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CME REVIEW

CAPS and NLRP3

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Abstract

Cryopyrin-associated periodic syndrome (CAPS) is a rare inherited autoinflammatory disorder characterized by systemic, cutaneous, musculoskeletal, and central nervous system inflammation. Gain-of-function mutations in *NLRP3* in CAPS patients lead to activation of the cryopyrin inflammasome, resulting in the inappropriate release of inflammatory cytokines including IL-1β and CAPS-related inflammatory symptoms. Several mechanisms have been identified that are important for the normal regulation of the cryopyrin inflammasome in order to prevent uncontrolled inflammation. Investigators have taken advantage of some of these pathways to develop and apply novel targeted therapies, which have resulted in improved quality of life for patients with this orphan disease.

Keywords Familial cold autoinflammatory syndrome · Muckle–Wells syndrome · neonatal onset multi-system inflammatory disease · inflammasome · cryopyrin-associated periodic syndromes

Introduction

In 1940, Kile and Rusk described a multi-generational family with several affected members exhibiting recurrent episodes of urticarial-like rash, limb pain, and fever following generalized cold exposure [1]. Over the next 60 years, many other patients and families from Europe and North America were reported with a similar inflammatory phenotype referred to variably as cold hypersensitivity, familial cold urticaria (FCU), and finally familial cold autoinflammatory syndrome (FCAS), in an attempt to differentiate this chronic systemic inflammatory disease from the more common acquired cold urticaria [2]. In 1962, Muckle and Wells investigated a family with a similar clinical picture of recurrent episodes of rash, limb pain, and fever, but not associated with cold exposure. Many of these patients developed progressive sensorineural hearing loss and end-stage renal disease secondary to AA amyloidosis [3]. Over the next few decades, additional reports of Muckle–Wells syndrome patients were published including some noting phenotypic overlap with FCAS. In 1980, Prieur described young patients with chronic severe urticarial-like rash, pain, and fever with significant central nervous system involvement including developmental delay and seizures due to chronic sterile meningitis and increased intracranial pressure. These patients were also reported with distal femur arthropathy resulting in significant disability [4]. Over the next 20 years, patients with similar clinical features were reported and the disease was referred to as either chronic infantile neurologic cutaneous articular (CINCA) syndrome or neonatal onset multi-system inflammatory disease (NOMID) with rare mention of phenotypic overlap with Muckle–Wells syndrome (MWS) [5].

The identification of heterozygous mutations in the same novel gene (*NLRP3*) in patients from all three phenotypes established this as a spectrum of one monogenic disease [6]. Since *NLRP3* codes for the protein cryopyrin, this disease continuum is now known as cryopyrin-associated periodic syndrome (CAPS) or cryopyrinopathies. CAPS patients have been reported from all over the world with estimated prevalence ranging between 1 and 3 per million [7]. The distribution of CAPS subtypes varies around the world as a majority of CAPS patients in North America are classified as FCAS due to large families with a founder mutation [8], while MWS is the most common phenotype reported in Europe. CINCA/NOMID patients are less common since most cases are de novo. In this review, we will discuss the clinical features, genetics, pathogenesis, and therapy of CAPS and examine

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the role and function of cryopyrin in human disease in order to help clinical immunologists and immune disease researchers gain a better understanding of this fascinating disease and important immune regulatory protein.

Clinical Description of CAPS

While FCAS, MWS, and CINCA/NOMID were described as unique disease entities, it is clear that these disorders are part of a clinical continuum with several shared features that differ in severity which is a determinant of level of therapy. There are also some unique features that are worth distinguishing since they may affect prognosis and clinical management. All of the subtypes have cutaneous, musculoskeletal, ocular, and central nervous system involvement to varying degrees. As more patients have been described, there are clearly patients with clinical features that overlap more than one subtype [6], which is consistent with the concept of a single disease spectrum (Table 1).

Most CAPS patients present with symptoms early in life consistent with the inherited nature of the disease, although the observation that some patients develop symptoms at or even before birth and others have delayed onset for many years may suggest environmental influences including exposure to microbial organisms or antigens [9]. An urticaria-like rash is often the first indication of disease and the most prominent shared clinical sign in CAPS patients. Fever is a common clinical sign, although it is often not a primary clinical complaint, and the recorded body temperature may not meet actual criteria for fever. Most CAPS patients report myalgia, arthralgia, headache, and fatigue, although these symptoms are often difficult to quantify objectively. Conjunctivitis and keratitis, while less prevalent than rash, can be observed in patients from all three subtypes. As expected in a disease continuum, chronicity or severity of shared symptoms ranges from the most severe in CINCA/NOMID to the least in FCAS; however, quality of life is decreased in all patients [10].

Generalized cold exposure as a trigger for symptoms is the most prominent clinical feature of FCAS and often is their chief complaint to medical providers. Patients report that exposure to temperatures below 72 °F for more than 30 min such as air conditioned rooms is sufficient to induce noticeable symptoms within a few hours of exposure. FCAS patients also often report chills in association with fever [2]. Cold can be one of many symptom triggers for MWS patients, but it is not reported consistently. FCAS and MWS patients have daily baseline symptoms of fatigue and flu-like malaise. A diurnal pattern of symptoms worsening in the afternoon and evening is common in many FCAS and MWS patients [2, 11]. Symptomatic flares in FCAS episodes usually last less than a day and MWS flares may last 1–3 days. Amyloidosis was reported in up to 30% of one MWS cohort prior to definitive therapy [3] but is much less common in FCAS patients. Hearing loss is common in MWS and CINCA/NOMID patients, but rarely seen in the FCAS subtype. Ocular findings including uveitis and papilledema can be observed in CINCA/NOMID patients and rarely in MWS patients [12, 13]. Central nervous system symptoms observed in many CINCA/NOMID patients including developmental delay and seizures are secondary to sterile meningitis and increased intracranial pressure that has only rarely been documented in MWS patients. Arthropathy involving the distal femur and dysmorphic features such as frontal bossing is also fairly unique to a subset of CINCA/NOMID patients [14].

Laboratory and Pathologic Findings

Chronic leukocytosis is common in most CAPS patients with acute increases of blood neutrophilia during symptom flares. Increased serum IL-6 levels have also been observed during flares [15]. In contrast, modest to significant elevations of acute

Table 1 Clinical features of CAPS

	FCAS	MWS	CINCA/NOMID
Cutaneous	Urticaria-like rash	Urticaria-like rash	Urticaria-like rash
Systemic	Fever/fatigue/chills	Fever/fatigue	Fever/fatigue
Musculoskeletal	Arthralgia/myalgia	Arthralgia/myalgia/arthritis	Arthralgia/myalgia/distal femur overgrowth
Ocular	Conjunctivitis/keratitis	Conjunctivitis/keratitis/uveitis	Conjunctivitis/keratitis/uveitis/papilledema
Auditory		Sensorineural hearing loss	Sensorineural hearing loss
Central nervous system	Headache	Headache	Headache, sterile meningitis, elevated intracranial pressure, developmental delay
Morbidity	Amyloidosis (rare)	Amyloidosis	Amyloidosis, developmental delay
Episode pattern	12–24 h	1–3 days	Chronic with 1–3 day flares
Triggers	Generalized cold/pneumovax	Stress/exercise/infection/pneumovax	Stress/exercise/infection/pneumovax

CAPS cryopyrin-associated periodic syndrome, *FCAS* familial cold autoinflammatory syndrome, *MWS* Muckle–Wells syndrome, *CINCA* chronic infantile neurologic cutaneous articular syndrome, *NOMID* neonatal onset multisystemic inflammatory disease

phase reactants such as C reactive protein and erythrocyte sedimentation rates are common at baseline and may not change significantly during a flare. Microcytic anemia and thrombocytosis may also occur due to chronic inflammation. Cerebrospinal fluid analysis often reveals chronic increased intracranial pressure and leukocytosis [16]. Skin biopsy shows dermal edema primarily with neutrophil infiltration in the dermis, especially in the perivascular regions and near sweat glands [15]. Bone radiologic examinations show calcified physeal lesions and osteoporosis, and pathologic analysis demonstrates disorganized cartilage without inflammation [14].

CAPS as an Autoinflammatory Syndrome

The unique and multi-systemic clinical and laboratory features of this disease continuum and low incidence of this orphan disease have resulted in many patients with misdiagnosis and significant delays in diagnosis [10]. Additionally, these patients often present to a wide variety of medical providers such as primary care physicians and different specialists including dermatologists, rheumatologists, ophthalmologists, otolaryngologists, neurologists, infectious disease specialists, allergists, and clinical immunologists resulting in the lack of a medical home. This clinical paradox is similar to the experience of patients with a group of rare inherited syndromes known as the hereditary recurrent fever disorders including familial Mediterranean fever, hyper IgD syndrome, and tumor necrosis factor receptor–associated periodic syndrome. The identification of the genetic basis for these diseases led to the description of a new immune disease classification known as the autoinflammatory disorders to differentiate conditions that do not fit into the classical categories of immune dysregulation including immunodeficiency, allergy, or autoimmunity [17].

NLRP3 as a Disease Gene

The availability of large families with autosomal dominant inheritance of FCAS and MWS, combined with advances in human molecular genetics, led to the identification of heterozygous mutations in *NLRP3* (also known as *CIAS1* or *PYPAF1*), a novel gene coding for a protein with initial unknown function referred to as cryopyrin [18–20]. Clinical similarities between MWS and NOMID prompted scientists to search for *NLRP3* mutations in NOMID patients [21, 22]. While *NLRP3* mutations were identified in these patients, many NOMID patients without significant CNS and cochlear inflammation and a few FCAS and MWS patients did not have identifiable mutations by standard Sanger sequencing. It was later determined that most of these "mutation negative" patients are somatic mosaics, often possessing a small percentage of mutant cells within the myeloid lineage resulting in difficult to detect mutations [23]. Somatic mosaicism is clinically relevant as it makes genetic diagnosis and counseling more challenging and could have implications for the use of more definitive cell-based therapies in the future [24]. Approximately 100 pathogenic *NLRP3* mutations have been reported (Infevers accessed March 4, 2019) in CAPS patients [25] with strong genotype–phenotype correlation along the disease continuum (Fig. 1). In addition, a few low penetrance variants in *NLRP3* have also been reported not only in patients with typical or atypical CAPS phenotypes but also in unaffected people with no significant symptomatology. [29]. These variants have been shown to have less in vitro functional consequences than classic CAPS mutations and have also been found to be risk alleles for more common diseases in genetic association studies [30].

Cryopyrin Function

The success of the Human Genome Project allowed investigators to mine data for gene families based on structural domain similarities, resulting in the discovery of a large group of innate immune sensor proteins known as nucleotide oligomerization domain (NOD)-like receptors (NLRs) [31]. NLRs contain PYRIN domains (like NLRP3) and/or caspase activation recruitment domains (CARDs), which promote self-assembly. In addition, NLRs possess central NOD domains where most disease mutations are located, suggesting an important functional role, and C-terminal Leucine-rich repeat domains. Some NLRs form the central structure of large intracellular multi-protein complexes known as inflammasomes that function to not only protect the cell from external and internal threats but also regulate homeostasis [32]. Inflammasomes are comprised of adaptor molecules, interacting regulatory proteins, chaperone proteins, and enzymatic effector molecules (Fig. 2).

Apoptosis speck-like protein containing CARD (ASC) is a multi-domain activating adapter molecule for caspase-1, which is mobilized during inflammasome assembly [33]. ASC is also referred to as PYCARD, representing the PYRIN domain at the N-terminus and CARD domain at the C-terminus [34–36]. The CARD domain facilitates caspase-1 binding and subsequent filament formation. ASC molecules congregate to form large masses near the nucleus resembling a "speck" readily visualized via microscopy; thus, speck formation is a valuable indicator of inflammasome activation [37]. ASC specks can also be expelled from the cell and internalized by nearby macrophages, causing further propagation of inflammation. ASC specks can also continue to be functional in the extracellular space [38, 39].

Caspases are cysteine proteases that act as enzymatic effector molecules in the inflammasome complex. Notably, caspase-1 is central to the canonical, or classical,

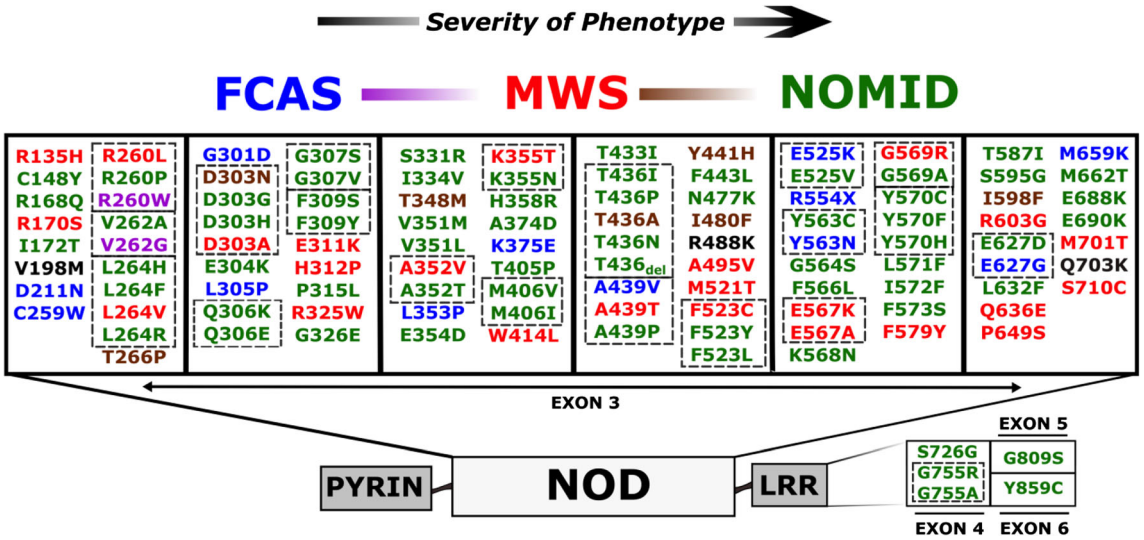

Fig. 1 *NLRP3* mutations reported in CAPS. Most CAPS disease-associated mutations are located in exon 3, which codes for the NOD domain, and there are a few mutations in C terminal exons that code for the LRR domain. Infevers (an online database for autoinflammatory mutations—https://infevers.umai-montpellier.fr/) [25–28] was accessed March 4, 2019, and all potential CAPS-associated mutations associated with a sub-phenotype were included. The presence of multiple mutations coding the same amino acid suggests mutational hotspots (indicated by interrupted line boxes). There is fairly consistent genotype–phenotype correlation indicated by colors: FCAS (blue), FCAS/MWS (purple), MWS (red), MWS/NOMID (brown), NOMID (green), and low penetrance mutations (black). All mutations are numbered according to the second methionine (although many mutation sequences utilize the first methionine which adds two amino acids to the reported variant). Familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), Neonatal onset multisystemic inflammatory disease (NOMID), nucleotide oligomerization domain (NOD), Leucine rich repeat (LRR)

inflammasome pathway [40], while caspase-4 and caspase-5 drive the non-canonical inflammasome pathway [41]. The canonical inflammasome pathway is defined by the caspase-1-mediated production of interleukin-1β (IL-1β) and IL-18. Cleavage of caspase by either pathway results in cleavage of gasdermin-D resulting in pyroptosis, a unique inflammasome-specific cell death distinguishable from apoptosis and necrosis, marked by the combined release of caspase-1 and lactate dehydrogenase [42]. Gasdermin-D is also associated with cleavage of pro-forms of inflammatory cytokines and release of mature cytokines [40, 43] such as IL-1β and IL-18 [44]. Release of cytokines also functions to further the inflammatory cascade by binding to IL-1 receptor or IL-18 receptor on the same or neighboring cells and increasing expression of inflammasome component proteins or pro-cytokines.

Normal inflammasome activation is dependent on a two-signal process. In the absence of either signal, the cryopyrin inflammasome remains inactive. Signal 1 is a priming step required to initiate recruitment of necessary components for assembly. Toll-like receptor (TLR) activation by PAMPs signals transcriptional factor NFκB to upregulate expression of crucial components of the inflammasome and pro-cytokines. Signal 2 then coordinates protein assembly and activation of the inflammasome complex [32]. There are a wide variety of signal 2 triggers including a myriad of DAMPs such as nucleic acids (ATP), aggregate proteins (amyloid), or crystals (monosodium urate or cholesterol) [45, 46]. Extracellular ATP can activate P2X7 receptor and promote ion efflux [47, 48]. Crystals or protein aggregates can cause lysosomal damage releasing proteases (cathepsins) or cell death generating further inflammasome stimuli. Several hypotheses have been proposed to elucidate the inherent ability of cryopyrin to respond to multiple stimuli including ion efflux and reactive oxygen species (ROS). Recent studies indicate a chief role of mitochondrial DNA or mitochondrial ROS in inflammasome activation [49].

Inappropriate inflammasome activation can lead to excessive inflammation and tissue damage illustrating the importance of selective triggers and tight regulation of inflammasomes. Regulation occurs at many levels, including transcriptional and post-translational processes influencing expression and modification of sensor proteins or other key inflammasome-associated proteins. For example, *NLRP3* is alternatively spliced which can affect protein function. Additionally, TTP and miR223 regulate transcription by binding upstream of *NLRP3* [50, 51]. Cytokines can also act like a positive feedback loop by binding to receptors and influencing transcriptional regulation of inflammasome components and pro-cytokines. Serine phosphorylation has also been implicated in regulating cryopyrin function [52, 53]. Some post-translational modifications can negatively regulate the inflammasome, such as S-nitrosylation by nitric oxide [54] or deubiquitination by E3 ligase, Ariadne homolog 2, or TRIM31 [55–57]. There are also endogenous cytokine receptor inhibitors that regulate downstream inflammation including IL-1 receptor antagonist (IL-1RA) and IL-18 binding protein which prevent cytokines from binding to their receptor [58].

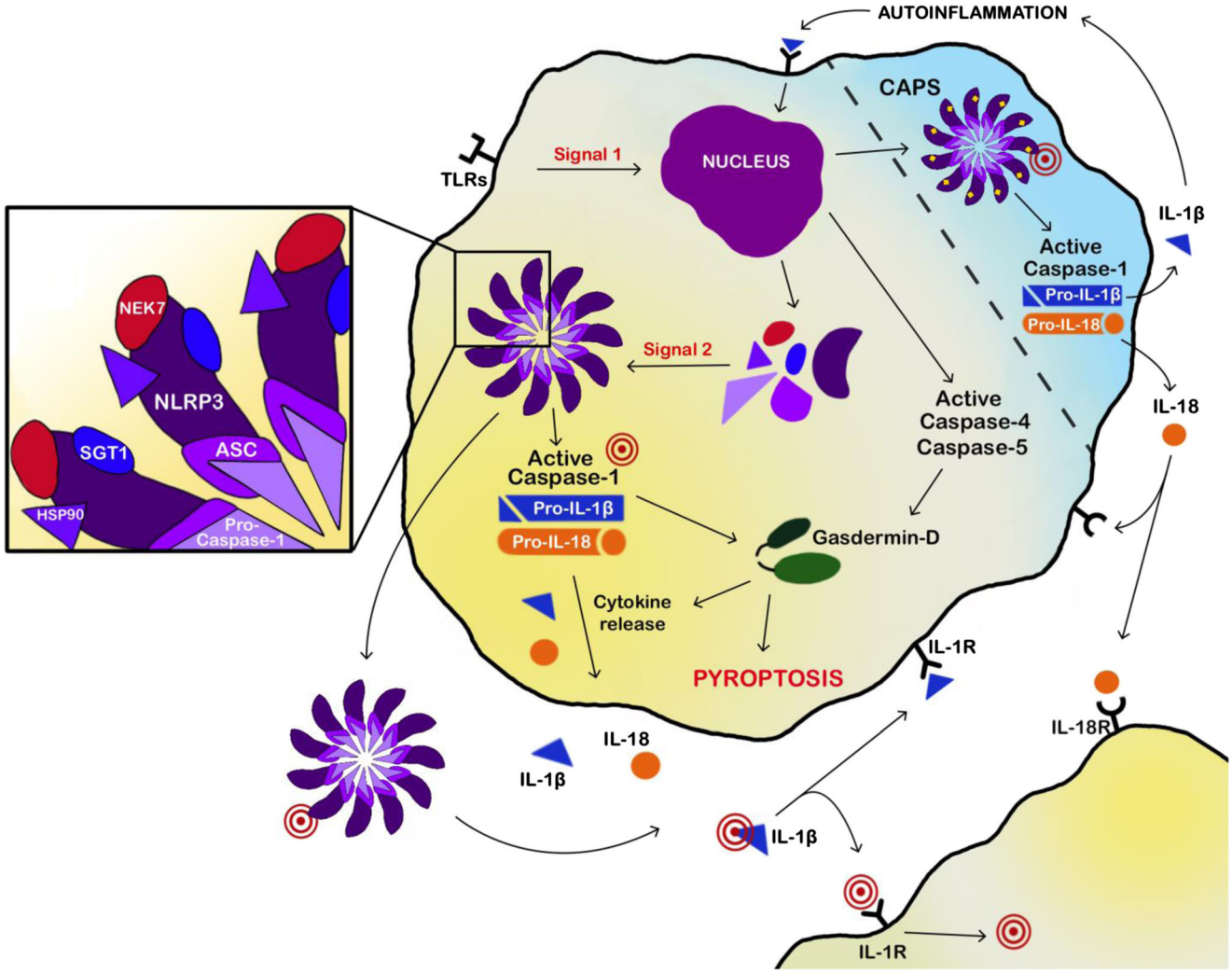

Fig. 2 Normal and mutant cryopyrin function. Normal activation of the cryopyrin inflammasome in monocytes and macrophages involves two signals: Signal 1 involves toll-like receptor (TLR) activation resulting in NFκB mediated expression of inflammasome protein components and pro-cytokines. Signal 2 involves various specific triggers such as nucleic acids, toxins, and crystals resulting in oligomerization of inflammasome protein components including cryopyrin, ASC, pro-caspase-1, NEK7, SGT1, and HSP90 into a multimeric ring like structure. Formation of the inflammasome leads to cleavage of caspases, gasdermin-D, and subsequent cleavage pro-IL-1β and pro-IL-18 with release of mature and active cytokines (IL-1β and IL-18) as well as pyroptosis. IL-1β and IL-18 bind to their respective receptors on the same cell resulting in autoinflammation or other cells resulting in a cascade of inflammatory signaling. Inflammasomes may be released from the cells as ASC specks where they may continue to be functional or be taken up by other macrophages. Activation of mutant (yellow dots) cryopyrin inflammasome does not depend on signal 2 resulting in inappropriate activation and inflammation. Several therapies directed at specific components (red targets) in the pathway are either available or in development

CAPS Disease Pathogenesis

CAPS-associated *NLRP3* mutations are gain of function leading to a hyperactive cryopyrin inflammasome, increased myeloid cell derived pro-inflammatory cytokine release, and systemic and tissue inflammation leading to disease symptoms. This is supported by in vitro studies using cell lines expressing recombinant inflammasome proteins [36]. Mutant cryopyrin does not require a signal 2 normally required for cryopyrin inflammasome assembly as observed in ex vivo studies using peripheral blood leukocytes isolated from CAPS patients and stimulated with LPS without ATP [59]. These cells demonstrate increased ASC speck formation, caspase-1 cleavage, IL-1β release, and pyroptosis. CAPS patient cells also demonstrate higher levels of reactive oxygen species due to elevated redox stress and ineffective anti-inflammatory mechanisms [60], and recently, CAPS mutations have been shown to have increased cryopyrin phosphorylation leading to inflammasome overactivation [52]. While the mechanisms have not been elucidated, monocytes from FCAS, but not MWS or CINCA/NOMID patients, produce IL-1β when cultured at 32 °C without LPS [61]. The excellent response of CAPS patients to IL-1 targeted therapy supports a significant role for IL-1β in CAPS disease pathogenesis.

CAPS knockin mutant mouse models were generated with *Nlrp3* mutations observed in FCAS, MWS, and CINCA/NOMID patients to further investigate mechanisms involved in CAPS pathogenesis. Bone marrow–derived cells from these mice show similar indications of hyperactivation of the cryopyrin inflammasome with cytokine release and speck formation with addition of LPS alone, or exposure to cold temperature in cells from FCAS, but not MWS or CINCA/NOMID mutant mice [62, 63]. The phenotype of the CAPS knockin mutant mice has many similarities to human CAPS in that the mice demonstrate systemic inflammation affecting the skin, eyes, joints, and central nervous system. Interestingly, the disease severity continuum is reversed in mice with FCAS mice being the most severe and CINCA/NOMID mice being the least affected [62, 64]. IL-1 targeted therapy in the mutant mice has not been as effective as observed in CAPS human patients [62]. Genetic studies utilizing various knockout mice in the inflammasome pathway show that the disease phenotype is dependent on ASC and caspase-1, partially dependent on IL-1β, IL-18, TNF, and pyroptosis and independent of IL-6 and IL-17 [24, 62, 65–67]. The murine disease is primarily myeloid cell driven with some data supporting a pathogenic role for mast cells [68] and no significant role for lymphocytes [62].

NLRP3 in Other Diseases

NLRP3 has been implicated in a wide variety of common diseases based on genetic association studies, gene expression analysis, or recombinant mouse models [32]. Cryopyrin activation is also shown to mediate the inflammatory response in tumor necrosis factor–associated periodic syndrome (TRAPS) patients, another monogenic auto inflammatory disorder displaying fever, rash, ocular, and musculoskeletal symptoms. Initially, TNF receptor shedding was reported as the pathogenic mechanism [17], but later, data including mutant knockin mouse studies supported a role for cryopyrin inflammasome activation through a number of potential mechanisms, including elevated mitochondrial reactive oxygen species generation [69, 70]. Effective IL-1 targeted therapy in TRAPS also points to a role for a dysfunctional cryopyrin inflammasome.

Targeting the NLRP3 Pathway in CAPS

The discovery of mutations in *NLRP3* in CAPS patients and the elucidation of cryopyrin function prompted investigators to attempt IL-1 targeted therapy. Anakinra, a recombinant form of IL-1RA, was initially studied in sepsis without success, but later approved in rheumatoid arthritis in 2001. It was therefore available for proof-of-concept trials in CAPS patients. Hawkins et al. treated two MWS patients with daily anakinra injections and showed that it prevented all CAPS related symptoms and reduced serum amyloid A to normal levels [71]. We treated three FCAS patients with two injections prior to an environmental challenge and demonstrated prevention of all FCAS-associated symptoms, blunted blood leukocytosis, and reduction in serum IL-6 levels [15]. Additional investigator-initiated trials using daily anakinra in patients with FCAS and MWS confirmed these translational therapeutic successes [72, 73], but it was the remarkable efficacy in patients with CINCA/NOMID [16], the most severe CAPS phenotype, that has had the most impact on patients and later resulted in FDA and EMA approval (Table 2).

The success of anakinra in CAPS suggested that inhibiting IL-1-mediated inflammation alone was sufficient to prevent CAPS-associated symptoms, and this was supported by similar clinical success with additional IL-1 targeted drugs in development. Rilonacept, a dimeric IL-1 receptor fusion protein with a longer half-life, provided similar efficacy in FCAS and MWS patients with favorable weekly dosing. A successful clinical trial supported Rilonacept as the first FDA-approved therapy in CAPS in 2008 [74]. Canakinumab, a monoclonal antibody against IL-1β demonstrated similar efficacy with every 2 month dosing and was approved for MWS

Table 2 Currently approved therapies for CAPS

	Anakinra	Rilonacept	Canakinumab
Pharmacology	IL-1 receptor antagonist	IL-1 receptor fusion protein	IL-1β monoclonal antibody
Half- life	~4–6 h	~8 days	~26 days
Approved dosage (Ped)	100 mg (1–8 mg/kg) sq	160–320 mg (2.2–4.4 mg/kg) sq	150–300 mg (2–4 mg/kg) sq
Dosage frequency	1 day	1 week	4–8 weeks
Side effects	Infection, site reaction	Infection, site reaction	Infection, vertigo
FDA approval (Age)	CINCA/NOMID (8 months)	FCAS/MWS (12 years)	FCAS/MWS (2 years)
EMA approval (Age)	CAPS (8 months)		CAPS (2 years)

CAPS cryopyrin-associated periodic syndrome, *FCAS* familial cold autoinflammatory syndrome, *MWS* Muckle–Wells syndrome, *CINCA* chronic infantile neurologic cutaneous articular syndrome, *NOMID* neonatal onset multisystemic inflammatory disease, *Ped* pediatric dosing, *Age* age approved for treatment, *mg* milligram, *kg* kilogram, *sq* subcutaneous

and FCAS in 2009 [75]. Early on, physicians realized that higher dosing of each of these treatments was required in more severely affected patients, while lower dosing was sometimes effective in milder patients further supporting the clinical spectrum of CAPS. While IL-1-targeted therapy may ameliorate clinical abnormalities including progressive hearing loss, brain MRI findings, and early renal disease from amyloidosis, the clinical response in patients with stable deafness, cartilage or bone hypertrophy, or chronic renal failure is often poor [9, 76]. Longer studies with these therapies showed continued efficacy over 1–2 years [77, 78], but clinical experience over the last decade has illustrated that some CAPS patients are less responsive over time and require higher or more frequent dosing or switching of therapies [79, 80] All of the IL-1 targeted therapies are associated with increased frequency of non-opportunistic infections prompting early use of antibiotics [74, 75, 77, 78]. Vaccination to prevent common bacterial and viral infections is warranted but needs to be balanced with reports of significant local reactions or symptomatic episodes following pneumococcal vaccines. Vertigo has been reported in some CAPS patients on canakinumab [75, 78]. Efficacy, safety, and cost concerns and the desire for effective oral medicines have prompted a search for alternative or adjunctive treatments including higher potency IL-1 blockers as well as small molecule inhibitors targeting downstream or upstream in the NLRP3 pathway.

IL-1 receptor blockers showed efficacy so targeting IL-1 receptor signaling with specific small molecule inhibitors is a logical approach [81] but has not progressed to clinical studies in CAPS patients. Since enzymes like caspases are often amenable to pharmacologic targeting, and caspase-1 inhibitors were in clinical development, specific caspase-1 inhibitors were studied in CAPS ex vivo and in vivo models [82]. While the drugs demonstrated some efficacy in pre-clinical studies, it was challenging to achieve adequate serum drug levels and clinical efficacy. Recently, there has been tremendous interest in targeting the cryopyrin inflammasome directly due to the role of NLRP3 in so many common inflammatory and non-inflammatory diseases. Successful preclinical studies using MCC950 in a CAPS mouse model [83] suggest that similar drugs may provide a more reliable long-term therapy for CAPS patients in the near future. Current recommendations for monitoring organ inflammation and targeting symptom resolution may be referenced in other works focused on management of CAPS [84].

Conclusions

The journey from the initial description of FCAS in 1940 to the discovery of *NLRP3* and function of the cryopyrin inflammasome and finally to the application of effective targeted therapies in patients around the world is one of the best examples of translational medicine success. The field began with important detailed clinical descriptions and classification of patients with FCAS, MWS, and CINCA/NOMID by astute clinicians followed by methodical application of modern human genetics techniques. Crucial molecular studies that defined the structure and function of the cryopyrin inflammasome followed by pre-clinical and clinical studies using novel targeted therapies have made a significant impact on our understanding of the regulatory pathways of the innate immune system, but more importantly on the lives of patients with CAPS. Although current anti-IL-1 therapies have proven successful in CAPS, continued mechanistic and therapeutic investigations will further elucidate the normal and pathogenic functions of cryopyrin and are likely to provide more direct and effective treatments not only for these patients but also for patients with more common diseases.

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Compliance with Ethical Standards

Conflict of Interest Dr. Hoffman has received speaking fees from Novartis; consulting fees from Novartis, SOBI, Regeneron, and IFM; and research funds from Glaxo Wellcome, Vertex, Burroughs Wellcome, and Jecure.

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