

The autoinflammatory diseases

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Summary

The monogenic autoinflammatory syndromes are conditions caused by mutations of genes coding for proteins that play a pivotal role in the regulation of the inflammatory response.

Due to their genetic nature, most of these disorders have an early onset.

Clinically they are characterised by recurrent flares of systemic inflammation presenting most of the time as sudden fever episodes associated with elevation of acute phase reactants and with a number of clinical manifestations such as rash, serositis, lymphadenopathy and arthritis.

Symptom-free intervals are characterised by complete wellbeing, normal growth and complete normalisation of acute phase reactants.

Familial Mediterranean fever (FMF), mevalonate-kinase deficiency (MKD) and tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) are the three monogenic disorders subsumed under the term periodic fevers, while a systemic inflammation dominated by a characteristic urticarial rash associated with a number of other clinical manifestations is typical of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA). These diseases represent the clinical spectrum of different mutations of a gene named cold-induced autoinflammatory syndrome 1 (CIAS-1, or NLRP3) coding for a protein called cryopyrin. Hence these disorders are also known as cryopyrin-associated periodic syndromes (CAPS).

Other conditions are characterised by typical granulomatous formations (granulomatous disorders). Blau's syndrome (familial juvenile systemic granulomatosis) presents with non-caseating granulomatous inflammation affecting the joint, skin, and uveal tract (the triad of arthritis, dermatitis and uveitis) and is associated with mutations of the NACHT domain of the gene CARD15 (or NOD2).

Key words: *autoinflammatory syndromes; periodic fever; familial Mediterranean fever; mevalonate-kinase deficiency; TRAPS; cryopyrin-associated periodic syndromes (CAPS); Blau's syndrome; PAPA syndrome; DIRA; inflammasome*

Introduction

Under the term monogenic autoinflammatory syndromes are subsumed a number of different conditions secondary to mutations of genes coding for proteins that play a pivotal role in the regulation of the inflammatory response.

Due to their genetic nature, most of these disorders have an early onset, ranging from the first hours to the second decade of life.

Only a limited number of patients experience a disease onset during adulthood.

Even if nowadays there is much more awareness of these disorders, the extreme rarity and relatively recent identification as autonomous entities, often result in delayed diagnosis.

Clinically the autoinflammatory syndromes are characterised by recurrent flares of systemic inflammation presenting in the majority of cases as sudden fever episodes associated with elevation of acute phase reactants together with a number of clinical manifestations such as rash, serositis (peritonitis, pleurisy), lymphadenopathy and arthritis. Symptom-free intervals are characterised by complete wellbeing, normal growth and complete normalisation of acute phase reactants.

Familial Mediterranean fever (FMF, MIM 249100), mevalonate-kinase deficiency (MKD, MIM 260920) and tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS, MIM 142680) are the three monogenic disorders subsumed under the term periodic fevers. A systemic inflammation dominated by a characteristic urticarial rash associated with a number of other clinical symptoms is, on the other hand, typical of familial cold autoinflammatory syndrome (FCAS, MIM 120100), Muckle-Wells syndrome (MWS, MIM 191900) and chronic infantile neurological cutaneous and articular syndrome (CINCA, MIM 607115). These diseases represent the clinical spectrum of different mutations of a gene named cold-induced autoinflammatory syndrome 1 (*CIAS-1*, or *NLRP3*) coding for a protein called cryopyrin. Hence these disorders are also known under the term cryopyrin-associated periodic syndromes (CAPS).

Other conditions are characterised by the appearance of typical granulomatous formations (granulomatous disorders). Blau's syndrome (MIM 186580), also known as familial juvenile systemic granulomatosis, presents with non-caseating granulomatous inflammation affecting the joint,

skin, and uveal tract (the triad of arthritis, dermatitis and uveitis) and is associated with mutations of the NACHT domain of the gene *CARD15* (or *NOD2*). Of note is that mutations in this same gene have been associated with Crohn's disease, another granulomatous disease.

Finally, other rare disorders dominated by the presence of sterile pyogen abscesses chiefly affecting skin, joints and bones (pyogenic disorders) include the PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum and acne) (MIM 604416), associated with mutations of the CD2-binding protein 1 (*CD2BP1* or *PSTPIP1*) gene, the Majeed syndrome (MIM 609628), characterised by chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anaemia and neutrophilic dermatosis, caused by mutations of *LPIN2* gene, and deficiency of the interleukin-1receptor antagonist (DIRA) (MIM 612852), a recently identified autosomal recessive autoinflammatory syndrome characterised by severe systemic inflammation beginning approximately at the time of birth with multifocal osteomyelitis, periostitis and pustulosis and caused by mutations of the *IL1RN* gene encoding interleukin-1 receptor antagonist.

Familial Mediterranean fever (FMF)

Familial Mediterranean fever was first described as a distinct entity in the second part of the twentieth century [1]. It is the most frequent among hereditary recurrent inflammatory disorders.

It affects populations of Mediterranean descent: Arabs from the East as well as from the West, Armenians, Turks, non-Ashkenazi and other Jews, Druzes, Lebanese, Italians and Greeks.

Among non-Ashkenazi Jews and Turks, the frequency of heterozygotes in the general population is very high, ranging from 1:3 to 1:6 [2].

In 1992, the gene associated with FMF was mapped to the short arm of chromosome 16 and cloned in 1997 [3, 4]. It was called *MEFV* for MEditerranean FeVer.

The full-length transcript of 3.7 Kb encodes a protein called pyrin/marenostrin consisting of 781 amino acids, that has been suggested as playing a role in the regulation of the so-called inflammasome (fig. 1). The inflammasome is a cytoplasmatic multiprotein complex that plays a crucial part in the production and secretion of pro-inflammatory cytokines, such as interleukin (IL)-1 β [5], and is involved

in the pathogenesis of various autoinflammatory diseases [6] (see below).

Pathogenesis

Several domains of the protein are remarkable: the pyrin domain is a specific domain of 90 amino acids located in the N-terminal region, and defines a novel class of proteins called the pyrin family. A second domain called B30.2 or SPRY is located in the C-terminal region of the protein and contains the most frequent mutations associated with FMF. Some pathogenetic data relating to the function of these domains have been established.

First, it has been shown that pyrin can interact with ASC (apoptotic speck protein) by homotypic pyrin binding domain; ASC mediates both NF- κ B and pro-caspase-1 activation with associated processing and secretion of interleukin IL-1 β , and apoptosis [7].

The second point derives from the discovery of the inflammasome.

Early works suggest that pyrin modulates the inflammasome by interacting both with its pyrin and B30.2 domains (fig. 1). Recently it has also been found that *PSTPIP1*, the protein involved in PAPA syndrome (see below), can activate pyrin, leading to the interaction between PYD and ASC, ASC dimerisation and recruitment and activation of caspase-1, independently of activation of the *NLRP3*-inflammasome (fig. 1). This hypothesis has recently been confirmed in FMF animal models [8].

Clinical picture

Almost 2/3 of patients have a disease onset before 5 years and almost all patients before the second decade of life [9–11].

In FMF fever attacks last from a few hours to 3 or 4 days, and are typically associated with signs of acute serosal inflammation. Peritonitis and monolateral pleurisy are present in more than 90 and 40% of patients respectively and are the cause of two of the most typical symptoms of FMF: severe abdominal pain and chest pain. Scrotitis and pericarditis may also be present in a minority of patients.

Large joints may be affected by arthritis or arthralgia in more than 50% of patients (chiefly knees, hips and ankles), and the erysipelas-like erythema of the lower limbs, which represents the most common skin lesion, is present in almost 25% of cases.

Attacks resolve spontaneously, and there is no regular periodicity of recurrences.

Their frequency varies considerably from one patient to another and, in the same patient, from one period of life to another.

Some factors may act as triggers of the inflammatory attacks, especially stress, viral disease or even drugs such as metamizol and cisplatin. Prodromes of FMF attacks may include discomfort at the impending attack site or various constitutional, emotional, and physical complaints, including irritability, dizziness, increased appetite, and altered taste sensation. A prodrome is a valid sign of an imminent attack in a subgroup of patients with FMF.

Except amyloidosis, which represents the major complication of the disease, chronic manifestations such as encapsulating peritonitis and chronic destructive arthritis affecting

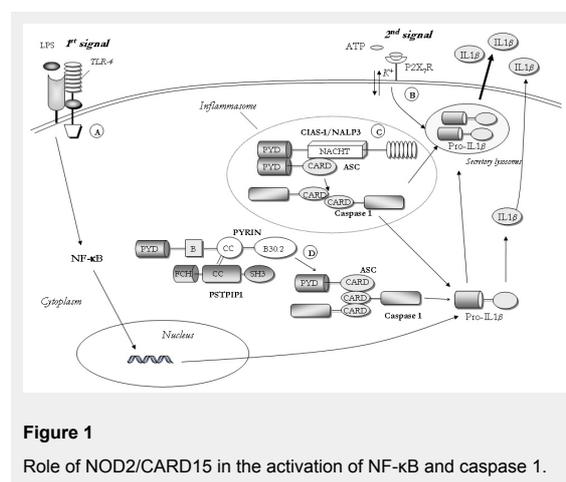


Figure 1

Role of NOD2/CARD15 in the activation of NF- κ B and caspase 1.

hips and knees in particular are rare. Splenomegaly, usually without specific consequences, may also be observed in a subgroup of patients with incompletely controlled inflammation.

Even if genetic testing is available, the diagnosis of FMF relies mainly on clinical arguments. Different sets of criteria have been developed in countries presenting a high prevalence of the disease [12, 13] but they have not yet been validated in populations presenting other autoinflammatory syndromes.

Molecular analysis of the *MEFV* gene provides genetic confirmation of the diagnosis, but it should be noted that interpretation of the molecular analysis can sometimes be difficult.

In the clinical context of FMF, the presence of 2 mutations on different alleles (homozygosity or compound heterozygosity) makes it possible to confirm the diagnosis but, at the same time, it cannot be ruled out in a patient with a clinical presentation consistent with the disease even if carrying one *MEFV* mutation only.

Although five mutations represent more than 85% of all the mutations, some rare or unknown mutations exist (<http://fmf.igh.cnrs.fr/infEVERS/>).

Before the colchicine era amyloid nephropathy was the main cause of death in FMF patients.

FMF-associated amyloidosis is a typical form of inflammatory (or AA) amyloidosis. It generally occurs in patients with severe inflammatory attacks beginning early in life (FMF phenotype 1) but may rarely occur even in patients with no recognised clinical inflammatory crisis [14] (FMF phenotype 2).

Increased SAA and C reactive protein between the FMF attacks represent a risk factor for the future development of AA amyloidosis [14, 15].

It has been established that the prevalence of amyloidosis varies according to ethnic groups, suggesting that genetic (presence of M694V mutation in the homozygous state, SAA polymorphisms) and/or environmental factors participate in the occurrence of amyloidosis in the disease [16, 17].

Treatment

Daily colchicine is the treatment of choice to prevent recurrence of attacks and occurrence of amyloidosis [18, 19]. The usual dose of colchicine is 1 mg/day. If the disease activity is not controlled, due either to recurrence of attacks or persistent elevated inflammatory parameters, especially SAA, the colchicine dose should be increased by 0.5 mg per day every 3–6 months up to 2.5 mg per day.

Diarrhoea due to colchicine is rare and can be managed by dividing the daily dose in two. A recent study suggests that in children the optimal colchicine dosage, i.e. that which reduces the frequency of attacks, ESR, CRP and fibrinogen levels during the attack-free periods can be calculated on the basis of body weight and body surface area [20]. In some cases, proteinuria due to amyloidosis disappears under treatment with colchicine [21]. Although colchicine intoxication remains a severe threat, long term daily colchicine is a relatively safe treatment. Adverse effects of colchicine on sperm function are controversial and long

term use of colchicine can be considered as globally safe including during pregnancy.

True non-responders to colchicine are very rare; the majority are non-compliant patients.

In these non-responders, no treatment has proven its efficacy. Interferon alpha has been proposed, but promising early results have not been confirmed. More recently, anti-IL-1 blockers, such as anakinra and canakinumab have shown efficacy in some patients who were resistant to colchicine, in agreement with the pathogenic data obtained on the role of pyrin in the IL-1 secretion pathway. The use of IL-1 blockers is however not validated and further studies are needed to determine the actual indication for their employment in FMF and their safety in the long run. TNF inhibitors have also been tried with success in some patients.

Periodic fever associated with mevalonate kinase deficiency

Periodic fever associated with mevalonate kinase deficiency (MKD) was originally identified in 1984 in six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause and a high serum IgD level [22]. For this reason this disorder has also been named hyper IgD syndrome or Dutch fever.

High IgD plasma levels were considered to be a diagnostic hallmark until mutations in the mevalonate kinase (*MVK*) gene, encoded on chromosome 12q24, were identified as the cause of the disease [23].

The complete deficiency of this enzyme causes a distinct syndrome called mevalonic aciduria (MA; MIM 251170), which is clinically characterised by severe mental retardation, ataxia, failure to thrive, myopathy and cataracts; notably, these patients also suffer from recurrent fever attacks. *MVK* is an essential enzyme in the isoprenoid biosynthesis pathway which produces several biomolecules involved in different cellular processes.

After identification of the molecular defect it became clear that the distribution of MKD is not limited to northern European populations. A relevant number of patients have also been observed among populations living around the Mediterranean basin [24] and Asia [25]. Moreover, due to the low sensitivity and specificity of IgD serum levels, the term hyper IgD syndrome has been replaced by periodic fever associated with mevalonate kinase deficiency.

Pathogenesis

Although the dysregulation of this biochemical pathway seems to play a pivotal role in the development of fever, at present the pathogenetic mechanisms leading to the autoinflammatory disease remain poorly understood. *MVK* catalyses the ATP-dependent phosphorylation of mevalonate to 5-phosphomevalonate, and is the first enzyme to follow the highly regulated enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase in isoprenoid biosynthesis. Cells from patients with the MKD phenotype still show residual *MVK* enzyme activities [26, 27] (from 1 to 8% of the activities with respect to control cells), while cells from patients with the MA phenotype show enzyme activity that is below laboratory detection level [28] (approximately 0.1% of normal individuals). This enzymatic deficiency is reflec-

ted in the high levels of mevalonic acid in plasma and urine of patients with MA and in the low to moderate levels of mevalonate acid in patients with periodic fever associated with MKD.

The precise molecular mechanism by which the depressed activity of MKV leads to inflammatory flares and fever episodes is still unknown. Two main hypotheses have been formulated: the first suggests that inflammation is related to elevated mevalonic acid levels. This concept was derived from the clinical observation that a reduction in the severity and frequency of fever episodes occurred in 6 MKD adult patients treated with simvastatin. The latter is a competitive inhibitor of HMG-CoA reductase which would result in lowering of mevalonate levels and a consequent reduction in inflammation.

In contrast, other *in vitro* studies have shown that shortage of isoprenoid end products, rather than an excess of mevalonate, contributes to inflammatory responses in MKD. Consistent with this theory, the shortage of non-sterol isoprenoid end products, mainly the geranylgeranyl groups, led to increased activation of caspase 1 in circulating monocytes with consequent hypersecretion of the 17 Kd active form of IL-1 β [29].

Clinical picture

MKD is essentially a paediatric disease. Its onset is very early in life, most often in infancy, and almost all patients develop the disease within the first decade of life.

Fever attacks have an abrupt onset and last 4–6 days. Severe abdominal pain often accompanied by vomiting and/or diarrhoea is the most frequent manifestation associated with fever attacks.

Irritability and cervical lymphadenopathy are common features too and splenomegaly may be found in about half of patients during acute episodes.

Axillary, inguinal and intra-abdominal lymph node enlargement may also be present. Mucocutaneous manifestations are frequent and include erythematous macules, urticaria-like lesions and, less commonly, oral aphthous lesions. Articular involvement occurs in the majority of patients as arthralgia or as oligoarticular, usually symmetrical, arthritis [24, 30, 31].

The symptoms of MKD persist for years but usually tend to become less pronounced with time. However, in some patients the disease may persist until adulthood.

Although amyloidosis was not considered to be a possible long-term complication of MKD(30), it has recently been described in a few patients [24, 32].

Neutrophilia and elevated acute phase reactants are present during fever attacks.

Increased plasma levels of IgD (>100 UI/ml) during fever episodes and in basal conditions have been considered in the past as a hallmark of the disease. However, the specificity of this finding is low [24, 33].

Concomitant elevation of IgA has been also reported [24, 34].

Increased urinary excretion of mevalonic acid is observed during fever spikes, and decreased MVK activity may also be a pointer to the diagnosis. However, the aforementioned determinations need highly specialised laboratory work

and, therefore, are often difficult to perform as screening tests.

Thus the decision to perform the molecular analysis of MVK gene in a child with periodic fever is usually taken on clinical grounds.

MKD is an autosomal recessive disease. So far more than 130 substitutions or deletions of the *MVK* gene have been reported [35] (<http://fmf.igh.cnrs.fr/infevers/>).

Some variants (i.e., V310M, A334T) are closely associated with a severe MA phenotype and severely impaired cellular MVK activity [36].

The most common mutation in *MVK* gene is the V377I variant, which is exclusively associated with the mild phenotype of MKD with some residual MVK activity [26]. It is found in a compound heterozygous state in the vast majority of patients with MKD [24, 36]. Other mutations such as H20P and I268T have also been associated either with MA and MKD phenotype (<http://fmf.igh.cnrs.fr/infevers/>). It is, therefore, conceivable that some patients may also present an intermediate phenotype, characterised by the typical fever attacks associated with some neurological manifestations (mental retardation, cerebellar ataxia) of variable severity [37]. It is therefore clear that mevalonic aciduria and periodic fever associated with MKD represent the two extremities of a wide clinical spectrum.

Treatment

Fever attacks usually respond dramatically to the administration of steroids (prednisone: 1 mg/kg/day in a single dose or with a short course of 3 to 5 days). However, due to the high frequency of the fever episodes, some patients may need almost continuous treatment. Thalidomide has proven to be ineffective [38].

The use of biological treatments is largely anecdotal and sometimes controversial.

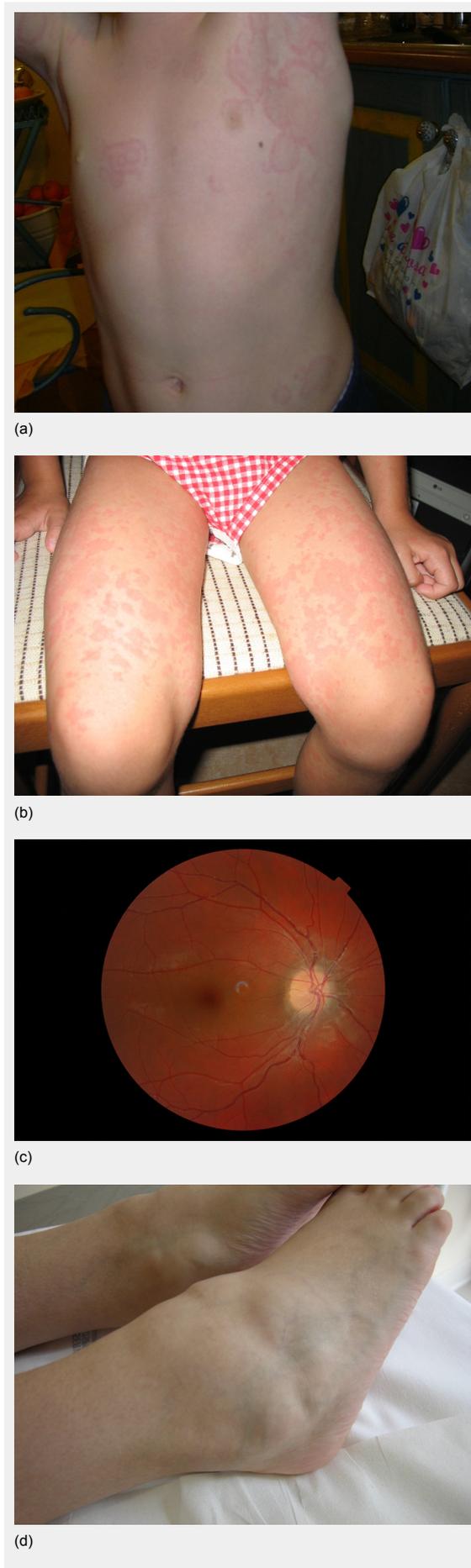
Anti-TNF therapy has been found to reduce the frequency and intensity of fever attacks in some patients [39] but not in others [40]. Recently, the use of the IL-1 receptor antagonist (anakinra) was found to be effective in a patient [41]. However, these observations require confirmation in large multicentre therapeutic trials.

TNF-receptor associated autoinflammatory syndrome (TRAPS)

A dominant mode of inheritance and long-lasting fever episodes identify an other periodic fever syndrome, defined by the acronym TRAPS, caused by mutations in the p55 TNF receptor (or TNFR1A), encoded by the TNF super family receptor 1A gene [42] (*TNFRSF1A*). Although TRAPS was initially described in subjects of Nordic origin [43], as emphasised by the name familial Hibernian fever, mutations in *TNFRSF1A* have been found in many populations, including Black Americans, Japanese and those of Mediterranean ancestry, where FMF is highly prevalent.

Pathogenesis

A total of 114 sequence variants of the *TNFRSF1A* have been recorded so far; of which 75 are associated with a TRAPS phenotype [35] (<http://fmf.igh.cnrs.fr/infevers/>)



The majority of TRAPS-related mutations are missense mutations resulting in single amino acid substitutions in the cysteine rich domains (CRD), CRD1, CRD2, or CRD3 of the ectodomain of the mature TNFR1 (also called p55 TNFR) protein [35, 44, 45].

These CRDs are involved in disulphide bond formation and in the folding of the extracellular portion of the protein. Hence mutations resulting in cysteine substitutions demonstrate a higher penetrance, usually being associated with a more aggressive phenotype and increased probability of developing renal amyloidosis compared to mutations not involving the CRD.

The status of two sequences, R92Q and P46L, has not been fully determined. P46L appears rather as a benign polymorphism and R92Q behaves in the main as an incomplete penetrance mutation [45–47].

In some patients, plasma concentrations of the soluble form of the receptor are low or paradoxically normal during attacks, and may also be low in between. This suggests a quantitative or qualitative abnormality of the soluble form of the receptor. Actually, the shedding of free TNFRs from the membrane produces a pool of soluble receptors which may scavenge circulating TNF by competing with membrane bound receptors. This latter phenomenon represents an important strategy for regulation of the effect of circulating free TNF during acute inflammation. It has been suggested that some *TNFRSF1A* mutations may interfere with the process of shedding [42], leading to a lack of appropriate TNF inhibition and therefore to uncontrolled inflammation. However, a defect of shedding of the receptor is not observed in all the mutations, suggesting that additional mechanisms could be involved in the pathogenesis of the disease.

At variance with the p75 receptor, p55 TNFR is also able to induce cell apoptosis, via activation of the caspase cascade. In fact, TNFR1 can trigger cellular activation via NF- κ B or apoptosis via activation of pro-apoptotic caspases. A defect of TNF-induced apoptosis has been identified in TRAPS patients [46, 48]. This defect observed in patients carrying structural *TNFRSF1A* mutations may represent an



(e)

Figure 2

(a) Skin rash in a TRAPS patient; (b) Typical urticarial rash in a Muckle Wells patient carrying the D303N mutation; (c) Chronic papilloedema in a CINCA patient; (d) Typical boggy synovitis in a patient affected with Blau's disease; (e) Bilateral pyogenic sterile arthritis of the knees in a 4-year-old patient with PAPA syndrome.

additional mechanism explaining the sustained activation of inflammatory cells during fever episodes.

Through transfection of the mutant form of TNFRI protein in different cell types it was possible to identify an additional relevant pathogenic mechanism related to the diseases. The mutated TNFRI does indeed display a defect of trafficking to the cell membrane with a clear accumulation in the endoplasmic reticulum. Currently the possible pathogenic consequences of ER retention of mutated TNFRI are under intensive investigation. Increased activation of pro-inflammatory MAP kinases secondary to a stress-induced overproduction of mitochondrial reactive oxygen species (ROS) has recently been shown [49].

Clinical picture

TRAPS attacks last generally more than five days and up to three weeks, even though attacks shorter than 5 days have been reported. Abdominal pain can simulate a surgical event; a wide spectrum of skin rashes can be observed in most patients: urticaria-like, plaques and patches (fig. 2a). The most distinctive lesion is an erythematous, swollen, warm and tender plaque of varying size with hazy edges. It tends to involve the upper and lower limbs but can be observed at the chest. Usually, the rash has a migratory course from the root to the extremity of the limbs.

This pseudo-cellulitis is often accompanied by painful myalgias that represent the other most distinctive manifestation of TRAPS attacks. Thoracic pain, scrotal pain, arthritis, orbital oedema and conjunctivitis are also observed during attacks.

At least in the Caucasian populations, the R92Q mutation is the most frequently observed variant of the *TNFRSF1A* gene. The majority of children with periodic fever with R92Q mutation display a milder disease course compared to patients carrying structural mutations, with a higher rate of spontaneous resolution or amelioration and much lower prevalence of amyloidosis. Notably, according to different studies, the allele frequency of R92Q variant in the general population ranges from 1.2 to 4%. These clinical observations support the limited pathogenic role of this variant. Based on these data and given the prevalence of this variant in the normal population, great caution should be exercised in interpreting a positive molecular analysis for the R92Q variant, especially in children with periodic fever [50].

Treatment

When given at the onset of an attack, corticosteroids can attenuate its length and severity. In the most severe forms of the disease, clinical signs of inflammation are almost permanent and require daily use of corticosteroids, leading to dependence and requiring the use of other anti-inflammatory drugs. Colchicine does not seem to prevent recurrences of TRAPS attacks.

TNF inhibitors seem designed as treatment of TRAPS. Etanercept, a TNFRSF1B receptor-immunoglobulin fusion molecule, mimics the effect of the normal soluble TNF receptor and thus compensates its deficit in TRAPS patients. Etanercept and other TNF inhibitors have provided various degrees of clinical improvement and allowed savings of steroids in many cases [51–53]. However, most of the

TRAPS patients experience a partial response when treated with Etanercept [54–58].

In other cases the efficacy tends to decrease with time. Interestingly, a paradoxical reaction with exacerbation of the inflammatory signs has been observed after administration of anti-TNF monoclonal antibody (infliximab) in some TRAPS patients and thus this drug should not be used in this indication [59]. Recently it has become clearer that the use of the anti-IL-1 inhibitors (such as recombinant IL-1 receptor antagonist anakinra) can have a better and longer-lasting effect on control of the clinical manifestations [55, 60].

The cryopyrin-associated periodic syndromes (CAPS)

Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous and articular syndrome (CINCA) represent autosomal dominant disorders [61–63] caused by different mutations in a single gene, *NLRP3* (NOD-like receptor 3, also known as cold-induced autoinflammatory syndrome 1, *CIAS1*), encoding a protein called cryopyrin [65, 65].

Mutations of the *NLRP3* gene are found in almost 70% of patients with a CAPS phenotype.

Pathogenesis

IL-1 β plays a pivotal role in the pathogenesis of many inflammatory conditions and represents a potential therapeutic target intervention in many inflammatory diseases. Growing knowledge of the pathogenic consequences of gene mutations involved in the monogenic autoinflammatory diseases has shed light on some pivotal pathophysiological mechanisms related to the activation and secretion of IL-1 β .

Unlike most cytokines, IL-1 β lacks a secretory signal peptide and is externalised by monocytic cells through a non-classical pathway, arranged in two steps. In the first one, toll-like receptor ligands, such as LPS, induce gene expression and synthesis of the inactive IL-1 β precursor (pro-IL-1 β). A second stimulus, such as exogenous ATP, strongly enhances IL-1 β proteolytic maturation and secretion. ATP-triggered IL-1 β secretion is mediated by P2X7 receptors expressed on the surface of monocytes; this mechanism is characterised by a series of events, only partially clarified, involving the secretory lysosomes.

Cryopyrin (NLRP3) is a key protein of the inflammasome. It is a member of the NOD-like receptor (NLR) protein family. In the presence of several stimuli, cryopyrin oligomerises and binds the adaptor protein ASC (Apoptosis associated Speck-like protein containing a CARD). This interaction directly activates two molecules of caspase-1 which, in turn, converts pro-IL-1 β to the mature, active 17 kDa form (fig. 1). Thus activated cryopyrin induces the release of the active form IL-1 β [66]. Experimental mouse models have revealed that monocytes from knockout mice deficient in cryopyrin cannot activate caspase-1 upon LPS and ATP stimulation, resulting in lack of IL-1 β secretion. On the contrary, mutations in the cryopyrin gene in humans are associated with its gain of function leading to an en-

hanced and quicker production of IL-1 β , even in the absence of a second signal. The speedier production and secretion of IL-1 β in CAPS monocytes is probably linked to overactivation of their redox state [67].

Clinical picture

FCAS is characterised by urticarial rash and fever spikes of short duration (usually <24 h) induced by cold exposure. Arthralgia and conjunctivitis are also common. Other symptoms observed following cold exposure include profuse sweating, drowsiness, headache, extreme thirst and nausea [68].

Muckle-Wells syndrome is characterised by recurrent episodes of urticaria (fig. 2b) and fever that may develop in early infancy. The fever episodes (usually below 38 °C) can be associated with the same clinical manifestations observed in FCAS (arthralgia, conjunctivitis, drowsiness), but usually are not strictly triggered by cold exposure. Acute phase reactants are elevated during fever episodes, and may also persist slightly increased during free intervals. During the course of the disease, neurosensory deafness and polyarthritides may develop. Amyloid A (AA) amyloidosis is a complication of the late stage of the disease [62, 69, 70].

CINCA represents the more severe phenotype associated with mutations of the cryopyrin gene. An urticaria-like rash may develop during the first weeks of life. Many affected individuals present a typical “facies” characterised by frontal bossing, saddle back nose and midface hypoplasia, causing a sibling-like resemblance. Bone involvement is another hallmark of the disease. The most characteristic feature is represented by bony overgrowths predominantly involving the knees (including the patella) and the distal extremities of hands and feet. Major alterations in the organisation of cartilage growth have been described in biopsy specimens [71]. Chronic inflammatory polyarthritides may also be present, sometimes resulting in bone erosions [72]. Central nervous system (CNS) manifestations include chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy, ventriculomegaly, sensorineural hearing loss and chronic papilloedema (fig. 2c), with associated optic-nerve atrophy and loss of vision. Mental retardation and seizures have also been reported. Patients exhibit persistent elevation of acute phase reactants, leucocytosis and chronic anaemia [63, 73–75].

Up to the present some 100 variants have been associated with either of the 3 phenotypic forms (<http://fmf.igh.cnrs.fr/infevers/>). Almost all the observed mutations are found in exon 3 of the NLRP3 gene, coding for the NACHT domain of cryopyrin that plays a crucial role in oligomerisation of the protein.

Treatment

The pivotal role of cryopyrin in driving caspase 1 activation and the massive secretion of mature IL-1 β observed in cryopyrin-mutated individuals suggested that anti-IL-1 treatment could represent an effective therapy. Initial isolated case reports suggested that the recombinant IL-1 receptor antagonist, anakinra, has a dramatic effect in controlling rash and constitutional symptoms of FCAS and Muckle-Wells patients [76]. These findings have been confirmed in different studies on CINCA patients [77].

Anakinra is given at a starting dosage of 1 mg/kg per day SC. Soon after the first injection all patients showed a dramatic improvement of urticarial rash, arthritis, headache and fever, with a complete resolution within one week from the beginning of the treatment. A rapid decrease in acute phase reactants is also observed in the first weeks of treatment, with complete normalisation in the majority of patients. The same excellent results were recently observed using other IL-1 blockers such as IL-1 Trap (rilonacept) and anti-IL-1 monoclonal antibodies (canakinumab) [78–80]. Rilonacept has recently been approved for FCAS or MWS patients aged over 11 years and canakinumab for CAPS patients aged over 4 years.

The positive effects of anti-IL-1 blockers persist over the time. Monitoring of patients under anakinra treatment with a follow-up of over 3 years revealed that all CINCA patients still displayed complete control of the inflammatory symptoms with almost complete normalisation of the general conditions. Improvement of hearing loss after anakinra treatment has been described in almost 30% of CINCA patients [77].

Periodic fever syndrome and mutations in NLRP 12

This disease was originally identified in two families originating from Guadeloupe, who presented a clinical picture involving recurrent fever and cold sensitivity associated with some of the following additional symptoms: neuronal hearing loss, aphthous ulcers, lymphadenopathy, abdominal pain and acute phase response. Using a candidate gene approach, mutations in another member of an NLR family (the same of *NLRP3*) was found. The affected members of the two families were indeed carriers of non-ambiguous mutations (i.e. nonsense and splice site) of the *NLRP12* gene. Evaluation of other additional families confirmed the relatively benign nature of this disorder, which is essentially featured by transitory occurrence of urticarial rash, muscle-skeletal pain and general discomfort following exposure to some environmental trigger factors, such as cold or fatigue.

Even if *NLRP12* has been shown to play a role in the regulation of the pro-inflammatory NF- κ B pathway [81], accelerated secretion of IL-1 secondary to a deregulated redox state has been suggested as an alternative pathogenic mechanism [82].

Blau syndrome

Blau syndrome, or familial juvenile systemic granulomatosis, is an autosomal-dominant, autoinflammatory disease characterised by a noncaseating granulomatous inflammation affecting the joint, the skin, and the uveal tract (the triad of arthritis, dermatitis, and uveitis) [83]. The gene responsible for Blau syndrome, *NOD2/CARD15*, encodes a protein containing a NACHT domain [84]. To date more than 10 different genetic mutations leading to substitutions in or near the NACHT domain of *NOD2/CARD15* have been documented in affected patients with either the familial or the sporadic presentation [84–86].

NOD2/CARD15 belongs to the superfamily of NOD (nucleotide oligomerisation domain)-like receptors (NLR), that are intracellular receptors for bacterial peptidoglycans. NOD2/CARD15 recognises muramyl dipeptide (MDP), the minimal motif of peptidoglycan of both Gram-positive and Gram-negative bacteria. After stimulation with MDP, NOD2/CARD15 is able to induce both NF- κ B activation and release of bioactive IL-1 β in a caspase 1-dependent manner. It is, therefore, conceivable that in Blau syndrome the mutation of the NACHT domain causes a gain of the protein's function resulting in a sustained pro-inflammatory state.

Disease onset is usually observed during the first years of life. A symmetrical polyarticular arthritis with a "boggy" appearance is the typical joint manifestation (fig. 2d) and is mainly due to an exuberant tenosynovitis. Eye involvement is characterised by intermediate uveitis or panuveitis. 50% of the patients with ocular involvement develop cataracts, and approximately one-third may evolve into secondary glaucoma. A typical tan-coloured, scaly, ichthyosiform rash is seen in almost 90% of the affected individuals [87, 88]. Patients are treated with oral steroids and immunosuppressive drugs (methotrexate, cyclosporin A) with variable outcomes. Recent anecdotal reports suggest a beneficial effect of anti-TNF (infliximab) [87] and anti-IL-1 treatment [88].

PAPA syndrome

Pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome (PAPA, MIM 604416) is a disorder caused by mutations of gene coding for the CD2-binding protein 1 (CD2BP1), or *PSTPIP1* [89, 90]. The manifestations of this disorder are pyogenic gangrenosum, cystic acne, and pyogenic sterile arthritis which represents the most common symptom of the disease. The arthritis usually has its onset in early childhood. It is pauciarticular in nature, affecting one to three joints at a time, and is characterised by recurring inflammatory episodes that resemble septic arthritis (fig. 2e) and lead to accumulation of pyogenic, neutrophil-rich material within the affected joints, which ultimately results in significant synovial and cartilage destruction [89–91]. Cultures of the skin lesions and joint fluid of these patients are sterile. Dermatological manifestations are also episodic and recurrent, with onset usually during the second decade of life, and are characterised by debilitating, aggressive, ulcerative skin lesions, usually of the lower extremities, indistinguishable from pyogenic gangrenosum. Sterile abscesses at injection sites may also be observed.

Positional cloning in informative families identified two mis-sense mutations within the CD2BP1 (or *PSTPIP1*) gene(90). *PSTPIP1* has been shown to bind pyrin [92]. It has been postulated that mutated *PSTPIP1* displays an

Table 1: The autoinflammatory diseases.

	Diseases	Gene Chromosome	Protein	Transmission	Clinical features
Periodic / recurrent fevers	Familial Mediterranean fever	<i>MEVF</i> 16p13.3	Pyrin	AR	Short duration of fever episodes: 24–48 hours. Abdominal and chest pain. Erysipelas-like erythema. High incidence of renal amyloidosis in untreated patients. Good response to colchicine. Possible response to IL-1 blockade.
	Mevalonate kinase deficiency	<i>MVK</i> 12q24	Mevalonate kinase	AR	Early onset (usually <12 months). Mean duration of fever episodes: 4–5 days. Poor conditions during fever episodes. Abdominal pain, vomiting and diarrhoea. Splenomegaly. Good response to steroids. High rate of self-resolution during adulthood. Amyloidosis is rare.
	TNF receptor associated periodic syndrome	<i>TNFRSF1A</i> 12p13	p55 TNF receptor	AD	Prolonged fever episodes: 1–3 weeks. Periorbital oedema, monocytic fasciitis. Incidence of renal amyloidosis: 15–25%. Response to TNF- and IL-1 blockade.
	NALP12-associated periodic Fever	<i>NALP12</i> 19q13	NALP12	AD	Periodic fever after cold exposure, hearing loss.
Cryopyrinopathies	FCAS, MWS, CINCA	<i>CIAS 1/NALP3</i> 1q44	Cryopyrin	AD	FCAS: rash, fever and arthralgia after cold exposure. MWS: recurrent or sub-chronic urticaria-like lesions, sensorineural hearing loss, amyloidosis. CINCA: as above + mental retardation, chronic aseptic meningitis and bone deformities. Good response to IL-1 blockade.
Granulomatous disorders	Blau's syndrome	<i>CARD15/NOD2</i> 16q12	CARD15	AD	Early onset (<5 years). Polyarticular granulomatous arthritis, uveitis, skin rash. Good response to anti-TNF monoclonal antibodies.
Pyogenic disorders	PAPA syndrome	<i>PSTPIP1</i> 15q24-q25.1	PSTPIP1	AD	Pyogenic sterile arthritis, pyogenic gangrenosum, cystic acne. Good response to IL-1 blockade.
	Majeed's syndrome	<i>LPIN2</i> 18p	LPIN2	AR	Multifocal osteomyelitis, congenital dyserythropoietic anaemia, inflammatory dermatosis.
	DIRA	<i>IL1RN</i> 2q	IL-1 receptor antagonist	AR	Neonatal-onset multifocal osteomyelitis, periostitis, and pustulosis. Dramatic response to anakinra.

FCAS = Familial cold autoinflammatory syndrome; MWS = Muckle-Wells syndrome; CINCA = Chronic infantile neurological cutaneous and articular syndrome; PAPA = Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome; CRMO = Chronic recurrent multifocal osteomyelitis; DIRA = Deficiency of the interleukin-1-receptor antagonist; AR = autosomal recessive; AD = autosomal dominant.

*Identification of the gene defect.

higher affinity for binding with pyrin, leading to increased susceptibility to inflammation.

PAPA syndrome has been reported to be generally responsive to oral glucocorticoids [89, 90]. However, sustained remission in a steroid-resistant patient and a consistent amelioration of the cutaneous manifestations have been anecdotally reported after anti-TNF [93, 94] and anti-IL-1 treatment [95].

Majeed's syndrome

In 1989 three related Arab children presenting an association of chronic recurrent multifocal osteomyelitis (CRMO), and inflammatory dermatosis were described by Majeed and co-workers [96].

Unlike isolated CRMO, bone manifestations have an earlier age at onset, present with a higher frequency of recurrence and show shorter and less frequent remissions. Congenital dyserythropoietic anaemia is characterised by microcytosis both peripherally and in the bone marrow, and the need of repeated blood transfusions may be required. Inflammatory dermatosis may vary from Sweet syndrome to chronic pustulosis. Recurrent fever episodes and growth failure have also been reported [96, 97]. Non-steroidal anti-inflammatory drugs are moderately helpful, whereas short courses of oral steroids promptly control disease relapses, even if steroid-dependence has been reported. Colchicine does not seem to be effective [97]. Splenectomy has reportedly been able to control the haematological manifestations [97].

In 2005 a linkage analysis was performed on two new Jordanian families allowing identification of the *LPIN2* gene mapped on chromosome 18p [98].

The existence of a monogenic disease associated with CRMO has raised the hypothesis that sporadic CRMO could also be included in the group of autoinflammatory diseases. This theory has been further supported by the recent identification on a chromosome 18 of a mis-sense mutation in the *PSTPIP2* gene in a spontaneous murine model of an autoinflammatory disorder characterised by chronic multifocal osteomyelitis [99].

DIRA (deficiency of the interleukin-1-receptor antagonist)

DIRA is a recently identified autosomal recessive autoinflammatory syndrome, due to the deficiency of the interleukin-1-receptor antagonist, which begins around birth with multifocal osteomyelitis, periostitis, and pustulosis. Persistent elevation of acute phase reactants (ESR and CRP) are observed from birth. The skin manifestations range from groupings of small pustules to a generalised pustulosis. The bone manifestations include osteolytic lesions with a sclerotic rim, epiphyseal ballooning of multiple distal and proximal long bones, widening of ribs and clavicles, heterotopic ossification or periosteal cloaking of the proximal femoral metaphysis and periosteal elevation of the diaphysis [100]. The patients so far described exhibit homozygous truncating mutations in the *IL1RN* gene. As a result of these mutations, there is no secretion of interleukin-1-receptor antagonist (IL1RA) protein, which usu-

ally inhibits the proinflammatory cytokines interleukin-1 including interleukin-1 β . Deficiency of IL1RA being causative of the disease, these patients show a dramatic response to the substitutive treatment with recombinant IL-1 receptor antagonist (anakinra) [100].

The multifactorial autoinflammatory diseases

Several multi-factorial inflammatory diseases present clinical similarities to inherited autoinflammatory diseases and are thought to be mainly autoinflammatory in nature [101]. Some of these disorders have also shown a bright response to IL-1 inhibitors.

The PFAPA (*Periodic Fever, Aphthous stomatitis, Pharyngitis and Adenitis*) syndrome is characterised by periodic fever attacks similar to those observed in monogenic periodic fevers in children negative for mutations of *MEFV*, *MVK* and *TNFRSF1A* genes. In fact, although some anecdotal familial cases of PFAPA have been reported, a genetic basis has never been demonstrated.

It was first described by Marshall et al. in 1987 [98].

It is characterised by regularly (often clockwork) recurrent episodes of fever lasting 3–6 days. The frequency of episodes varies but they usually present every 2–6 weeks. The diagnosis is based on clinical criteria that require the presence of a disease onset before the age of 5 years and at least one of the three associated constitutive symptoms (aphthosis, cervical adenitis, pharyngitis) in the absence of upper respiratory tract infection or cyclic neutropenia [102].

Pharyngitis is the most frequent and characteristic symptom associated with fever attacks. It is erythematous or exudative, and self-limiting. The throat swab is always negative. The stomatitis is characterised by small lesions that may appear some days before the occurrence of fever and present with a spontaneous self-remission. The cervical lymph nodes are usually tender and enlarged during fever episodes, with subsequent gradual normalisation with resolution of the fever attack. Acute phase reactants and neutrophils are elevated during the attacks and normalise completely during the periods of complete wellbeing.

The disease runs a benign course and tends to remit spontaneously with time. Typically a single administration of oral steroids at the beginning of the episode promptly aborts the fever attack; however, this treatment is reported to shorten the disease-free intervals [103].

Children with PFAPA syndrome often appear in good condition during the fever spikes as well. This is a clinical feature that may help to distinguish PFAPA from the other form of periodic fever associated with a genetic defect.

The diagnostic criteria for PFAPA syndrome have been shown to have low specificity.

In fact, almost 50% of genetically positive children (especially MKD) also fulfill the PFAPA criteria, which, therefore, do not represent a specific tool capable of selecting patients with strong probability of being negative at genetic testing. In this line, some clinical manifestations during fever attacks, such as abdominal and chest pain and gastrointestinal symptoms (vomiting and/or diarrhoea), should be considered evocative for a higher risk of carrying mutations of known genes [104, 105].

Gout and pseudogout (two common adult rheumatic diseases) are caused respectively by deposition of monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPPD) crystals in the joints and periarticular tissues. It has been shown that both MSU and CPPD crystals are able to activate the inflammasome [106]. For this reason IL-1 blockade has been used in colchicine-resistant gout with a good response [107].

Another disease sharing a number of clinical features (systemic inflammation, arthritis, rash, persistent elevation of acute phase reactants) with inherited autoinflammatory diseases is systemic onset juvenile idiopathic arthritis (SoJIA). In some studies, gene expression analysis revealed the presence of a prevalent IL-1 β signature in SoJIA [108, 109] and a variable percentage of these patients (from 40 to 87% according to the different studies) show a dramatic and persistent response to anti-IL-1 blockade similar to that observed in CAPS patients [108, 110].

Idiopathic recurrent pericarditis too presents many features that are consistent with an autoinflammatory disease. A recent study described 3 steroid-dependent and colchicine-resistant children with recurrent pericarditis treated by anakinra with a dramatic response. The author reports that pericarditis recurred when anakinra treatment was discontinued, and that no further episodes occurred after it was resumed [111].

Finally, recent evidence has shown that the same pathogenic mechanisms responsible for the activation of innate immunity in inherited autoinflammatory diseases may also play a crucial role in sustaining inflammation in several extremely frequent multi-factorial illnesses, such as type II diabetes [112] and atherosclerosis [113], opening new perspectives on the management of these diseases.

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Figures (large format)

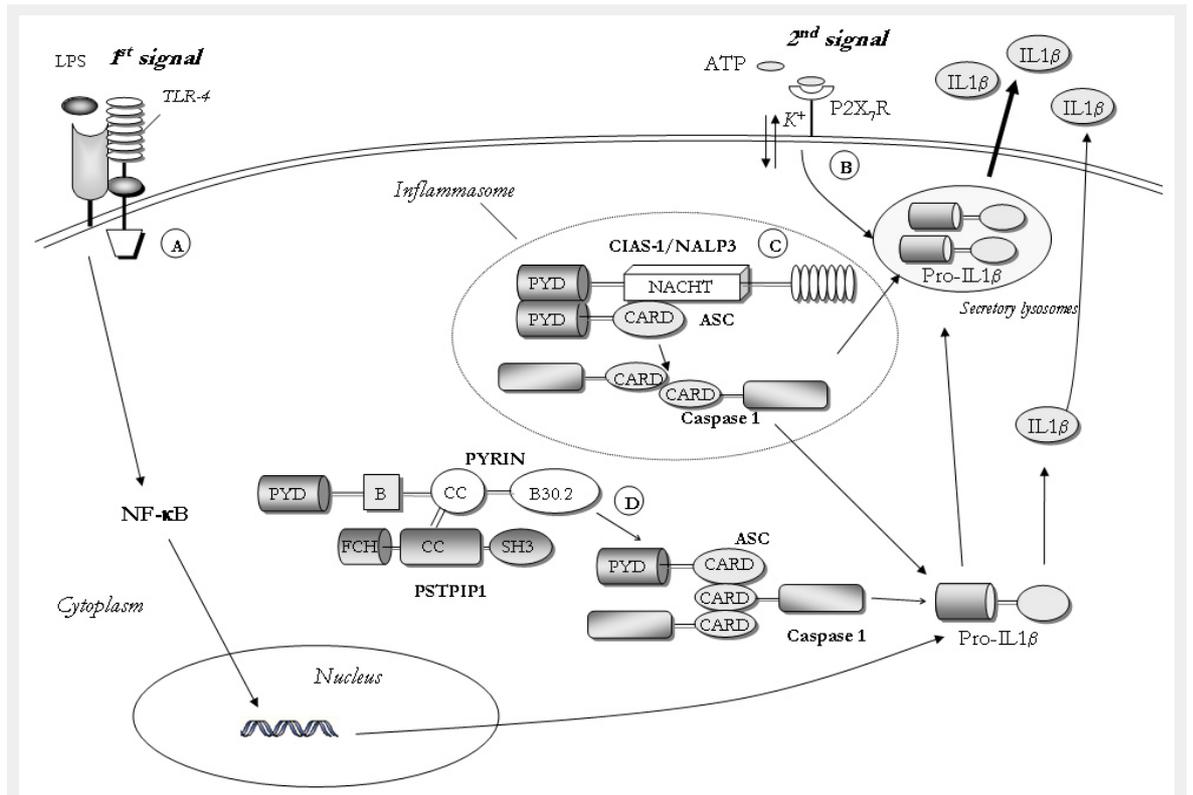


Figure 1
 Role of NOD2/CARD15 in the activation of NF-κB and caspase 1.



(a)



(b)



(c)



(d)



(e)

Figure 2

(a) Skin rash in a TRAPS patient; (b) Typical urticarial rash in a Muckle Wells patient carrying the D303N mutation; (c) Chronic papilloedema in a CINCA patient; (d) Typical boggy synovitis in a patient affected with Blau's disease; (e) Bilateral pyogenic sterile arthritis of the knees in a 4-year-old patient with PAPA syndrome.