalised exposure to cold may precipitate attacks of fever in familial cold autoinflammatory syndrome (FCAS).

2. Attacks of HIDS may be triggered by trauma, illnesses or vaccine reactions [117,144]. A severe inflammation reaction following vaccination against Streptococcus pneumoniae has been described in patients with CAPS [142]

3. Urate and CPP crystals cause NLRP3 inflammasome activation in gout and calcium pyrophosphate deposition disease (CPPD) [77]

4. The pyrin inflammasome is activated upon bacterial toxin-induced modification of host Rho GTPases [125].

**5.** Dying cells have the capacity to activate the innate immune system and induce a sterile inflammatory response [145,146]; necrotic cells are sensed by the Nlrp3 inflammasome with subsequent release of IL-1β [147]. In a mouse model mitochondria were critical to activation of the Nlrp3 inflammasome by direct binding of Nlrp3 to the inner mitochondrial lipid cardiolipin.

**6.** The relationship between IFN-*α* and brain pathology in AGS is poorly understood [148]. Viral infection and replication introduces single-stranded RNA (ssRNA), double-stranded RNA (dsRNA) and DNA:RNA hybrids, with induction of type I IFN genes. The AGS phenotype may resemble congenital viral and individual subsets of SLE [43,44].

## Autoinflammation in the more common chronic systemic conditions

It is now accepted that innate immune-mediated inflammation plays a key role in the pathogenesis of some of the more common chronic systemic conditions, such as Crohn’s disease [4], type 2 diabetes (T2D) and a myeloid subset of rheumatoid arthritis (RA) [149], as well as in diseases not formerly considered inflammatory, such as neurodegenerative conditions [150]. There is increasing evidence that cell intrinsic or environmental alterations in protein homeostasis may contribute to the pathogenesis in these conditions; thioredoxin-interacting P (TXNIP) serves as a functional link between ER stress, NLRP3 inflammasome activation and inflammation related to T2DM [151].

## Therapies

As the field of autoinflammatory disorders has developed so rapidly clinicians and researchers have produced guidelines to optimise and disseminate recommendations for universal management of children and young adults with these disorders. An international panel of 22 experts was established to develop evidence-based recommendations for the management and treatment of CAPS, TRAPS and MKD using the European League Against Rheumatism (EULAR) standard operating procedures for developing best practice [152,153].

## Proposed new Nomenclature – an expanded classification of autoinflammatory diseases

The continuously expanding number of monogenic diseases, for which susceptibility genes have been found, and which present with a range of overlapping clinical features, both autoinflammatory and autoimmune in nature, has raised the question as to how to (sub)classify those conditions, as the terms autoinflammation and/or autoimmunity are insufficient to adequately describe them. In addition to the challenge posed by these conditions with overlapping features, a range of other diseases, with variable clinical manifestations of immunodeficiency and immune dysregulation/autoimmunity have been genetically delineated. These include PLCG2-associated antibody deficiency and immune dysregulation (PLAID) [154], haploinsufficiency of CTLA-4, caused by heterozygous germline mutations [155] and

XLPDR disorder, due to deficiency of POLA1, which encodes the catalytic subunit of DNA polymerase-α [156]. This latter condition also has an associated IFN signature.

Despite these observations, a combination of both pathogenic innate and adaptive immune responses underlie the immunopathology of most inflammatory conditions. As reviewed in [46] some clinical features, like B-cell immunodeficiency, may arise in conditions which are mainly innate-immune driven, and autoinflammatory in phenotype, such as deficiency of adenosine deaminase 2 (DADA2) [157,158] but B-cell immunodeficiency may also be found in monogenic autoimmune conditions, like haploinsufficiency of CTLA-4 and PLAID. Furthermore, AGS7 has the potential to progress from being primarily innate-immune driven to becoming an antibody-mediated disease.

In light of the expanding number of overlapping syndromes of both autoinflammation and autoimmunity we propose to broaden the classification of diseases by assigning the term **autoimmuno-inflammatory disease**. Conditions like PLAID, where the clinical picture combines features of immunodeficiency as well as autoimmunity, and, arguably, the cold urticaria element of PLAID is innate immune related, might also be considered; following the template proposed above complex conditions of that nature could be referred to as an **autoimmuno-inflammatory-immunodeficiency.** However the primary immunodeficiency diseases (PI) constitute an extensively classified group of conditions, and it may not be possible to find a satisfactory all-purpose blanket term for novel complex conditions with features of immunodeficiency as well as autoimmunity and autoinflammation.

## Summary of developments and outlook

The identification of a genetic aetiology for an increasing number of autoinflammatory diseases has led to a growing recognition that dysregulation of this normal defence mechanism may be more prevalent than previously realised in other diseases. Autoinflammation is likely to play a variable role in a wide spectrum of human disease, acting within a milieu of complex processes, involving innate and adaptive immunity. Understanding the role of autinflammation in various diseases processes is essential if new targets are to be identified for future therapies.

A major part of the human immune system's basic function is to control the host's relationship with his/her microbiota, referring to the the totality of microorganisms that inhabit the human body in health and disease. Recent major technological advances, including single cell sampling and shotgun sequencing enables detailed study of individual microbiota and inflammatory disease can related to components of the microbiome [159] (the combined genetic material of the microorganisms), and to the intracellular pathways that pathogens within the microbiome may dysregulate survive [160]. It is most likely that the widespread influence of intracellular microbes on innate immune defences and autoinflammatory diseases will be elaborated in significant detail in the next decade.

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## Author contribution statement:

TS, DP, SS and MMcD wrote the manuscript.

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## References

1. Aksentijevich I, Centola M, Deng Z*, et al.* Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. *Cell* 1997; **90**: 797-807.
2. Bernot A, Clepet C, Dasilva C*, et al.* A candidate gene for familial Mediterranean fever. *Nature Genetics* 1997; **17**: 25-31.
3. de Jesus AA, Canna SW, Liu Y*, et al.* Molecular mechanisms in genetically defined autoinflammatory diseases: disorders of amplified danger signaling. *Annu Rev Immunol* 2015; **33**: 823-874.
4. Savic S, Dickie LJ, Wittmann M*, et al.* Autoinflammatory syndromes and cellular responses to stress: Pathophysiology, diagnosis and new treatment perspectives. *Best Practice and Research: Clinical Rheumatology* 2012; **26**: 505-533.
5. McDermott MF, Aksentijevich I, Galon J*, et al.* Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999; **97**: 133-144.
6. McDermott MF, Aksentijevich I. The autoinflammatory syndromes. *Current Opinion in Allergy and Clinical Immunology* 2002; **2**: 511-516.
7. Brydges S, Kastner DL. The systemic autoinflammatory diseases: Inborn errors of the innate immune system. In: Current Topics in Microbiology and Immunology. (ed)^(eds), 2006; 127-160.
8. Ciccarelli F, De Martinis M, Ginaldi L. An update on autoinflammatory diseases. *Current Medicinal Chemistry* 2014; **21**: 261-269.
9. Stoffels M, Kastner DL. Old Dogs, New Tricks: Monogenic Autoinflammatory Disease Unleashed. *Annu Rev Genomics Hum Genet* 2016.
10. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PLoS Medicine* 2006; **3**: 1242-1248.
11. Weatherall DJ. Pharmacological treatment of monogenic disease. *Pharmacogenomics Journal* 2003; **3**: 264-266.
12. Drenth JPH, Cuisset L, Grateau G*, et al.* Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. *Nature Genetics* 1999; **22**: 178-181.
13. Houten SM, Kuis W, Duran M*, et al.* Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. *Nature Genetics* 1999; **22**: 175-177.
14. Canna SW, Goldbach-Mansky R. New monogenic autoinflammatory diseases—a clinical overview. *Seminars in Immunopathology* 2015; **37**: 387-394.
15. Martinon F, Burns K, Tschopp J. The Inflammasome: A molecular platform triggering activation of inflammatory caspases and processing of proIL-β. *Molecular Cell* 2002; **10**: 417-426.
16. Hoffman HM, Mueller JL, Broide DH*, et al.* Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nature Genetics* 2001; **29**: 301-305.
17. Dodé C, Le Dû N, Cuisset L*, et al.* New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: A novel mutation underlies both syndromes. *American Journal of Human Genetics* 2002; **70**: 1498-1506.
18. Aganna E, Martinon F, Hawkins PN*, et al.* Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever,

cold sensitivity, sensorineural deafness, and AA amyloidosis. *Arthritis and Rheumatism* 2002; **46**: 2445-2452.

19. Feldmann J, Prieur AM, Quartier P*, et al.* Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. *American Journal of Human Genetics* 2002; **71**: 198-203.
20. Aksentijevich I, Nowak M, Mallah M*, et al.* De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): A new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis and Rheumatism* 2002; **46**: 3340-3348.
21. Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome [8]. *New England Journal of Medicine* 2003; **348**: 2583-2584.
22. Goldbach-Mansky R, Dailey NJ, Canna SW*, et al.* Neonatal-onset multisystem inflammatory disease responsive to interleukin-1β inhibition. *New England Journal of Medicine* 2006; **355**: 581-592.
23. Lovell DJ, Bowyer SL, Solinger AM. Interleukin-1 blockade by anakinra improves clinical symptoms in patients with neonatal-onset multisystem inflammatory disease. *Arthritis and Rheumatism* 2005; **52**: 1283-1286.
24. Gattorno M, Obici L, Cattalini M*, et al.* Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): An open-label, phase II study. *Annals of the Rheumatic Diseases* 2016.
25. van der Hilst JCH, Moutschen M, Messiaen PE*, et al.* Efficacy of anti-IL-1 treatment in familial mediterranean fever: A systematic review of the literature. *Biologics: Targets and Therapy* 2016; **10**: 75-80.
26. Savic S, Dickie LJ, Battellino M*, et al.* Familial mediterranean fever and related periodic fever syndromes/autoinflammatory diseases. *Current Opinion in Rheumatology* 2012; **24**: 103-112.
27. Aksentijevich I, Masters SL, Ferguson PJ*, et al.* An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *New England Journal of Medicine* 2009; **360**: 2426-2437.
28. Marrakchi S, Guigue P, Renshaw BR*, et al.* Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *New England Journal of Medicine* 2011; **365**: 620-628.
29. Onoufriadis A, Simpson MA, Pink AE*, et al.* Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *American Journal of Human Genetics* 2011; **89**: 432-437.
30. Wulffraat NM, Woo P. Canakinumab in pediatric rheumatic diseases. *Expert Opinion on Biological Therapy* 2013; **13**: 615-622.
31. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB*, et al.* Use of canakinumab in the cryopyrin-associated periodic syndrome. *New England Journal of Medicine* 2009; **360**: 2416-2425.
32. Schlesinger N. Anti-interleukin-1 therapy in the management of gout. *Current Rheumatology Reports* 2014; **16**.
33. Gattorno M, Piccini A, Lasigliè D*, et al.* The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-

onset juvenile idiopathic arthritis. *Arthritis and Rheumatism* 2008; **58**: 1505-1515.

34. Dinarello CA, van der Meer JWM. Treating inflammation by blocking interleukin-1 in humans. *Seminars in Immunology* 2013; **25**: 469-484.
35. Saito M, Fujisawa A, Nishikomori R*, et al.* Somatic mosaicism of CIAS1 in a patient with chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis and Rheumatism* 2005; **52**: 3579-3585.
36. Shinar Y, Tohami T, Livneh A*, et al.* Acquired familial Mediterranean fever associated with a somatic MEFV mutation in a patient with JAK2 associated post-polycythemia myelofibrosis. *Orphanet Journal of Rare Diseases* 2015; **10**.
37. Rowczenio DM, Trojer H, Omoyinmi E*, et al.* Brief Report: Association of Tumor Necrosis Factor Receptor‐Associated Periodic Syndrome With Gonosomal Mosaicism of a Novel 24‐Nucleotide TNFRSF1A Deletion. *Arthritis & Rheumatology* 2016; **68**: 2044-2049.
38. Crow YJ, Hayward BE, Parmar R*, et al.* Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 cause Aicardi-Goutières syndrome at the AGS1 locus. *Nature Genetics* 2006; **38**: 917-920.
39. Volpi S, Picco P, Caorsi R*, et al.* Type I interferonopathies in pediatric rheumatology. *Pediatric Rheumatology* 2016; **14**.
40. Crow YJ. Type I interferonopathies: Mendelian type I interferon up-regulation. *Current Opinion in Immunology* 2015; **32**: 7-12.
41. Stetson DB, Ko JS, Heidmann T*, et al.* Trex1 Prevents Cell-Intrinsic Initiation of Autoimmunity. *Cell* 2008; **134**: 587-598.
42. Rice GI, Bond J, Asipu A*, et al.* Mutations involved in Aicardi-Goutières syndrome implicate SAMHD1 as regulator of the innate immune response. *Nature Genetics* 2009; **41**: 829-832.
43. Rice GI, Rodero MP, Crow YJ. Human Disease Phenotypes Associated With Mutations in TREX1. *Journal of Clinical Immunology* 2015; **35**: 235-243.
44. Lee-Kirsch MA, Gong M, Schulz H*, et al.* Familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus, maps to chromosome 3p. *American Journal of Human Genetics* 2006; **79**: 731-737.
45. Rice GI, Del Toro Duany Y, Jenkinson EM*, et al.* Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type i interferon signaling. *Nature Genetics* 2014; **46**: 503-509.
46. Savic S, McDermott MF. Clinical genetics in 2014: New monogenic diseases span the immunological disease continuum. *Nature Reviews Rheumatology* 2015; **11**: 67-68.
47. Sullivan KE, Stiehm ER. Stiehm's Immune Deficiencies. ed). 2014.
48. Liu Y, Ramot Y, Torrelo A*, et al.* Mutations in proteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis and Rheumatism* 2012; **64**: 895-907.
49. Liu Y, Jesus AA, Marrero B*, et al.* Activated STING in a vascular and pulmonary syndrome. *New England Journal of Medicine* 2014; **371**: 507-518.
50. van Kempen TS, Wenink MH, Leijten EF*, et al.* Perception of self: distinguishing autoimmunity from autoinflammation. *Nat Rev Rheumatol* 2015; **11**: 483-492.
51. Wu J, Li X, Zhu G*, et al.* The role of Resveratrol-induced mitophagy/autophagy in peritoneal mesothelial cells inflammatory injury via NLRP3 inflammasome activation triggered by mitochondrial ROS. *Exp Cell Res* 2016; **341**: 42-53.

52. Abdelaziz DH, Khalil H, Cormet-Boyaka E*, et al.* The cooperation between the autophagy machinery and the inflammasome to implement an appropriate innate immune response: do they regulate each other? *Immunol Rev* 2015; **265**: 194-204.

53. Jabir MS, Hopkins L, Ritchie ND*, et al.* Mitochondrial damage contributes to Pseudomonas aeruginosa activation of the inflammasome and is downregulated by autophagy. *Autophagy* 2015; **11**: 166-182.

54. Liu L, Yang M, Kang R*, et al.* HMGB1-DNA complex-induced autophagy limits AIM2 inflammasome activation through RAGE. *Biochem Biophys Res Commun* 2014; **450**: 851-856.

55. Cho MH, Cho K, Kang HJ*, et al.* Autophagy in microglia degrades extracellular beta-amyloid fibrils and regulates the NLRP3 inflammasome. *Autophagy* 2014; **10**: 1761-1775.

56. Rodgers MA, Bowman JW, Liang Q*, et al.* Regulation where autophagy intersects the inflammasome. *Antioxid Redox Signal* 2014; **20**: 495-506.

57. Shi H, Zhang Z, Wang X*, et al.* Inhibition of autophagy induces IL-1beta release from ARPE-19 cells via ROS mediated NLRP3 inflammasome activation under high glucose stress. *Biochem Biophys Res Commun* 2015; **463**: 1071-1076.

58. Agyemang AF, Harrison SR, Siegel RM*, et al.* Protein misfolding and dysregulated protein homeostasis in autoinflammatory diseases and beyond. *Semin Immunopathol* 2015; **37**: 335-347.

59. Bachetti T, Chiesa S, Castagnola P*, et al.* Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS). *Ann Rheum Dis* 2013; **72**: 1044-1052.

60. Bachetti T, Ceccherini I. Tumor necrosis factor receptor-associated periodic syndrome as a model linking autophagy and inflammation in protein aggregation diseases. *J Mol Med (Berl)* 2014; **92**: 583-594.

61. Luciani A, Villella VR, Esposito S*, et al.* Defective CFTR induces aggresome formation and lung inflammation in cystic fibrosis through ROS-mediated autophagy inhibition. *Nat Cell Biol* 2010; **12**: 863-875.

62. Luciani A, Villella VR, Esposito S*, et al.* Cystic fibrosis: A disorder with defective autophagy. *Autophagy* 2014; **7**: 104-106.

63. Luciani A, Villella VR, Esposito S*, et al.* Targeting autophagy as a novel strategy for facilitating the therapeutic action of potentiators on DeltaF508 cystic fibrosis transmembrane conductance regulator. *Autophagy* 2012; **8**: 1657-1672.

64. Assani K, Tazi MF, Amer AO*, et al.* IFN-gamma stimulates autophagy-mediated clearance of Burkholderia cenocepacia in human cystic fibrosis macrophages. *PLoS One* 2014; **9**: e96681.

65. Al-Khodor S, Marshall-Batty K, Nair V*, et al.* Burkholderia cenocepacia J2315 escapes to the cytosol and actively subverts autophagy in human macrophages. *Cell Microbiol* 2014; **16**: 378-395.

66. Brehm A, Liu Y, Sheikh A*, et al.* Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type i IFN production. *Journal of Clinical Investigation* 2015; **125**: 4196-4211.

67. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *New England Journal of Medicine* 2005; **352**: 2039.

68. Elborn JS. Cystic fibrosis. *The Lancet* 2016.

69. Grassmé H, Carpinteiro A, Edwards MJ*, et al.* Regulation of the inflammasome by ceramide in cystic fibrosis lungs. *Cell Physiol Biochem* 2014; **34**: 45-55.

70. Tang A, Sharma A, Jen R*, et al.* Inflammasome-mediated IL-1β production in humans with cystic fibrosis. *PLoS One* 2012; **7**: e37689.

71. Becker KA, Grassmé H, Zhang Y*, et al.* Ceramide in Pseudomonas aeruginosa infections and cystic fibrosis. *Cell Physiol Biochem* 2010; **26**: 57-66.

72. Dixey J, Redington AN, Butler RC*, et al.* The arthropathy of cystic fibrosis. *Annals of the Rheumatic Diseases* 1988; **47**: 218-223.

73. Bonfield TL, Panuska JR, Konstan MW*, et al.* Inflammatory cytokines in cystic fibrosis lungs. *American journal of respiratory and critical care medicine* 1995; **152**: 2111-2118.

74. Horsley A, Helm J, Brennan A*, et al.* Gout and hyperuricaemia in adults with cystic fibrosis. *Journal of the Royal Society of Medicine* 2011; **104 Suppl 1**: S36-39.

75. Garnett JP, Nguyen TT, Moffatt JD*, et al.* Proinflammatory mediators disrupt glucose homeostasis in airway surface liquid. *Journal of immunology* 2012; **189**: 373-380.

76. Brennan AL, Gyi KM, Wood DM*, et al.* Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* 2007; **6**: 101-109.

77. Martinon F, Petrilli V, Mayor A*, et al.* Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006; **440**: 237-241.

78. Ghaemi-Oskouie F, Shi Y. The role of uric acid as an endogenous danger signal in immunity and inflammation. *Curr Rheumatol Rep* 2011; **13**: 160-166.

79. Rajamaki K, Nordstrom T, Nurmi K*, et al.* Extracellular acidosis is a novel danger signal alerting innate immunity via the NLRP3 inflammasome. *J Biol Chem* 2013; **288**: 13410-13419.

80. Ribeiro CM, Boucher RC. Role of endoplasmic reticulum stress in cystic fibrosis-related airway inflammatory responses. *Proc Am Thorac Soc* 2010; **7**: 387-394.

81. Tosco A, De Gregorio F, Esposito S*, et al.* A novel treatment of cystic fibrosis acting on-target: cysteamine plus epigallocatechin gallate for the autophagy-dependent rescue of class II-mutated CFTR. *Cell Death Differ* 2016.

82. Saitoh T, Akira S. Regulation of inflammasomes by autophagy. *J Allergy Clin Immunol* 2016; **138**: 28-36.

83. Choi AJ, Ryter SW. Autophagy in inflammatory diseases. *Int J Cell Biol* 2011; **2011**: 732798.

84. Zhang PX, Cheng JJ, Zou SY*, et al.* Pharmacological modulation of the AKT/microRNA-199a-5p/CAV1 pathway ameliorates cystic fibrosis lung hyper-inflammation. *Nature Communications* 2015; **6**.

85. Zhang PX, Cheng J, Zou S*, et al.* Pharmacological modulation of the AKT/microRNA-199a-5p/CAV1 pathway ameliorates cystic fibrosis lung hyper-inflammation. *Nat Commun* 2015; **6**: 6221.

86. Iannitti RG, Napolioni V, Oikonomou V*, et al.* IL-1 receptor antagonist ameliorates inflammasome-dependent inflammation in murine and human cystic fibrosis. *Nature Communications* 2016; **7**.

87. Blohmke CJ, Mayer ML, Tang AC*, et al.* Atypical activation of the unfolded protein response in cystic fibrosis airway cells contributes to p38 MAPK-mediated innate immune responses. *J Immunol* 2012; **189**: 5467-5475.

88. Fitch G, Williams K, Freeston JE*, et al.* Ultrasound and magnetic resonance imaging assessment of joint disease in symptomatic patients with cystic fibrosis arthropathy. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* 2016.

89. Ng HP, Zhou Y, Song K*, et al.* Neutrophil-mediated phagocytic host defense defect in myeloid Cftr-inactivated mice. *PloS one* 2014; **9**: e106813.
90. Pohl K, Hayes E, Keenan J*, et al.* A neutrophil intrinsic impairment affecting Rab27a and degranulation in cystic fibrosis is corrected by CFTR potentiator therapy. *Blood* 2014; **124**: 999-1009.
91. Su X, Looney MR, Su HE*, et al.* Role of CFTR expressed by neutrophils in modulating acute lung inflammation and injury in mice. *Inflamm Res* 2011; **60**: 619-632.
92. Tirouvanziam R, Gernez Y, Conrad CK*, et al.* Profound functional and signaling changes in viable inflammatory neutrophils homing to cystic fibrosis airways. *Proc Natl Acad Sci U S A* 2008; **105**: 4335-4339.
93. Chan HC, Jiang XH, Ruan YC. Emerging role of cystic fibrosis transmembrane conductance regulator as an epigenetic regulator: linking environmental cues to microRNAs. *Clin Exp Pharmacol P* 2014; **41**: 615-622.
94. Said-Sadier N, Padilla E, Langsley G*, et al.* Aspergillus fumigatus stimulates the NLRP3 inflammasome through a pathway requiring ROS production and the Syk tyrosine kinase. *PLoS One* 2010; **5**: e10008.
95. Moriyama M, Chen IY, Kawaguchi A*, et al.* The RNA- and TRIM25-Binding Domains of Influenza Virus NS1 Protein Are Essential for Suppression of NLRP3 Inflammasome-Mediated Interleukin-1beta Secretion. *J Virol* 2016; **90**: 4105-4114.
96. Triantafilou K, Kar S, van Kuppeveld FJ*, et al.* Rhinovirus-induced calcium flux triggers NLRP3 and NLRC5 activation in bronchial cells. *Am J Respir Cell Mol Biol* 2013; **49**: 923-934.
97. Courtney JM, Dunbar KE, McDowell A*, et al.* Clinical outcome of Burkholderia cepacia complex infection in cystic fibrosis adults. *J Cyst Fibros* 2004; **3**: 93-98.
98. Etherington C, Naseer R, Conway SP*, et al.* The role of respiratory viruses in adult patients with cystic fibrosis receiving intravenous antibiotics for a pulmonary exacerbation. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* 2014; **13**: 49-55.
99. Flight WG, Bright-Thomas RJ, Tilston P*, et al.* Incidence and clinical impact of respiratory viruses in adults with cystic fibrosis. *Thorax* 2014; **69**: 247-253.
100. Allen IC, Scull MA, Moore CB*, et al.* The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA. *Immunity* 2009; **30**: 556-565.
101. Gavrilin MA, Abdelaziz DH, Mostafa M*, et al.* Activation of the pyrin inflammasome by intracellular Burkholderia cenocepacia. *Journal of immunology* 2012; **188**: 3469-3477.
102. Abdulrahman BA, Abu Khweek A, Akhter A*, et al.* Autophagy stimulation by rapamycin suppresses lung inflammation and infection by Burkholderia cenocepacia in a model of cystic fibrosis. *Autophagy* 2011; **7**: 1359-1370.
103. Di Lorenzo F, Silipo A, Bianconi I*, et al.* Persistent cystic fibrosis isolate Pseudomonas aeruginosa strain RP73 exhibits an under-acylated LPS structure responsible of its low inflammatory activity. *Mol Immunol* 2015; **63**: 166-175.
104. Martinon F, Chen X, Lee AH*, et al.* TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages. *Nature Immunology* 2010; **11**: 411-418.

105. Qiu Q, Zheng Z, Chang L*, et al.* Toll-like receptor-mediated IRE1α activation as a therapeutic target for inflammatory arthritis. *EMBO Journal* 2013; **32**: 2477-2490.

106. Bulua AC, Simon A, Maddipati R*, et al.* Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). *Journal of Experimental Medicine* 2011; **208**: 519-533.

107. Dickie LJ, Aziz AM, Savic S*, et al.* Involvement of X-box binding protein 1 and reactive oxygen species pathways in the pathogenesis of tumour necrosis factor receptor-associated periodic syndrome. *Annals of the Rheumatic Diseases* 2012; **71**: 2035-2043.

108. Martino MEB, Olsen JC, Fulcher NB*, et al.* Airway epithelial inflammation-induced endoplasmic reticulum Ca2+ store expansion is mediated by X-box binding protein-1. *Journal of Biological Chemistry* 2009; **284**: 14904-14913.

109. Rimessi A, Bezzerri V, Patergnani S*, et al.* Mitochondrial Ca2+-dependent NLRP3 activation exacerbates the Pseudomonas aeruginosa-driven inflammatory response in cystic fibrosis. *Nat Commun* 2015; **6**: 6201.

110. Abais JM, Xia M, Zhang Y*, et al.* Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? *Antioxid Redox Signal* 2015; **22**: 1111-1129.

111. Hernandez ML, Mills K, Almond M*, et al.* IL-1 receptor antagonist reduces endotoxin-induced airway inflammation in healthy volunteers. *Journal of Allergy and Clinical Immunology* 2015; **135**: 379-385.

112. Tang A, Sharma A, Jen R*, et al.* Inflammasome-mediated IL-1beta production in humans with cystic fibrosis. *PLoS One* 2012; **7**: e37689.

113. Bronner DN, Abuaita BH, Chen X*, et al.* Endoplasmic Reticulum Stress Activates the Inflammasome via NLRP3- and Caspase-2-Driven Mitochondrial Damage. *Immunity* 2015; **43**: 451-462.

114. Lubamba BA, Jones LC, O'Neal WK*, et al.* X-box-binding protein 1 and innate immune responses of human cystic fibrosis alveolar macrophages. *Am J Resp Crit Care* 2015; **192**: 1449-1461.

115. Savic S, Ouboussad L, Dickie LJ*, et al.* TLR dependent XBP-1 activation induces an autocrine loop in rheumatoid arthritis synoviocytes. *J Autoimmun* 2014; **50**: 59-66.

116. Iannitti RG, Napolioni V, Oikonomou V*, et al.* IL-1 receptor antagonist ameliorates inflammasome-dependent inflammation in murine and human cystic fibrosis. *Nat Commun* 2016; **7**: 10791.

117. Bodar EJ, van der Hilst JCH, Drenth JPH*, et al.* Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: Introducing a vaccination provocation model. *Netherlands Journal of Medicine* 2005; **63**: 260-264.

118. Campbell L, Raheem I, Malemud CJ*, et al.* The relationship between NALP3 and autoinflammatory syndromes. *International Journal of Molecular Sciences* 2016; **17**.

119. Galeotti C, Meinzer U, Quartier P*, et al.* Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. *Rheumatology (United Kingdom)* 2012; **51**: 1855-1859.

120. Park YH, Wood G, Kastner DL*, et al.* Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. *Nat Immunol* 2016; **17**: 914-921.

121. Wittmann M, Kingsbury SR, McDermott MF. Is caspase 1 central to activation of interleukin-1? *Joint Bone Spine* 2011; **78**: 327-330.

122. Celsi F, Piscianz E, Romano M*, et al.* Knockdown of MVK does not lead to changes in NALP3 expression or activation. *Journal of Inflammation (United Kingdom)* 2015; **12**.

123. Van de Weert-van Leeuwen PB, Van Meegen MA, Speirs JJ*, et al.* Optimal complement-mediated phagocytosis of Pseudomonas aeruginosa by monocytes is cystic fibrosis transmembrane conductance regulator-dependent. *Am J Respir Cell Mol Biol* 2013; **49**: 463-470.

124. Bento CF, Puri C, Moreau K*, et al.* The role of membrane-trafficking small GTPases in the regulation of autophagy. *Journal of Cell Science* 2013; **126**: 1059-1069.

125. Xu H, Yang J, Gao W*, et al.* Innate immune sensing of bacterial modifications of Rho GTPases by the Pyrin inflammasome. *Nature* 2014; **513**: 237-241.

126. Harris J, Hartman M, Roche C*, et al.* Autophagy controls IL-1β secretion by targeting Pro-IL-1β for degradation. *Journal of Biological Chemistry* 2011; **286**: 9587-9597.

127. Shi CS, Shenderov K, Huang NN*, et al.* Activation of autophagy by inflammatory signals limits IL-1β production by targeting ubiquitinated inflammasomes for destruction. *Nature Immunology* 2012; **13**: 255-263.

128. Wolf AJ, Reyes CN, Liang W*, et al.* Hexokinase Is an Innate Immune Receptor for the Detection of Bacterial Peptidoglycan. *Cell* 2015.

129. Poulton KR, Nightingale S. A new metabolic muscle disease due to abnormal hexokinase activity. *Journal of Neurology Neurosurgery and Psychiatry* 1988; **51**: 250-255.

130. Wang ZV, Deng Y, Gao N*, et al.* Spliced X-box binding protein 1 couples the unfolded protein response to hexosamine biosynthetic pathway. *Cell* 2014; **156**: 1179-1192.

131. Chouchani ET, Pell VR, Gaude E*, et al.* Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. *Nature* 2014; **515**: 431-435.

132. Kong F, Ye B, Lin L*, et al.* Atorvastatin suppresses NLRP3 inflammasome activation via TLR4/MyD88/NF-κB signaling in PMA-stimulated THP-1 monocytes. *Biomedicine and Pharmacotherapy* 2016; **82**: 167-172.

133. Mimura N, Fulciniti M, Gorgun G*, et al.* Blockade of XBP1 splicing by inhibition of IRE1alpha is a promising therapeutic option in multiple myeloma. *Blood* 2012; **119**: 5772-5781.

134. Coll RC, Robertson AA, Chae JJ*, et al.* A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nat Med* 2015; **21**: 248-255.

135. Youm YH, Nguyen KY, Grant RW*, et al.* The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med* 2015; **21**: 263-269.

136. Yang JL, Xu H, Shao F. The immunological function of familial Mediterranean fever disease protein Pyrin. *Science China Life Sciences* 2014; **57**: 1156-1161.

137. Masters SL, Lagou V, Jéru I*, et al.* Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation. *Science Translational Medicine* 2016; **8**.

138. Zhou Q, Wang H, Schwartz DM, *et al.* Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. *Nature Genetics* 2015; **48**: 67-73.

139. Wartz IE, O'Rourke KM, Zhou H, *et al.* De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-κB signalling. *Nature* 2004; **430**: 694-699.

140. Takeuchi M, Kastner DL, Remmers EF. The immunogenetics of Behçet's disease: A comprehensive review. *Journal of Autoimmunity* 2015; **64**: 137-148.

141. Zhou Q, Xiaomin Y, Demirkaya E, *et al.* Biallelic hypomorphic mutations in a linear deubiquitinasedefine otulipenia, an early-onset autoinflammatory disease. *Proceedings of the National Academy of Sciences of the United States of America* 2016; **In Press**.

142. Jéru I, Cochet E, Duquesnoy P, *et al.* Involvement of TNFRSF11A molecular defects in autoinflammatory disorders. *Arthritis and Rheumatology* 2014; **66**: 2621-2627.

143. Jo EK, Kim JK, Shin DM, *et al.* Molecular mechanisms regulating NLRP3 inflammasome activation. *Cellular and Molecular Immunology* 2016; **13**: 148-159.

144. Walker UA, Hoffman HM, Williams R, *et al.* Brief Report: Severe Inflammation Following Vaccination Against Streptococcus pneumoniae in Patients with Cryopyrin-Associated Periodic Syndromes. *Arthritis and Rheumatology* 2016; **68**: 516-520.

145. Iyer S, He Q, Janczy J, *et al.* Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. *Immunity* 2013; **39**: 311-323.

146. Iyer SS, Pulskens WP, Sadler JJ, *et al.* Necrotic cells trigger a sterile inflammatory response through the Nlrp3 inflammasome. *Proceedings of the National Academy of Sciences of the United States of America* 2009; **106**: 20388-20393.

147. Lawlor KE, Khan N, Mildenhall A, *et al.* RIPK3 promotes cell death and NLRP3 inflammasome activation in the absence of MLKL. *Nature Communications* 2015; **6**.

148. Alarcón-Riquelme ME. Nucleic acid by-products and chronic inflammation. *Nature Genetics* 2006; **38**: 866-867.

149. Dennis Jr G, Holweg CTJ, Kummerfeld SK, *et al.* Synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics. *Arthritis Research and Therapy* 2014; **16**.

150. Lenart N, Brough D, Denes A. Inflammasomes link vascular disease with neuroinflammation and brain disorders. *J Cereb Blood Flow Metab* 2016.

151. Abderrazak A, Syrovets T, Couchie D, *et al.* NLRP3 inflammasome: From a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases. *Redox Biology* 2015; **4**: 296-307.

152. Ter Haar NM, Oswald M, Jeyaratnam J, *et al.* Recommendations for the management of autoinflammatory diseases. *Annals of the Rheumatic Diseases* 2015; **74**: 1636-1644.

153. Sarrabay G, Touitou I. Autoinflammation: Management of hereditary recurrent fevers - SHARE experience. *Nature Reviews Rheumatology* 2015; **11**: 567-569.

154. Ombrello MJ, Remmers EF, Sun G, *et al.* Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. *New England Journal of Medicine* 2012; **366**: 330-338.

155. Kuehn HS, Ouyang W, Lo B, *et al.* Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. *Science* 2014; **345**: 1623-1627.

156. Starokadomskyy P, Gemelli T, Rios JJ*, et al.* DNA polymerase-α regulates the activation of type i interferons through cytosolic RNA:DNA synthesis. *Nature Immunology* 2016; **17**: 495-504.

157. Zhou Q, Yang D, Ombrello AK*, et al.* Early-onset stroke and vasculopathy associated with mutations in ADA2. *New England Journal of Medicine* 2014; **370**: 911-920.

158. Elkan PN, Pierce SB, Segel R*, et al.* Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *New England Journal of Medicine* 2014; **370**: 921-931.

159. Proal AD, Albert PJ, Marshall TG. The human microbiome and autoimmunity. *Current Opinion in Rheumatology* 2013; **25**: 234-240.

160. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; **157**: 121-141.

## Legends for Figures and Table

### Figure 1: Diseases classified according myeloid (autoinflammation) or lymphoid lineage (autoimmune).

Diseases of the immune system are classified according to whether the lymphocyte responsible for the disease is of myeloid (autoinflammation) or lymphoid lineage (autoimmune). Clinical heterogeneity within immunological diseases may reflect the variable expression of autoinflammatory and autoimmune factors in disease causation.

A disease spectrum that includes rare monogenic diseases at the polar ends of the spectrum, and polygenic diseases, involving both myeloid and lymphoid cells in pathogenesis, occupying the centre [10]. This diagram adds a third variable, environmental triggers, to further define the pathogenesis of these diseases. The figure does not include all immunologically recognised diseases because of their large number.

HIDS- hyper IgD syndrome, CAPS- cryopyrin-associated autoinflammatory syndrome, FMF- familial Mediterranean fever, TRAPS- tumour necrosis factor receptor associated periodic syndrome, sJIA- systemic juvenile idiopathic arthritis, AOSD- adult onset Still's disease, RA- rheumatoid arthritis, CF- cystic fibrosis, SLE- systemic lupus erythematosus, T1D- type 1 diabetes,  APS-1- autoimmune polyglandular syndrome type 1, PLAID- PLCG2 associated antibody deficiency and immune dysregulation, ALPS- autoimmune lymphoproliferative syndrome, IPEX- immune dysregulation polyendocrinopathy enteropathy X-linked syndrome.

**Figure 2: Priming, assembly and degradation of the NLRP3 inflammasome.** An activating signal is required for the NLRP3 inflammasome to be assembled - examples include ATP-dependent K efflux, particulate substances, such as urate crystals entering the cell through lysosomal degredation pathways, mitochondrial damage and release of mtDNA or mtROS and intracellular pathogen recognition. The ligand for the NLRP3 inflammasome in humans is pro-caspase-1. Once activated, caspase-1 cleaves and activates inactive cytokines pro-IL-1β and pro-IL-18. A second priming signal is required to induce pro-IL-1β and pro-IL-18 expression. This is typically through NF-κB signalling, downstream of TLRs, or through XBP-1 downstream of the UPR. Once the inflammatory stimulus has subsided the NLRP3 inflammasome is cleared by autophagolysosomal degradation.

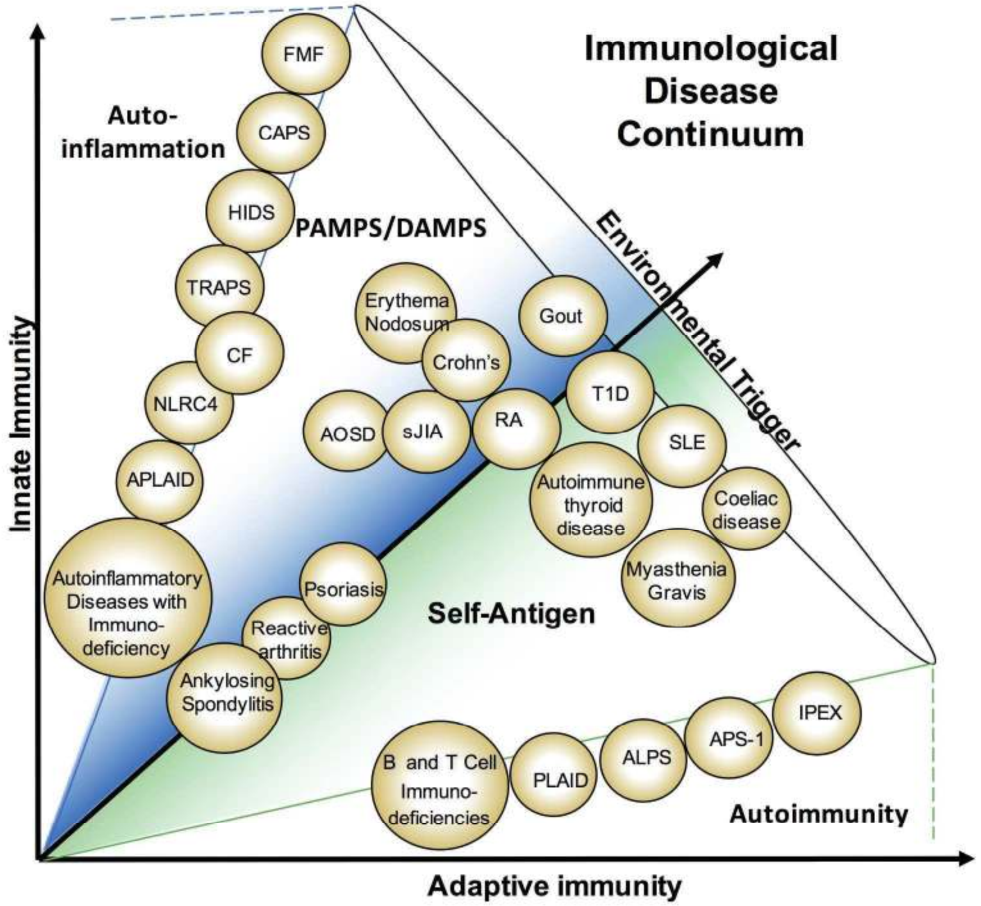
**Figure 3: Cystic fibrosis as an autoinflammatory disease.** CF shares many common features of autoinflammatory diseases. Due to the mutated CFTR, there is increased ROS signalling and reduced antioxidant secretion. CF also manifests with hyperuricaemia, low airway surface pH, ASL dehydration and high glucose levels, all thought to be triggers of the NLRP3 inflamamsome. CFTR mutations may cause extreme ionic imbalances, many of which have been linked with NLRP3 inflammasome activation. As the CFTR is misfolded in many genotypes of CF, this results in ER stress, UPR activation, and XBP1 signalling. Finally, increased lung infections provide frequent activation of the TLR-NF-κB inflammatory signalling pathway, priming the NLRP3 inflamamsome.

**Figure 4: Inflammasome/IL-1 pathways in autoinflammation.**

When mutations in the NLRP3 inflammasome pathway or excessive/continuous stimuli interfere with its activation or priming, this inflammasome becomes the hub of life-limiting innate immune-driven diseases. Gout (yellow arrow), TRAPS (green arrow), MWS (red arrow), FMF (blue arrow) and HIDS (orange arrow) are examples of autoinflammatory conditions where the NLRP3 inflammasome is at the centre of disease pathology.

**Table 1: Autoinflammatory diseases.**

An update on the mechanisms involved in the autoinflammatory diseases mentioned in this review. A more comprehensive list of these diseases exists in de Jesus *et al.*'s review [3].



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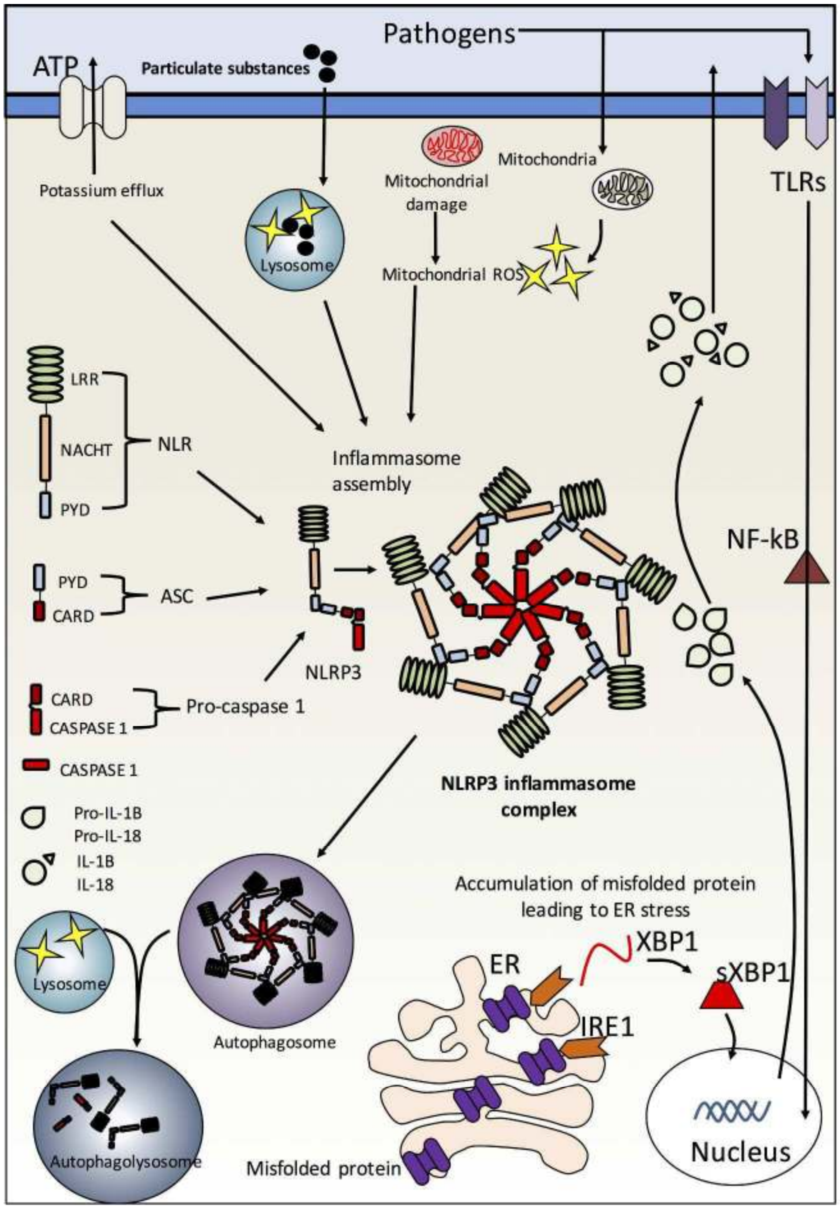

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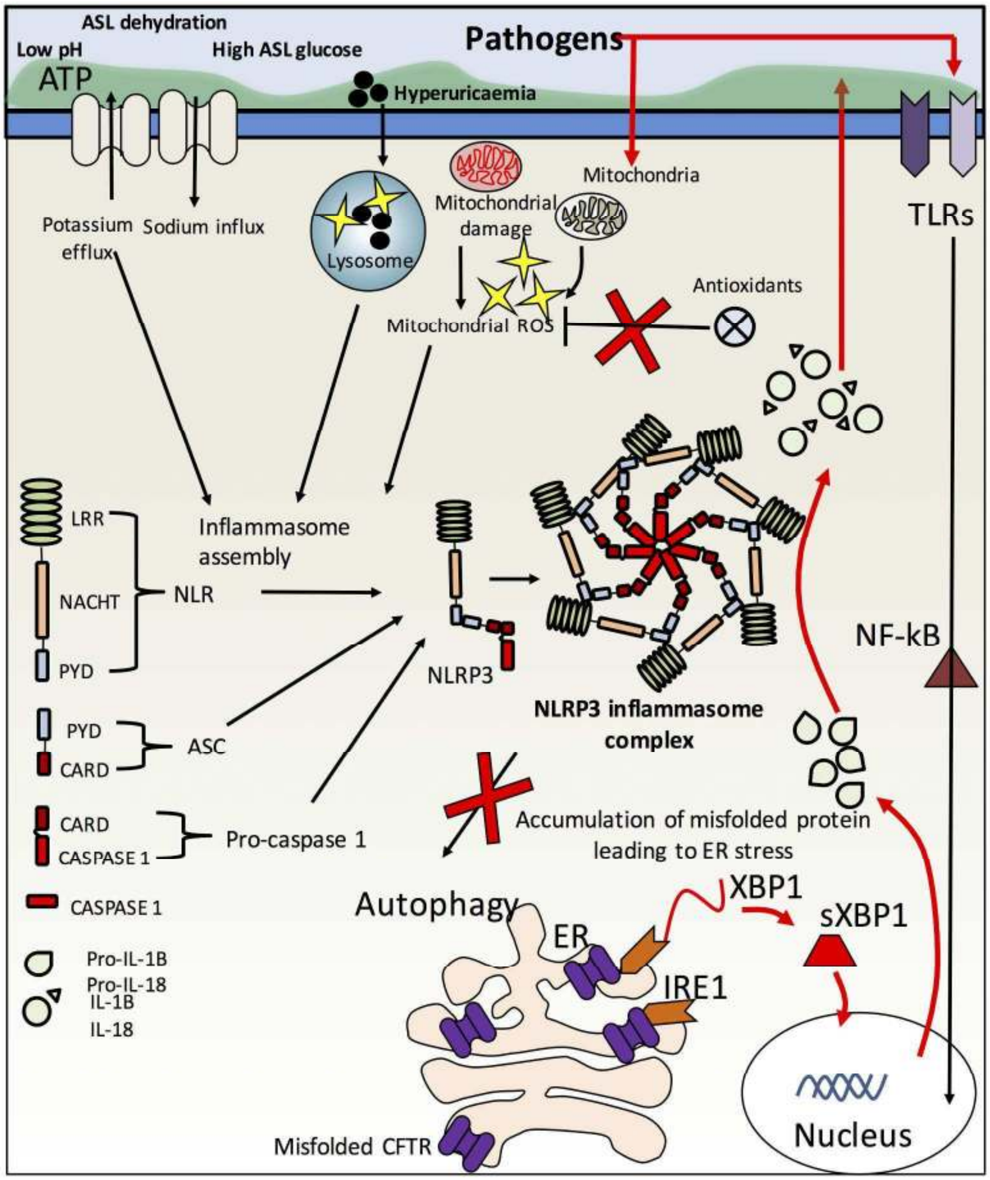

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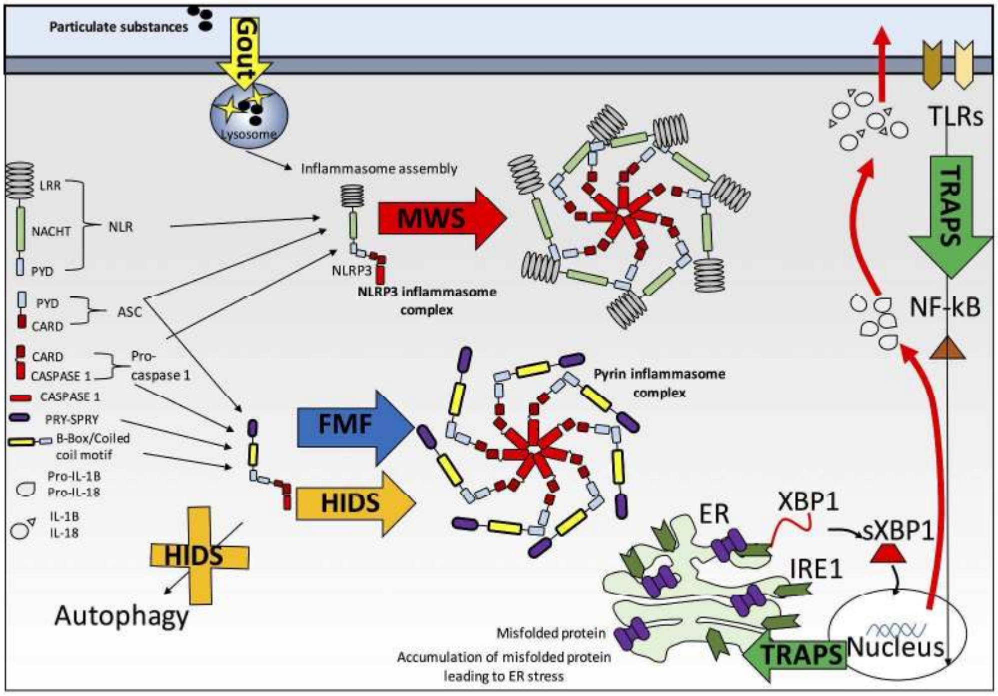

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| Category | Name | Gene | Mechanism | Therapy |
|---|---|---|---|---|
| **IL-1** | HIDS | *MVK* | Mutated mevalonate kinase causes reduced isoprenoid synthesis, leading to reduced prenylation of RhoA, activating the pyrin inflammasome. Reduced prenylation disrupts autophagy and ROS clearance, activating NLRP3. | IL-1 inhibition |
| | CAPS (FCAS, MWS, CINCA, NOMID) | *NLRP3* | Constitutive NLRP3 inflammasome activation | IL-1 inhibition |
| | DIRA | *IL1RN* | IL-1RA deficiency | IL-1 inhibition |
| | DITRA | *IL36RN* | IL-36RA deficiency | IL-1 inhibition |
| | MAS | *NLRC4* | Uncontrolled macrophage activation, with increased secretion of IL-18, IFN-gamma and GM-CSF. Mechanism unknown. | Not defined - tocilizumab |
| | PAAND | *MEFV* | Pyrin inflammasome activation | IL-1 inhibition |
| | FMF | *MEFV* | Pyrin inflammasome activation | NSAIDS, colchicine, IL-1 inhibition |
| **UPR** | Cystic fibrosis | *CFTR* | Mutated CFTR, causing multisystem disease due to ionic imbalance and ER stress. NLRP3, NLRC4, UPR. | Antibiotics and NSAIDs |
| | TRAPS | *TNFR1* | TNF receptor activation, UPR, NLRP3 activation | IL-1 inhibition |
| **IFN** | Aicardi-Goutières syndromes (AGS) | *TREX1, RNASEH2B, RNASEH2C, RNASEH2A, SAMHD1, ADAR* | Aberrant sensing of DNA/RNA, with excessive IFN-producing responses | JAK inhibitors, Sifalimumab |
| | CANDLE/PRAAS syndrome | *PSMB8* | Gain of function mutation, UPR, IFN signature | JAK inhibitors |
| | Bechet's disease | Polygenic, *HLA-B51* | Unknown. Autoinflammation/autoimmune destruction of blood vessels with IFN signature. | Anti-TNF inhibitors |
| | XLPR | *POLA1* | Dysfunctional DNA polymerase-α catalytic subunit | |
| | SAVI | *STING* | Gain of function mutation | JAK inhibitors |
| **Immunodeficiency/ Immunodysfunction** | HCTLA4 | *CTLA4* | Dysregulated FoxP3$^+$ Treg cells | Immunoglobulin replacement thaerapy |
| | DADA2 | *CECR1* | Reduced ADA2 enzyme function | Steroids, plasma to restore ADA2 |
| | AGS7 | *IFIH1* | Dysfunctional sensing of nucleic acids | None |
| | PLAID | *PLCG2, CTLA-4* | Adaptive immunodeficiency | Antihistamines |
| **Granulomatous disease** | Blau Syndrome | *CARD15/NOD2* | Hyperactive NF-κB signalling | Steroids, anti-TNF inhibitors, IL-1 inhibition |
| | Crohn's disease | Polygenic, *CARD15/NOD2* | Hyperactive NF-κB signalling | Anti-TNF inhibitors |
| **Dysregulated Ubiquitination** | Haploinsufficiency of A20 | *TNFAIP3* | Loss of NF-κB and IL-1 negative feedback | IL-1 inhibition |
| | OTULIN | *OTULIN* | Dysfunctional ubiquitation and hyperactive NF–κB signalling | Steroids, anti-TNF inhibitors, IL-1 inhibition |

Autoinflammatory diseases

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