Published in final edited form as:
Curr Rheumatol Rep. 2011 April ; 13(2): 123–131. doi:10.1007/s11926-011-0165-y.

Current Status of Understanding the Pathogenesis and Management of Patients With NOMID/CINCA

Raphaela Goldbach-Mansky

Abstract

Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic, cutaneous, and arthritis (CINCA) syndrome is the most severe clinical phenotype in the spectrum of cryopyrin-(NLRP3/NALP3) associated periodic syndromes (CAPS). The study of patients with NOMID/CINCA has been instrumental in characterizing the extent of organ-specific inflammatory manifestations and damage that can occur with chronic interleukin (IL)-1β overproduction. Mutations in CIAS1/NLRP3 lead to constitutive activation of the "NLRP3 inflammasome," an intracellular platform that processes and secretes increased amounts of IL-1β. The pivotal role of IL-1β in NOMID/CINCA has been demonstrated in several clinical studies using IL-1—blocking agents that lead to rapid resolution of the inflammatory disease manifestations. NOMID/CINCA is a monogenic autoinflammatory syndrome; and the discovery of the role of IL-1 in NOMID has led to the exploration in the role of IL-1 in other disorders including gout and Type II diabetes. The inflammation in NOMID/CINCA is continuous with intermittent flares, and organ manifestations encompus the central nervous system, eye, inner ear, and bones. This review discusses updates on the pathogenesis of NOMID/CAPS, emerging long term-outcome data regarding IL-1—blocking agents that have influenced our considerations for optimal treatment, and a monitoring approach tailored to the patient's disease severity and organ manifestations.

Introduction

The monogenic autoinflammatory syndrome CAPS (cryopyrin-associated periodic syndrome) includes a spectrum of diseases ranging from the milder manifestations of familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) to the clinically most severe form, neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurologic, cutaneous, and arthritis (CINCA) syndrome in Europe.

NOMID/CINCA typically occurs sporadically without a family history and de novo mutations in NLRP3 (CIAS1) are found in 50% to 60% of patients [1, 2]. Genetic mutations in the NACHT domain of CIAS1/NLRP3 were first discovered via positional cloning in large families with FCAS and MWS [3], and founder mutations in FCAS have been described [4]. To date, more than 90 mutations associated with a CAPS phenotype have been reported [5]. The clinical phenotype in NOMID involves more extensive organ inflammation than in FCAS and MWS, and the molecular basis for this disparity is still not well-understood. Gene-phenotype studies indicate that certain mutations are associated only with a mild clinical phenotype, and others with more severe phenotypes, but there remains considerable phenotypic heterogeneity in the disease extent in patients with the same mutation [6, 7]. The protein encoded by CIAS1/NLRP3 is a component of an interleukin (IL)-1β and IL-18 activating platform, an "inflammasome," and the pivotal role of IL-1 in patients with CAPS has been clinically confirmed in several studies blocking IL-1β.

Patients with NOMID/CINCA present with fever and aneutrophilic rash and with eye, central nervous system (CNS), and inner ear inflammation. Failure to control the

inflammation can lead to irreversible organ damage and disability. These observations and the rapid clinical response to IL-1—blocking therapy have made it imperative to treat patients early and aggressively in an attempt to retard and prevent organ damage. It is important to stress that lumping the different phenotypes of FCAS, MWS, and NOMID under the syndrome CAPS is justified on the basis of the disease pathogenesis, but as the extent of organ damage and permanent disability vary considerably among patients with FCAS, MWS, and NOMID, the clinical outcome measures and monitoring requirementsmust be tailored to each patient's individual needs and disease severity. Recent in vitro and in vivo studies focusing on identifying triggers that activate the inflammasome have led to the recognition that the NLRP3 inflammasome is a critical sensor of cellular stress and a platform that coordinates an immune response to cellular stressors through the activation and secretion of the proinflammatory cytokines IL-1β and IL-18. Interestingly, an important role for IL-18 in the contribution to the inflammatory phenotype in NOMID and CAPS in human disease seems unlikely given the impressive and mostly complete responses to IL-1 blockade; this notion is supported by recent data showing sustained responses after several years of treatment.

The Clinical Phenotype of CAPS and NOMID

Inflammatory Organ Manifestations and Organ Damage as a Result of Chronic Cumulative Inflammatory Damage Inflammatory episodes of fever, urticarial rash, and joint pain, and elevations in acute-phase reactants are present in all CAPS patients, regardless of the overall disease severity. In FCAS, the episodes are triggered by cold exposure and are self-limited within 12–24 h. Although they are associated with a significant impact on the quality of life; they are not associated with organ damage or physical disability. In MWS, progressive hearing loss develops later in life than in NOMID patients, but the cognitive and physical disability and short stature seen in NOMID patients are not observed in MWS. Amyloidosis in MWS is mainly reported in patients from Europe (see below). In contrast, NOMID patients have cognitive impairment; develop progressive hearing and vision loss, short stature, and physical disability from bone and joint deformities; and have increased mortality [8, 9]. Careful clinical phenotyping of NOMID/CINCA patients before and after therapy with IL-1—blocking agents has allowed to distinguish which organ manifestations respond to IL-1 blockade, and has shed light on the pathogenesis of the organ damage. Organ manifestations that are inflammatory in nature and those that represent organ damage inNOMID/CINCApatients are listed in Table 1 and discussed below:

1. Systemic inflammation presents clinically with fever, fatigue, loss of energy, and myalgias caused by the systemic release of proinflammatory cytokines, namely IL-1β in CAPS. IL-1 was discovered as a potent pyrogenic mediator, which was further demonstrated in several phase 1 and phase 2 studies in the early-1990s in which recombinant IL-1α or IL-1β was injected into patients with solid tumors [10]. Systemic inflammation is monitored by serial measurements of acute-phase reactants, white blood cell count, and platelet count. Chronic systemic inflammation causes growth retardation in children, and heights below the third percentile were seen in about 75% of patients in our initial cohort [8]. Osteopenia/ osteoporosis is common, and patients are at increased risk for the development of amyloidosis, which has a higher prevalence in Europe, where the incidence can be as high as 25% in cases of MWS [11]. Although amyloidosis was also seen in NOMID/CINCA patients in France and elsewhere in Europe [9, 12], we have thus far not seen amyloidosis in any of the approximately 40 patients with NOMID in the United States. This is in line with epidemiologic studies suggesting that environmental factors in old world countries may significantly contribute to the risk of developing amyloidosis [13].

2. The skin manifestations in CAPS are urticaria like and caused by a neutrophilic infiltrate in the dermis. Interestingly, skin lesions can clinically wax and wane and even disappear before effective treatment is initiated. Permanent skin damage is typically not observed, although in all CAPS patients with longstanding disease who arediagnosed in adulthood, flushing and light erythema can be observed. This is also the case for clubbing, which is present in patients of the entire spectrum of CAPS.

3. Eye involvement can include conjunctivitis; anterioruveitis; corneal infiltrates; papilledema; and, rarely,posterior uveitis. These inflammatory lesions can result in permanent damage, including band keratopathy, corneal clouding, retinal scarring, and optic nerve atrophy, all of which can lead to impairment in vision and present as progressive loss of visual field and/or visual acuity [8,14, 15].

4. Progressive hearing loss is a consequence of cochlear inflammation, which can be visualized on ontrastenhanced, fluid-attenuated inversion recovery MRI [8]. MRI enhancement of the cochlea can improve with treatment, which suggested an inflammatory-induced hearing loss. Interestingly, damage to the neuroepithelial Corti hair cells was found in necrobiopsy of the inner ears of MWS patients [12]. Inner ear inflammation leads to hearing loss that can initially improve on treatment in some patients [8], however persistent and chronic, longstanding and severe hearing loss is irreversible. Sensorineural hearing loss in most patients with NOMID/CINCA becomes clinically evident in the first decade of life, which is in contrast to MWS, in which progressive neurosensory hearing loss often develops significantly later in life. Hearing loss is absent in patients with FCAS.

5. 5. CNS manifestations can be the most devastating. Aseptic meningitis and increased intracranial pressure are common. MRI findings indicative of inflammation are leptomeningeal enhancement and cochlear enhancement. Findings suggestive of organ damage include ventriculomegaly and brain atrophy both are sequela of long-standing increased intracranial pressure. Arachnoid adhesions likely develop due to chronic leptomeningeal inflammation. Although these findings are present in many untreated NOMID patients, they are not observed in patients with milder disease [16]. A range of severity of cognitive impairment in patients with NOMID is also observed [8, 9, 12]. Other CNS manifestations include seizures, stroke and other vascular occlusive events, often at sites of intravascular catheters [8].

6. The incidence of the characteristic bony overgrowth in NOMID varies considerably among reports. The initial reports with higher incidence rates were likely biased by the fact that patients with severe bone deformities were recognized more easily as having NOMID [9, 17,18]. The “bony lesions” often lead to tumor-like protrusions originating from the growth plates. Reduced longitudinal growth of the affected bone results in limb length discrepancies and joint contractures, which can be associated with significant loss of mobility and, in some patients, the inability to walk. Physical disability in patients with NOMID is also caused by the severe growth retardation. Other variable findings include frontal bossing and, flattening of the nasal bridge.

New Perspectives on the Pathogenesis of CAPS/NOMID

Recently, several studies have addressed issues regarding the pathogenesis of NOMID. These include the genetic cause of disease in “mutation-negative” NOMID patients, the reason for continued growth of existing bone lesions in NOMID despite IL-1—blocking therapy, understanding triggers of disease flares in NOMID and MWS, identifying mediator

pathways downstream of IL-1 (with particular interest in the role of IL-17), and understanding the spectrum of increasing disease severity in CAPS. Mutation-Negative NOMID/CINCA: Does It Exist? About 30% to 50% of patients who present clinically with NOMID/CINCA and respond favorably to therapy with IL-1—blocking agents are negative for mutations in NLRP3/CIAS1 by genetic analysis based on Sanger sequencing of DNA prepared from peripheral blood. There is no difference in clinical phenotype in patients with and those "without" mutations except for a difference in IL-1 release from peripheral blood mononuclear cells. (Gattorno et al.) Recent reports have shown the presence of somatic mosaicism in such "mutation-negative" patients [19, 20].

Low-level mosaicism causing disease was also reported in a patient with clinical NOMID who had a de novo somatic genetic mutation (D303H) in CIAS1 in 30% to 38% of circulating leukocytes and epithelial cells [21]. The extent to which somatic mosaicism in NOMID/CINCA can account for mutation-negative cases and the cell types carrying the mutations are areas of active investigation.

Why Do Bone Lesions Continue to Grow on Interleukin-1—Blocking Therapy? Bone lesions in NOMID/CINCA do not have an inflammatory cell infiltrate [17] and continue to grow upon treatment with anakinra [12, 22]. Bone lesions in NOMID have clinical and histologic similarities to those from patients with fibrous dysplasia (FD) and osteochondral myxomas, which suggests the possibility of shared mediator pathways between the different disorders. NOMID cell lines derived from a tumor like lesion and also from nonlesional cartilage from the same patient showed that most NOMID tumor cells have characteristics of osteoblast progenitor cells that were isolated from fibroblastoid tumors in mice and humans. NOMID tumor cells have increased cyclic adenosine monophosphate (cAMP)—dependent protein kinase A (PKA) activity, which can lead likely to inflammation-independent activation of caspase-1 via overexpression of the proto-oncogene (and early osteoblast transcription factor) Ets-1.

Upregulation of caspase-1 was also seen in the lesional cells from the murine FD model. As previously described in osteochondral myxomas and FD, in NOMID tumor cells, activation of Wnt signaling was also observed [23]. These data suggest a shared amplification loop involving cAMP/PKA and caspase-1 in NOMID tumor cells and mice with FD-like bone lesions. This shared amplification loop is inflammation independent and can help explain the failure of IL-1—blocking therapy to control continued growth of the bone lesions once they are established.

What Triggers Disease Flares in NOMID?—In FCAS patients, cold exposure is a specific trigger of inflammatory flares, but the triggers of disease flares in most NOMID/CINCA and MWS patients do not involve cold exposure; however, infections and physical and mental stress are known to exacerbate disease. Recent studies of the function of cryopyrin (NLRP3) have shed some light on possible disease triggers. CIAS1/NLRP3 was an unknown gene in humans before its discovery as the genetic cause of CAPS. Its structure containing a "leucine-rich repeat" and a NACHT domain is similar to that of pathogen-resistance receptors found in plants that recognize pathogen-specific signals [24]. This structural similarity raised the suspicion that NLRP3 may be a human intracellular "danger receptor." Since then, 23 human nucleotide-binding oligomerization domain—like receptor (NLR) family members have been identified [25]. Like NLRP3, three other NLR family members can form complexes with the adaptor protein apoptosis-associated speck-like protein containing a caspase activation and recruitment (CARD) domain (ASC) and pro—caspase-1 to generate IL-1β—activating platforms termed inflammasomes [26]. The NLRP3 inflammasome serves a dual role as a sensor for pathogen/danger recognition and as a platform to coordinate an early immune response via the processing and secretion of the

potent proinflammatory cytokine IL-1β [27]. An increasing number of varied stimuli can activate the NLRP3 inflammasome. These include exogenous danger signals such as microbial stimuli, including lipopolysaccharide; nucleic acids; muramyl dipeptide; several toxins (eg, nigericin, maitotoxin); environmental large inorganic crystalline structures, such as asbestos and silica, and adjuvants, including aluminum hydroxide (alum), which was previously used to boost vaccine responses. Endogenous triggers such as adenosine triphosphate, uric acid crystals, hyaluronan and heparan sulfate, and amyloid-β fibrils are released when tissues are stressed or cells are dying [25]. Whether members of a specific subset of the above-listed activators of the NLRP3 inflammasome are triggers that activate the inflammasome in patients with CIAS1/NLRP3 mutations, fueling a continuous baseline activity and triggering disease flares in NOMID/CINCA, is an interesting question in need of further investigation.

Is There a Common NLRP3 Activation Pathway?—The number of disparate NLRP3 activators makes it unlikely that each of them can bind directly to the NLRP3 inflammasome, which led to the hypothesis of the existence of a common molecule or pathway that can activate the inflammasome. The induced production of reactive oxygen species (ROS) by many of these triggers of the inflammasome has made the production of ROS an attractive candidate for such an activator of the NLRP3 inflammasome. ROS production is an evolutionary-conserved pathway to signal cellular stress, even in plants. One study suggested that ROS production following cellular stress leads to dissociation of a TXNIP/oxidoreductase thioredoxin complex, and that released TXNIP can bind to the leucine-rich repeat domain of NLRP3 and activate the inflammasome [27]. Another study suggested that inflammasome activation was caused by increases in the antioxidant enzyme superoxide dismutase-1 [28]. When ROS production was examined in patients with CAPS, the basal levels of ROS and the antioxidant system activation were both upregulated compared to controls. Upon stimulation with lipopolysaccharide, rapid further induction of ROS and of reducing conditions led to IL-1β processing and secretion that was accelerated in CAPS [29]. These data suggest a mechanism by which the inflammasome could be “constitutively”overactive in mutation-positive CAPS. Mitochondria are the major source of ROS production; thus, the impact of manipulation of the respiratory chain in mitochondria on inflammasome activation has been studied. Manipulations that prevent the removal of damaged mitochondria by blocking mitophagy/autophagy and by blocking complexes in the respiratory chain led to accumulation of ROS and subsequent inflammasome activation. ROS generation and inflammasome activation were both suppressed when the outer membrane voltage-dependent anion channels were blocked. These data suggest a role for mitochondrial dysfunction in NLRP3 inflammasome regulation [30]. Targeting a common pathway that modulates NLRP3 inflammasome activation could be an attractive new treatment strategy in diseases in which increased inflammasome activation has been implicated, including metabolic diseases such as gout and diabetes.

Is There a Role for Tissue-Specific Interleukin-1 Production?—The vast majority of in vitro evaluations of the triggers and responses of inflammasome activation have been conducted in myeloid cells, mainly from blood. However, the organ-specific disease pattern of NOMID/CINCA is difficult to explain on the basis of systemic IL-1 release in the blood. Interestingly, for example, hearing loss did not develop in cancer patients who were treated with subcutaneous recombinant IL-1α or IL-1β injections, and hearing loss is also absent in another neonatalonset autoinflammatory disease, DIRA (deficiency of the IL-1 receptor antagonist), which is caused by homozygous loss-of function mutations in the IL-1 receptor antagonist (IL1RN), which leads to absence of functional IL-1 receptor antagonist and uninhibited signaling of IL-1α and IL-1β [31]. Increasing evidence indicates that nonmyeloid, organ-specific cell lines from the brain, joints, and epidermis of the skin are

capable of producing and processing IL-1β and could thus initiate recruitment of immune cells into the tissue [32]. However, supportive studies in affected tissues are needed to confirm the relevance of organ-specific IL-1 production in human disease.

Which Mediator Pathways Downstream of Interleukin-1 Are Important in CAPS?—The development of human NLRP3 mutation knockin murine models has allowed the characterization of inflammatory mediators and adaptive immune responses downstream of IL-1 [33, 34]. The mice present with systemic inflammation and massive infiltrates of granulocytes in multiple organ tissues. One group reported high levels of IL-17, increased T-helper type 17 (Th17) cell differentiation and the development of anti-DNA antibodies [34], but another group showed that the disease also developed in Rag1 knockout mice, carrying the NLRP3 mutation which lack mature T and B cells, demonstrating that the disease can develop in the absence of Th17 cells [33]. Although IL- 1 is known to contribute to Th17 differentiation, the contribution of IL-17 to autoinflammation in the monogenic IL-1 diseases remains controversial.

Is the Clinical Severity Gradient Seen in CAPS a Function of the Amount of Abnormal Interleukin-1β Production?—Although IL-1β is central to the pathogenesis of CAPS, it has been challenging to measure IL-1 production in serum or plasma, likely because of IL-1 binding to large proteins [35]. Administration of the long-acting anti-IL-1β antibody canakinumab has allowed the quantitation of IL-1β—canakinumab complexes and the calculation of basal levels of IL-1β production based on the amount of IL-1β bound in these complexes. Healthy controls were estimated to produce about 6 ng/dL of IL-1β, and patients with FCAS/MWS about 31 ng/dL [36]. These levels are even higher in NOMID/CINCA patients (personal observations). These data lend support to the notion that the severity gradient of clinical disease from FCAS to NOMID may be a consequence of the amount of IL-1 production, which could also explain the substantially higher doses of IL-1—blocking therapy needed to control inflammation in patients with NOMID.

Can Interleukin-1—Blocking Therapy Get Into the Brain?—Of particular concern has been the ability of IL-1 blocking agents to cross the blood–brain barrier to ensure optimal suppression of CNS inflammation in NOMID. The pharmacokinetics of two dose levels of anakinra thus were studied in a nonhuman primate model. The study confirmed hat anakinra can even cross the blood–brain barrier in animals without meningitis; the drug exposure in the cerebrospinal fluid (CSF) was 0.28% of that in serum, but the decline in CSF anakinra concentration was slower than in serum. At a 10-mg/kg dose, the exposure in both serum and CSF increased by 3.7-fold compared with the 3-mg/kg dose [37], thus providing a rationale to increase anakinradoses in patients with ongoing CNS inflammation who are receiving lower drug doses. This seems particularly important because residual CNS inflammation has been observed in long-term follow-up studies [12].

Long-Term Management of CAPS

Clinical Trials in CAPS and Safety of Interleukin-1 Blockade—Treatment with IL-1—blocking therapies is lifelong, as drug withdrawal leads to disease flares. Three different strategies to block IL-1 have been used in clinical trials. Anakinra (Kineret; Biovitrum, Stockholm, Sweden) is a recombinant human IL-1 receptor antagonist with a halflife of 4–6 h that was approved by the US Food and Drug Administration (FDA) in 2001 for the treatment of rheumatoid arthritis. Rilonacept (Arcalyst; Regeneron Pharmaceuticals, Tarrytown, NY) is a recombinant human IL-1 receptor–Ig fusion protein with a half-life of 34–57 h that was approved by the FDA in February 2008 for treatment of CAPS. Finally, canakinumab (Ilaris; Novartis, Basel, Switzerland) is a humanized anti–IL-1β antibody with a half-life of 21–28 days that was approved by the FDA in June 2009 for treatment of

CAPS. Anakinra is administered via daily subcutaneous injections. Despite several open-label trials in CAPS, this drug has not been approved by the FDA for the treatment of CAPS [8, 12, 38–40]. The efficacy of anakinra in reducing the clinical symptoms and in controlling serum inflammatory markers for up to 26–42 months in cohorts of 10 [12] and more than 20 [22] patients with NOMID/CINCA was sustained, and quality of life improved as well [41]. Improvements in growth parameters and neurological outcomes were seen; however, persistence of CNS inflammation and ongoing hearing loss were observed in some patients [12, 22]. Anakinra doses ranged from 1 to 10 mg/kg per day, with good tolerability of treatment [12]. The two longer-acting IL-1—blocking medications, rilonacept and canakinumab, were approved by the FDA for the treatment of FCAS and MWS under the orphan drug program and have been studied in controlled trials that led to their approval. Weekly subcutaneous injections of rilonacept were efficacious in the treatment of FCAS and MWS in a placebo-controlled study (n=44) [42]. In an open-label dose-finding study, five patients showed long term efficacy at 2-year follow-up [43]. Four patients, three with MWS, required higher doses of medication for optimal disease control. Subcutaneous injections of canakinumab every 8 weeks were given to 35 patients in a randomized withdrawal study [44]. Complete remission was seen in 97% of the patients upon treatment, and randomization to placebo led to disease flares in 81% of patients, whereas all patients on treatment remained in remission. Several long-term outcome studies with the different agents are ongoing. All three currently approved IL-1—blocking agents are generally well-tolerated. There is no evidence of an increase of opportunistic infections in CAPS and no evidence of an increase in malignancies. The most common side effect with anakinra is an injection site reaction within the first 4 weeks of therapy. The development of injection site reactions is uncommon after the first month of therapy. The incidence of infection was only marginally higher in anakinra-treated rheumatoid arthritis patients compared with those receiving placebo. Most patients continued on the study drug after the infection resolved. However, the combination of anakinra with the tumor necrosis factor—blocking agent etanercept for up to 24 weeks led to an incidence of serious infections of up to 7% [45]. The most commonly reported adverse reactions associated with rilonacept were injection site reactions, which were mild. In 360 patients treated with rilonacept and 179 treated with placebo, the incidence of infection was 34% and 27%, respectively. One Mycobacterium intracellulare infection after bursal injection in a patient with Still's disease and one death from Streptococcus pneumoniae meningitis occurred [46]. In the canakinumab studies, injection site reactions occurred in up to 9% of patients, and up to 14% of patients developed vertigo with the injections [47].

Therapeutic and Monitoring Considerations in NOMID/CINCA Based on Disease Phenotype and Severity

Measuring Disease Response in NOMID and Monitoring Based on the localization of inflammation in NOMID/CINCA described in the first section and evidence that most of the organ manifestations, except for the continued growth of bone lesions, are IL-1 mediated, the disease outcomes and the monitoring of disease activity need to be tailored to the severity of the underlying disease. A consensus to assess symptoms of CAPS was recently published [48]. However, the difference in organ manifestations and disability in the spectrum of CAPS requires assessment and monitoring plans tailored to the organ manifestations seen at baseline. Table 2 lists a comprehensive assessment approach for patients with NOMID that was developed to determine disease extent of organ involvement before the use of IL-1—blocking therapy, to follow organ inflammation on treatment, and to monitor progression of organ damage and organ function. Dose adjustments of IL-1—blocking agents to achieve inflammatory remission need to be made with the goal of suppressing inflammation systemically and at the organ level (particularly CNS and inner ear inflammation). Current dosing regimens are derived from open-label studies in NOMID

with anakinra, but dynamic dose adjustments to determine individual dose levels that optimally suppress inflammation need to be defined more clearly. This is particularly important for the longer-acting agents with limited experience in treating NOMID patients with severe disease.

Conclusions

Studying patients with NOMID/CINCA has allowed us to define the extent of organ disease and damage caused by overproduction and secretion of IL-1β. Although caspase-1 cleaves IL-1β and IL-18, clinical trials with IL-1—blocking agents have confirmed the pivotal role of IL-1β in patients across the entire spectrum of CAPS. The disease severity in NOMID requires special assessment and monitoring of the involved organs and aggressive treatment adjustments to control not only the systemic, but also the organspecific disease manifestations. Characterizing the underlying disease extent and monitoring organ-specific inflammation in NOMID is important, as cumulative inflammation can lead to progressive and permanent organ damage. Ongoing studies in NOMID need to address optimal dosing of IL-1— blocking therapies with the goal of preventing the progression of organ damage (secondary prevention) and preventing the development of any organ damage in young patients who do not yet have organ damage at the time of treatment initiation (primary prevention). Understanding the role of the NLRP3 inflammasome as a sensor of cellular stress and danger and the characterization of conditions that lead to NLRP3 inflammasome activation have revealed a role for the NLRP3 inflammasome and IL-1 beyond NOMID, CAPS, and monogenic autoinflammatory diseases, but also including polygenic metabolic diseases, such as gout, type 2 diabetes, and atherosclerosis.

Acknowledgments

Disclosure Dr. Goldbach-Mansky has received grant support from Novartis and Regeneron Pharmaceuticals.

References

1. Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E, et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet. 2002; 71:198–203. [PubMed: 12032915]
2. Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, et al. De novo CIAS1 mutations, cytokineactivation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrinassociated autoinflammatory diseases. Arthritis Rheum. 2002; 46:3340–8. [PubMed: 12483741]
3. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet. 2001; 29:301–5. [PubMed: 11687797]
4. Hoffman HM, Gregory SG, Mueller JL, Tresierras M, Broide DH, Wanderer AA, et al. Fine structure mapping of CIAS1: identification of an ancestral haplotype and a common FCAS mutation, L353P. Hum Genet. 2003; 112:209–16. [PubMed: 12522564]
5. [Accessed January 2011] Infevers: an online database for autoinflammatory mutations. Available at http://fmf.igh.cnrs.fr/ISSAID/infevers/index.php.
6. Neven B, Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L, et al. Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. Blood. 2004; 103:2809–15. [PubMed: 14630794]
7. Aksentijevich I, Putnam D, Remmers EF, Mueller JL, Le J, Kolodner RD, et al. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. Arthritis Rheum. 2007; 56:1273–85. [PubMed: 17393462]

8. Goldbach-Mansky R, Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. N Engl J Med. 2006; 355:581–92. [PubMed: 16899778]
9. Prieur AM, Griscelli C, Lampert F, Truckenbrodt H, Guggenheim MA, Lovell DJ, et al. A chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome. A specific entity analysed in 30 patients. Scand J Rheumatol Suppl. 1987; 66:57–68. [PubMed: 3482735]
10. Dinarello CA. Biologic basis for interleukin-1 in disease. Blood. 1996; 87:2095–147. [PubMed: 8630372]
11. Muckle TJ. The `Muckle-Wells' syndrome. Br J Dermatol. 1979; 100:87–92. [PubMed: 427013]
12. Neven B, Marvillet I, Terrada C, Ferster A, Boddaert N, Couloignier V, et al. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheum. 2010; 62:258–67. [PubMed: 20039428]
13. Touitou I, Sarkisian T, Medlej-Hashim M, Tunca M, Livneh A, Cattan D, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum. 2007; 56:1706–12. [PubMed: 17469185]
14. Dollfus H, Hafner R, Hofmann HM, Russo RA, Denda L, Gonzales LD, et al. Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease syndrome:ocular manifestations in a recently recognized chronic inflammatory disease of childhood. Arch Ophthalmol. 2000; 118:1386–92. [PubMed: 11030821]
15. Rigante D, Stabile A, Minnella A, Avallone L, Ziccardi L, Bersani G, et al. Post-inflammatory retinal dystrophy in CINCA syndrome. Rheumatol Int. 2010; 30:389–93. [PubMed: 19424698]
16. Kitley JL, Lachmann HJ, Pinto A, Ginsberg L. Neurologic manifestations of the cryopyrin-associated periodic syndrome. Neurology. 2010; 74:1267–70. [PubMed: 20404307]
17. Hill SC, Namde M, Dwyer A, Poznanski A, Canna S, Goldbach-Mansky R. Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA). Pediatr Radiol. 2007; 37:145–52. [PubMed: 17136361]
18. Torbiak RP, Dent PB, Cockshott WP. NOMID—a neonatal syndrome of multisystem inflammation. Skeletal Radiol. 1989; 18:359–64. [PubMed: 2781338]
19. Saito M, Fujisawa A, Nishikomori R, Kambe N, Nakata-Hizume M, Yoshimoto M, et al. Somatic mosaicism of CIAS1 in a patient with chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheum. 2005; 52:3579–85. [PubMed: 16255047]
20. Saito M, Nishikomori R, Kambe N, Fujisawa A, Tanizaki H, Takeichi K, et al. Disease-associated CIAS1 mutations induce monocyte death, revealing low-level mosaicism in mutationnegative cryopyrin-associated periodic syndrome patients. Blood. 2008; 111:2132–41. [PubMed: 18063752]
21. Arostegui JI, Lopez S, Pascal M, Clemente D, Aymerich M, Balaguer F, et al. A somatic NLRP3 mutation as a cause of a sporadic case of chronic infantile neurologic, cutaneous, articular syndrome/neonatal-onset multisystem inflammatory disease: novel evidence of the role of low-level mosaicism as the pathophysiologic mechanism underlying mendelian inherited diseases. Arthritis Rheum. 2010; 62:1158–66. [PubMed: 20131270]
22. Goldbach-Mansky R, Plass N, Chapelle D, NOMID study group. Treatment of neonatal-onset multisystem inflammatory disease (NOMID/CINCA) with IL-1 blocker anakinra, after 3 years on treatment. Arthritis Rheum. 2008; 58:S633.
23. Almeida MQ, Tsang KM, Cheadle C, Watkins T, Grivel JC, Nesterova M, et al. Protein kinase A regulates caspase-1 via Ets-1 in bone stromal cell-derived lesions: a link between cyclic AMP and pro-inflammatory pathways in osteoblast progenitors. Hum Mol Genet. 2011; 20:165–75. [PubMed: 20940146]
24. Ausubel FM. Are innate immune signaling pathways in plants and animals conserved? Nat Immunol. 2005; 6:973–79. [PubMed: 16177805]
25. Ting JP, Duncan JA, Lei Y. How the noninflammasome NLRs function in the innate immune system. Science. 2010; 327:286–90. [PubMed: 20075243]

26. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell. 2002; 10:417–26. [PubMed: 12191486]
27. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxininteracting protein links oxidative stress to inflammasome activation. Nat Immunol. 2010; 11:136–40. [PubMed: 20023662]
28. Meissner F, Molawi K, Zychlinsky A. Superoxide dismutase 1 regulates caspase-1 and endotoxic shock. Nat Immunol. 2008; 9:866–72. [PubMed: 18604212]
29. Tassi S, Carta S, Delfino L, Caorsi R, Martini A, Gattorno M, et al. Altered redox state of monocytes from cryopyrin-associated periodic syndromes causes accelerated IL-1beta secretion. Proc Natl Acad Sci U S A. 2010; 107:9789–94. [PubMed: 20445104]
30. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature. Dec 1.2010 Epub ahead of print.
31. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, Royen-Kerkhoff A, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med. 2009; 360:2426–37. [PubMed: 19494218]
32. Yazdi AS, Drexler SK, Tschopp J. The role of the inflammasome in nonmyeloid cells. J Clin Immunol. 2010; 30:623–27. [PubMed: 20582456]
33. Brydges SD, Mueller JL, McGeough MD, Pena CA, Misaghi A, Gandhi C, et al. Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity. Immunity. 2009; 30:875–87. [PubMed: 19501000]

Table 1

Symptoms, inflammatory organ manifestations, and end-organ damage in NOMID/CINCA

Organ system	Symptoms	Inflammatory manifestations	End-organ damage
Systemic inflammation	Fever Headaches Arthralgia and myalgia	Systemic inflammation (ESR, CRP, SAA)	Growth retardation Osteoporosis Amyloidosis (more common in Europe)
Skin	Rash	Neutrophilic urticaria-like rash	Skin erythema, exuberant skin (rare), clubbing
Eye	Pink eyes Eye pain Acute and chronic vision change	Conjunctivitis Anterior uveitis Corneal infiltrates Posterior uveitis Papilledema	Band keratopathy Corneal clouding Retinal scarring Optic nerve atrophy (visual field constriction)
Inner ear/ Colchea	Progressive hearing loss	Cochleitis (cochlear inflammation)	Progressive permanent hearing loss
Central nervous system	Headache Early-morning vomiting Cognitive impairment Cognitive impairment	Leptomeningitis (CSF pleocytosis) Increased intracranial pressure	Brain atrophy Arachnoid adhesions
Musculoskeletal/ osseous manifestations	Joint pain Bone pain	Bony enlargement (not inflammatory)	Bone deformities Contractures Limb length discrepancy

CINCA chronic infantile neurologic, cutaneous, and arthritis (syndrome), CNS central nervous system, CRP C-reactive protein, CSF cerebrospinal fluid, ESR erythrocyte sedimentation rate, NOMID neonatal-onset multisystem inflammatory disease, SAA serum amyloid A.

Table 2

Monitoring organ-specific inflammation and damage in NOMID

Organ system	Monitoring disease activity in NOMID patients
Systemic inflammation	Symptomatic assessment (including rash) Acute-phase reactants (ESR, CRP, SAA), urine protein Height and weight, head circumference Dexa scan every 2–3 y until z scores normalize Physical examination
Eye	Ophthalmology subspecialty evaluation Monitor (anterior and posterior uveitis, corneal infiltrates), if present at baseline Monitor papilledema (improves quickly but resolves over 1–3 y) Visual acuity and visual field examination (yearly)
Inner ear/cochlea	Audiometry (every 3–6 mo) for first 3 y Cochlear MRI to monitor cochlear inflammation (if present at baseline)
CNS	Lumbar puncture (opening pressure, WBC count, protein) FLAIR MRI IQ testing, monitor school performance (early intervention program as needed)
Musculoskeletal/osseous	X-ray Rehabilitation

CNS central nervous system, CRP C-reactive protein, dexa dual-energy x-ray absorptiometry, ESR erythrocyte sedimentation rate, FLAIR fluid attenuated inversion recovery, NOMID neonatal-onset multisystem inflammatory disease, SAA serum amyloid A, WBC white blood cell count