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Therapy of autoinflammatory syndromes

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Abstract

The therapy of autoinflammatory syndromes is an excellent example of the power of translational research. Recent advances in our understanding of the molecular and immunologic basis of this newly identified classification of disease have allowed for the application of novel, effective, targeted treatments with life-changing effects on patients. Although colchicine and TNF-α inhibitors are important therapies for specific autoinflammatory syndromes, the novel IL-1–targeted drugs are particularly effective for many of these diseases. Recently, the pharmaceutical industry has adopted a strategy of confirming the efficacy of new targeted drugs in often-ignored patients with orphan diseases, and US Food and Drug Administration policies have allowed for accelerated approval of these drugs, creating a win-win situation for patients and industry. This article reviews the general approach to the therapy of autoinflammatory diseases, focusing on current approved therapies and novel approaches that might be used in the future.

Keywords

Autoinflammatory; IL-1; inflammasome

The traditional clinical classification of immune-mediated diseases, including allergy, immunodeficiency, and autoimmunity, is based on differences in immunologic mechanisms and clinical symptomatology and has defined the medical specialties caring for patients with immune-mediated illnesses for more than 60 years. However, in the last 10 years, a new category of immunologic disease, known as autoinflammatory diseases, has been created to account for disorders that did not fit well into the classical disease groups.[1] Although patients with these disorders can present with classic rheumatologic symptoms, including inflammation involving the joints, skin, muscles, and eyes, the underlying inflammatory mechanisms do not involve autoantibodies or antigen-specific T cells.[2] Some patients also display episodic or precipitated symptoms, including urticaria and conjunctivitis, similar to those seen in allergic patients, but there is no evidence of IgE-mediated inflammation. Recurrent fever is a common feature of both autoinflammatory disorders and infections caused by immune deficiency. However, insufficient immune response to pathogens is not an immunologic characteristic of autoinflammatory diseases.

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The autoinflammatory disorders are characterized by dysregulation of innate immunity, the arm of the immune system considered to be more primitive and less specific. Instead of lymphocyte or antibody responses to specific antigens based on a memory of prior exposure, innate immune cells, such as macrophages and dendritic cells, sense conserved pathogen-associated molecular patterns. The primary effectors of the innate immune response are myeloid cells, such as neutrophils and monocytes, and proinflammatory cytokines, including IL-1β and TNF-α.[3] Cells from patients with some autoinflammatory disorders appear to be hypersensitive to exogenous pathogen-associated molecular patterns and endogenous danger-associated molecular patterns or constitutively active, resulting in uncontrolled cytokine-mediated inflammation. The possible triggers or mechanisms underlying the increased innate immune responses have begun to be elucidated after advances in the genetic basis of these disorders. The role of the adaptive immune system in the pathophysiology of these disorders is still unclear.[4]

The diseases for which the autoinflammatory label was first applied are the hereditary fever disorders (Table I),[5–57] including familial Mediterranean fever (FMF), TNF receptor–associated periodic syndrome (TRAPS), and hyper-IgD syndrome. In addition, the cryopyrin-associated periodic syndromes (CAPS) have been included in this family and encompass a spectrum of diseases, including familial cold autoinflammatory syndrome (FCAS), the mildest form; Muckle-Wells syndrome (MWS), which is of intermediate severity; and neonatal-onset multisystem inflammatory disease (NOMID), the most severe phenotype (Fig. 1). Each of the hereditary fever diseases is characterized by recurrent episodes of systemic inflammation, including fever and other constitutional symptoms, as well as specific tissue inflammation, including joint and skin symptoms.[2,61] However, there are specific clinical features for each syndrome that might help the clinician to differentiate and direct appropriate diagnostic tests.[3] There are several recent reviews that describe the diagnostic approach to recurrent fever patients, but this is beyond the scope of this review.[62]

In the last decade, there have been major advances in our knowledge of the genetic basis and pathogenesis of the hereditary fever disorders. This has resulted in an expansion of the autoinflammatory disease category to include diseases with related genetic abnormalities but different clinical features, such as Blau syndrome, the syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne, mevalonic aciduria, pseudogout,[61] and the recently described deficiency of IL-1 receptor antagonist.[5,6] Further expansion of the category has resulted from the elucidation of the biology of several more common and complex diseases, such as gout, Crohn disease, systemic-onset juvenile idiopathic arthritis, and adult-onset Still disease. Finally, the expanding autoinflammatory disease family now includes other systemic inflammatory diseases with similar clinical features, such as Schnitzler syndrome, Behçet disease, and the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (Table I).[3] The accompanying review in this journal focuses on the genetics and biology of the growing family of auto-inflammatory syndromes, whereas this review focuses on current and future therapy.

GENERAL THERAPEUTIC CONSIDERATIONS

The primary treatment goal of reduction of inflammation in the autoinflammatory syndromes is similar to the clinical management of allergic and autoimmune diseases. Therefore it is not surprising that there is significant overlap in the therapeutic approaches for all of these conditions. Like most inflammatory diseases, the autoinflammatory disorders have features of chronic inflammation with effects on quality of life caused by constitutional symptoms and the potential for significant long-term morbidity, such as systemic amyloid A (AA) amyloidosis.[63,64] Similar to many classic inflammatory disorders, the autoinflammatory diseases are also often characterized by episodic symptomatic flares that are either unpredictable or elicited by specific triggers, such as cold exposure in patients with FCAS.[65] Therefore optimal therapies for the autoinflammatory diseases should be effective at both decreasing chronic inflammation and preventing acute flares but safe enough to be used for extended periods of time in these lifelong disorders. Until recently, controlled trials in patients with autoinflammatory syndromes were uncommon because of disease rarity and consequently a lack of pharmaceutical industry interest. This has changed in the last few years through the efforts of the US Food and Drug Administration (FDA) orphan disease program and industry recognition of the advantages of treating rare diseases as a proof of concept.

The pharmacologic approach to autoinflammatory disorders also parallels that of other inflammatory diseases. Traditional drugs, such as colchicine, used commonly in gout for centuries, are also the standard of care for FMF.[66] Recent advances in targeting specific cytokines, such as TNF-α, have had a major effect on the care of patients with autoimmune diseases, such as rheumatoid arthritis, but also have had a similar influence on the treatment of autoinflammatory disorders, including TRAPS and inflammatory bowel disease.[7] However, corticosteroids, used commonly in both allergic and autoimmune diseases, are often not effective in the primarily innate immune-driven autoinflammatory syndromes, such as FMF and CAPS, and newer drugs that target IL-1 and have had only a modest effect on the therapy of autoimmune disease are increasingly seen as the drug of choice for most autoinflammatory diseases.[67]

COLCHICINE

The therapy with the most important and widespread effect on autoinflammatory disorders is colchicine, a medication extracted from the meadow saffron and used since the first century for rheumatologic diseases, such as gout.[66] The serendipitous discovery of its effectiveness in the treatment of FMF in the early 1970s[68] and subsequent well-designed clinical trials demonstrating efficacy at preventing acute FMF episodes and chronic inflammation–driven systemic amyloidosis have resulted in significantly decreased morbidity and mortality throughout the world in thousands of patients because of its wide availability and low cost (Table I).[8–12] Although there are clear side effects caused by colchicine toxicity, including gastrointestinal, hematologic, and neuromuscular symptoms, it can be used safely in most patients if dosed appropriately and specific interacting drugs are avoided. Although colchicine has been the standard of care for FMF for more than 25 years, it was only recently that the FDA approved this ancient drug for gout and FMF.

The primary mechanism of action of colchicine is believed to be the inhibition of microtubule polymerization by binding to tubulin, which blocks cell mitosis in cells such as neutrophils. This is supported by the finding of decreased late-phase leukocyte accumulation in tissue from patients with FMF.[69] However, more recent data suggest that colchicine has additional anti-inflammatory mechanisms involving altered expression of adhesion molecules and chemotactic factors. Colchicine also has an effect on uric acid crystal deposition and possibly on the generation of reactive oxygen species,[70] factors that might play a role in the activation of pathways involved in other autoinflammatory disorders. Although colchicine is the standard of care for FMF, it is not effective in some patients with FMF or many patients with other autoinflammatory diseases and cannot be used in some patients because of side effects or concurrent medical conditions.

TARGETING TNF-α IN AUTOINFLAMMATORY DISEASE

The first translational success story in the autoinflammatory syndromes began with the positional cloning of the gene for TNF receptor 1 as the cause of TRAPS.[1] Although the mechanisms involved in increased TNF-α–mediated inflammation in TRAPS are still unclear, this discovery prompted the use of available TNF-targeted therapies in these patients. Two open-label trials of etanercept, a soluble TNF receptor antagonist approved for the treatment of rheumatoid arthritis, in patients with TRAPS confirmed its clinical efficacy in preventing symptomatic episodes.[7,13] However, further therapeutic experience demonstrated persistence of chronic subclinical inflammation and development of systemic amyloidosis in some patients while receiving the therapy. Surprisingly, the use of other TNF-α–directed therapies with presumed enhanced potency, such as mAbs to TNF-α commonly used in patients with rheumatoid arthritis and inflammatory bowel disease, resulted in worsening of disease in some patients with TRAPS.[71,72] Recent experiences suggest that the mechanisms involved in TRAPS intersect with the IL-1 pathway (Table I).[14]

REGULATION OF THE IL-1 PATHWAY

IL-1, previously known as leukocytic pyrogen, was implicated in the pathogenesis of fever at its original discovery 40 years ago.[73] It has now been implicated as an important mediator in multiple inflammatory diseases.[74] However, the specific mechanisms regulating the release of active IL-1β remained unclear until the recent description of the inflammasome, a protein complex that activates caspase 1, allowing for the posttranslational cleavage of pro–IL-1β to its mature releasable form.[75] Once released, IL-1β exerts its effects by binding to the IL-1 receptor expressed on numerous cell types, resulting in the activation of nuclear factor κB signaling pathways that lead to an inflammatory cascade involving multiple cytokines, such as IL-6 (Fig. 2). This process is highly regulated at several levels to prevent uncontrolled IL-1–mediated inflammation, and therefore it provides a number of targets for pharmacotherapy.[76]

There are numerous proposed exogenous and endogenous activators of the inflammasome, including specific bacterial and viral pathogens and specific endogenous danger signals, such as ATP,[77] uric acid crystals,[78] and asbestos.[79] The wide variety of potential triggers suggests that there is a common mechanism that activates the inflammasome, and

possibilities include reactive oxygen species,[80] cell membrane perturbation, and potassium efflux. The components of the inflammasome are intracellular and include cryopyrin (also known as NALP3), adaptor proteins (ASC and Cardinal), and chaperone proteins (HSP90 and SGT1).[75,81] Once cryopyrin is activated, oligomerization of these protein components occurs through several specific protein-protein interaction domains to form a multimeric complex, which binds to and activates caspase 1, allowing for the cleavage of pro–IL-1β (Fig. 2).[82] The mechanisms involved in the subsequent cellular release of mature IL-1β are still unclear. Mature IL-1β can then bind to the IL-1 receptor but must compete with a natural inhibitor known as IL-1 receptor antagonist.[76]

IL-1–TARGETED THERAPY

The clear role of IL-1 in the host response to infection made it an obvious target for the treatment of septic shock, an acute multi-system inflammatory condition with significant morbidity and mortality. The cloning of the gene for the IL-1 receptor antagonist allowed for the development of a recombinant form, known as anakinra, as a therapeutic anti-inflammatory agent. The initial experience with IL-1 receptor antagonist in septic patients was promising, but larger trials failed to show significant efficacy in this complex, multiphase inflammatory response.[83] Anakinra was later studied in patients with rheumatoid arthritis, in whom it showed statistically and clinically significant improvement in inflammatory symptoms but only modest efficacy compared with other biologic therapies. Since its approval in 2001, it has been used primarily in patients with rheumatoid arthritis who do not have an adequate response to TNF-targeted therapy.[84] However, the ready availability of anakinra allowed for proof-of-concept trials in many of the autoinflammatory diseases, where it has had a major effect, despite its use being limited to off-label indications.

Anakinra has several pharmacologic features that might limit its effectiveness, including a short half-life requiring daily injections and common painful injection-site reactions. Therefore many physicians believed that an IL-1–targeted compound with more favorable pharmacokinetics might be more effective in blocking inflammation. This concept encouraged the development of longer-acting IL-1–targeted drugs, such as rilonacept and canakinumab, for use in inflammatory diseases, such as rheumatoid arthritis. Rilonacept is a recombinant fusion protein consisting of portions of the IL-1 receptor and the IL-1 receptor accessory protein in line with an IgG Fc region. This combination results in a drug with high affinity for IL-1β and a half-life of more than 8 days, allowing for weekly injections.[85] Canakinumab is a humanized mAb to IL-1β with a half-life of more than 3 weeks and pharmacokinetic data suggesting extended effective dosing frequencies of more than 2 months (Table II).[86] Both of these drugs were initially developed for the treatment of rheumatoid arthritis, but inconsistent or modest efficacy and failure to identify biomarkers that predict response resulted in a redirection of efforts toward the orphan disease CAPS and others (Fig. 3).

TARGETING IL-1 IN PATIENTS WITH CAPS

The identification of a major role for IL-1 in the pathogenesis of CAPS was the culmination of an international translational effort of several groups involving human disease genetics, genomics, molecular biology, and clinical immunology. Classic linkage analysis led to the discovery of the novel *NLRP3 (CIAS1)* gene as the cause of the 3 previously distinct types of CAPS, including FCAS, MWS, and NOMID.[87–91] At the same time, several groups were mining the genome for genes with conserved protein domain structures with similarities to molecules regulating apoptosis and innate immune function, resulting in the identification of a new protein family known as nucleotide-binding domain, leucine-rich repeats (NLRs) that includes cryopyrin (Fig. 4).[92–94] *In vitro* studies with recombinant cryopyrin and other NLRs demonstrated interactions with specific adaptor proteins that play a role in the activation of caspase 1 and pro–IL-1β cleavage.[75,95] *Ex vivo* studies with mononuclear cells from patients with CAPS confirmed increased IL-1β release and provided the final preclinical studies before introduction into patients with CAPS.[96,97]

Anakinra in patients with CAPS

Hawkins et al[98] were the first to treat patients with CAPS with anakinra, resulting in immediate reduction of MWS-related symptoms and a reduction in serum inflammatory markers, such as C-reactive protein (CRP) and SAA, which is often associated with the development of amyloidosis. Anakinra was also shown to prevent cold-induced symptoms when administered to patients with FCAS before a cold room challenge. These studies revealed a role of the skin in the pathogenesis of disease and showed that disease-associated serum IL-6 levels were completely dependent on IL-1β.[65] These initial reports in patients with MWS and FCAS had an immediate effect on the treatment of patients with CAPS. However, some of the most dramatic therapeutic responses to anakinra were observed in patients with NOMID, the most severe form of CAPS.[99]

Since these initial reports, similar responses to anakinra have been observed in patients with CAPS to anakinra therapy with a variety of doses and treatment regimens. Some patients have required more than 3 mg/kg/d,[15] whereas others have responded to doses as low as 0.3 mg/kg/d.[100] Certain patients could be dosed every other day, whereas others required twice-daily dosing. Some patients with FCAS have limited anakinra therapy to specific environmental exposures or seasons to decrease the frequency of the often painful injections. All patients with CAPS have a response to therapy if treated with a high enough dose. In the one NOMID case in which anakinra was reported to be ineffective, dosing was not increased to greater than 1.6 mg/kg/d.[101] In addition to improvement in daily symptoms and systemic markers of inflammation, some patients have also experienced resolution or significant improvement in long-term complications, such as hearing[15,102] and vision loss[103] and amyloidosis-related renal disease.[16,104] However, no improvement has been observed in the abnormal bone growth characteristic of NOMID.[15]

Many open-label trials of anakinra therapy have now been reported in patients with CAPS, confirming persistent efficacy.[16,17] The most definitive and comprehensive report of anakinra treatment in patients with CAPS is the study led by Goldbach-Mansky[15] in patients with NOMID. Significant reductions in clinical symptoms and systemic inflammation was

observed with anakinra therapy for more than 6 months. In addition to improved growth and quality of life, improvements in hearing and decreases in CSF pressure and cochlear or leptomeningeal enhancement on magnetic resonance imaging were also observed. Anakinra has become the standard of care for patients with NOMID, despite a lack of FDA approval and limited interest by the manufacturer. However, its use was limited in most patients with FCAS because of the requirement for frequent dosing and painful injection-site reactions (Table I).

Newer IL-1–targeted therapies in patients with CAPS

Although anakinra was able to achieve FDA approval for the treatment of rheumatoid arthritis, its modest efficacy and limited market share was discouraging for developers of novel IL-1 inhibitors. However, the remarkable success of IL-1 inhibition in patients with CAPS and the orphan disease development program at the FDA provided an excellent opportunity for collaborative studies between industry and the physicians that care for patients with CAPS, with a common goal of bringing effective treatments to patients in a timely fashion. Two novel biologic agents, rilonacept and canakinumab, have now been approved for CAPS (Fig. 3).

Rilonacept, also known as IL-1 TRAP, was initially studied in a pilot trial, with 5 patients with FCAS treated with weekly subcutaneous doses. This study demonstrated clear clinical and laboratory responses similar to those observed with daily anakinra[105] and was the foundation for the first randomized, placebo-controlled trial in 44 patients with FCAS and MWS[18] using a novel, validated, self-reporting daily diary to derive a key symptom score that was the primary clinical end point of the study.[106] Significant differences were observed between active drug and placebo in key symptom scores, number of flares, and CRP and SAA concentrations in both the treatment and withdrawal phase of this 2-part multicenter study in the United States. The primary side effect noted was injection-site reactions in the treatment group that never resulted in drug discontinuation. There was also a trend toward increased infection frequency in the first phase of the study.[18] This consistent clinical response and favorable safety profile led to FDA orphan drug approval in 2008 for patients with FCAS and MWS older than 12 years. Similar efficacy was maintained throughout an 18-month open-label extension study; however, 2 deaths were reported in this study phase (one from pneumococcal meningitis and the other from coronary artery disease) that highlight potential risks of targeting IL-1.[107] Now more than 100 US patients with CAPS (approximately 30% of the estimated US CAPS population) are currently taking rilonacept.

Initial pharmacokinetic studies of canakinumab in patients with CAPS were performed with intravenous administration. Initial reports suggested prolonged clinical efficacy beyond what was expected based on the drug's half-life. Mathematic pharmacokinetic modeling showed a feedback mechanism in which IL-1β production was driven primarily by IL-1β,[108] and this model was used to determine the every 8-week subcutaneous dosing in the pivotal trial in 31 patients with MWS and NOMID.[19] In this trial all active drug–treated patients remained in remission, whereas 81% of those receiving placebo had disease flares. In an open-label phase 97% of treated patients had complete or near-complete clinical response and reduction of CRP and SAA to normal levels. The only side effect noted was an increased frequency of

infection, and the only reported severe adverse events included urosepsis and vertigo.[19] Based on these results, the FDA approved canakinumab in 2009 for patients with FCAS and MWS older than 4 years. Preliminary results of an open-label extension study suggest continued effectiveness. Studies of canakinumab in patients with NOMID are underway (Table 1).

IL-1–TARGETED THERAPY IN OTHER AUTOINFLAMMATORY DISEASES

The successful use of IL-1 inhibitors in patients with CAPS and translational studies suggesting a role for IL-1 in other autoinflammatory diseases has prompted its use in the other inherited autoinflammatory syndromes and several more common autoinflammatory disorders. Anakinra has been used to prevent attacks and reduce systemic inflammatory markers in patients with colchicine-resistant FMF,[20–25] hyper-IgD syndrome,[26–28] and even etanercept-resistant TRAPS.[14,29,30] Similar remarkable responses were also reported in patients with Blau syndrome,[31,32] pyogenic arthritis, pyoderma gangrenosum, and acne[6,33,34] and deficiency of IL-1 receptor antagonist.[5,6] Anakinra has also been shown to be effective during acute gout episodes,[35,36] chronic gout,[35] and pseudogout[37,38] and in the management of Schnitzler syndrome,[39–45] systemic-onset juvenile idiopathic arthritis,[46–48] and adult-onset Still disease.[49–56] Rilonacept was reported to be effective at reducing chronic gout associated joint pain, as well as CRP levels, in a recent pilot study.[57] Rilonacept and canakinumab are currently in clinical trials for systemic-onset juvenile idiopathic arthritis, with promising results (Table I).

ADVERSE EFFECTS OF TARGETED BIOLOGIC THERAPIES

Many of the anti-inflammatory targeted drugs have ideal therapeutic properties of efficient inhibition of disease-related pathways with limited off-target adverse events. However, clinical experience with anticytokine drugs has revealed on-target side effects and shown the important roles of specific cytokines in the host response to infection. Although drugs inhibiting the TNF-α pathway are now used extensively for the therapy of rheumatoid arthritis and inflammatory bowel disease, increased rates of opportunistic infections due to mycobacteria and fungi, and mild-to-severe bacterial and viral infections have been observed in large trials and during postmarketing surveillance studies in these populations. However, many of these infections have been associated with the concomitant use of other immune-modulating drugs and might be related to infections associated with the underlying disease.[58] Similarly, slightly increased rates of mild-to-severe bacterial and viral infections have been observed in large trials and during postmarketing surveillance with anakinra in patients with rheumatoid arthritis, but there does not appear to be an increased risk from opportunistic infections.[58] It is not clear whether the safety experience with newer longer acting anti–IL-1–targeted drugs or with any biologic therapy in autoinflammatory diseases, in which there might be fewer concomitant therapies, will be similar to what has been observed in these large diverse populations. Increased rates of upper respiratory tract infections and reports of severe bacterial infections (meningitis and urosepsis) have been observed in the small CAPS trials with both rilonacept and canakinumab. All of these biologic drugs are injectable and can be associated with injection-site reactions. However, this is much less of a problem with the newer IL-1 medicines.

NOVEL THERAPEUTIC TARGETS FOR AUTOINFLAMMATORY DISEASES

The elucidation of the multistep mechanisms involved in IL-1β release reveals a number of possible targets at different steps in the pathway (Fig. 2). Studies demonstrating the involvement of ATP,[77,59] potassium efflux,[60] uric acid,[78] or reactive oxygen species[79,80] in the activation of the inflammasome point to a role for drugs targeting purine receptors (P2X7 inhibitors), potassium channels (glyburide like compounds), or uric acid levels (uricosuric agents). Drugs with membrane-stabilizing function or antioxidant properties might also be successful in blocking steps upstream of the inflammasome. These drugs could be very effective at blocking several common inflammasome-mediated disorders but might not have a role in the treatment of autoinflammatory disorders because of mutations in the inflammasome pathway resulting in hyperactive or constitutive activation that is not dependent on upstream activators.

The identification of heat shock protein chaperones in the inflammasome complex suggests a role for drugs targeting these molecules[81] or other therapies that might affect inflammasome stability or function. Caspase 1 inhibitors are currently in development and have shown promise in CAPS *ex vivo* models[97] but have been limited by side effects and dosing issues for *in vivo* therapy. Theoretically, targeting the inflammasome directly could have the best efficacy and safety profile for autoinflammatory diseases, such as CAPS, because of the effect on other inflammasome-mediated cytokines, such as IL-18; however, the existence of several different inflammasomes consisting of closely related NLRs might require significant specificity.

The complex mechanisms of lysosomal IL-1β release or signal transduction pathways of IL-1 receptor signaling (eg, mitogen-activated protein/extracellular signal regulated kinase or NF κB) also provide a number of potential therapeutic targets, which could have effects on additional cytokine-mediated inflammation. Finally, biologic agents targeting downstream cytokines, such as IL-6, might also have a role in the therapy of autoinflammatory diseases (Fig. 2). Each of these approaches might have certain advantages over currently available therapy, including oral routes, lower costs, or better side effect profiles. It is also possible that approaches involving combination therapies will have the most success.

SUMMARY

The recent recognition of a new class of immunologic disorders known as autoinflammatory diseases has changed the way we look at pathologic inflammation and allowed for a better understanding of the mechanisms regulating the innate immune system. This disease category has now expanded from the original rare, inherited, recurrent fever syndromes to include much more common diseases. Translational research concerning the single-gene autoinflammatory disorders has not only improved our knowledge of pathophysiology but has rapidly led to improved diagnosis and therapy of the patients with these diseases and holds promise to improve future treatment for more complex auto-inflammatory disease, such as gout and systemic-onset juvenile idiopathic arthritis. The availability of targeted therapies for proinflammatory cytokines, such as anakinra for IL-1β, allowed for hypothesis

testing and drove the development of newer IL-1β–directed therapies, including rilonacept and canakinumab. Future therapies will take advantage of our expanding knowledge of the inflammatory mechanisms involved in both rare and common autoinflammatory diseases.

Abbreviations used

CAPS	Cryopyrin-associated periodic syndromes
CRP	C-reactive protein
FCAS	Familial cold autoinflammatory syndrome
FDA	US Food and Drug Administration
FMF	Familial Mediterranean fever
MWS	Muckle-Wells syndrome
NLR	Nucleotide-binding domain, leucine-rich repeat
NOMID	Neonatal-onset multisystem inflammatory disease
SAA	Systemic amyloid A
TRAPS	TNF receptor–associated periodic syndrome

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What do we know?

- Autoinflammatory disorders are primarily driven by the innate immune system and include rare inherited syndromes and more common and genetically complex inflammatory diseases.
- Translational research has advanced our understanding of the cause of inherited autoinflammatory syndromes and has led to effective targeted therapy with significant clinical effect.
- Colchicine is still the standard of care for FMF and is used widely around the world.
- IL-1 is one of the central mediators of autoinflammatory diseases and is the target of 3 approved biologic therapies, including anakinra, rilonacept, and canakinumab.

What is still unknown?

- The underlying genetic basis and pathophysiologic mechanisms for many inherited autoinflammatory syndromes
- Specific mechanisms underlying the activation of the inflammasome
- The long-term efficacy and safety of IL-1–targeted therapies
- The role of novel upstream and downstream inflammasome-targeted therapies in the future

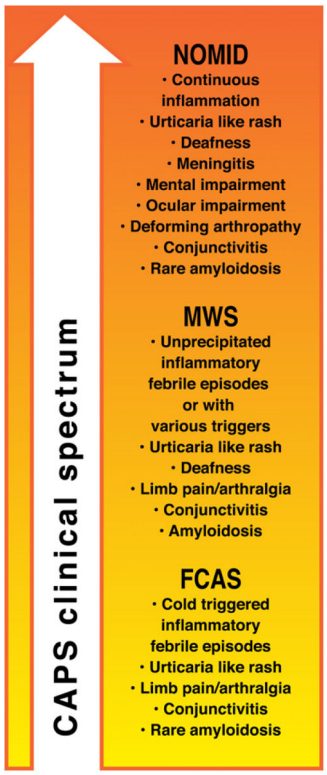

FIG. 1.
The clinical continuum of CAPS, including NOMID, MWS, and FCAS.

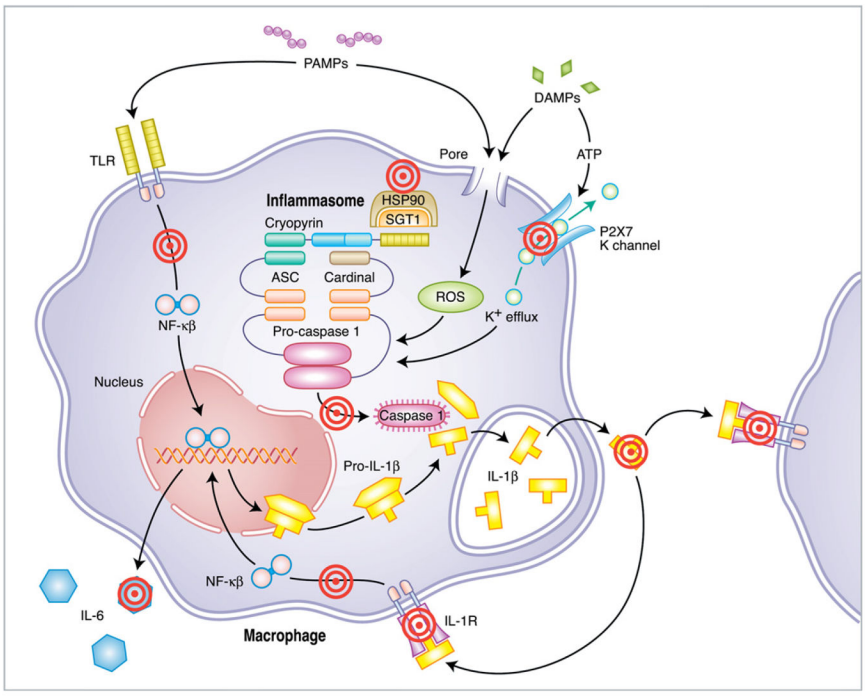

FIG. 2.

Targeting the multistepped pathways of IL-1β–mediated inflammation. The inflammasome is an intracellular protein complex that is activated by numerous pathogen-associated molecular patterns *(PAMPs)* and danger-associated molecular patterns *(DAMPs)*. This activation involves several hypothesized mechanisms, including potassium efflux secondary to ATP-gated channels, reactive oxygen species *(ROS)*, and membrane perturbation. Activation of the inflammasome leads to the cleavage and activation of caspase 1, which cleaves pro–IL-1β to its mature active form, which is subsequently released from the cell. Once released, IL-1β binds to the IL-1 receptor, leading to downstream signaling and a cascade of inflammation involving other proinflammatory cytokines. Pro–IL-1β expression is driven by Toll-like receptor *(TLR)* activation and autocrine IL-1 receptor activation. There are several points along this pathway that can be targeted to inhibit IL-1–mediated inflammation, including specific inflammasome triggers, common activation mechanisms, specific components of the inflammasome, inflammasome stability, caspase 1, IL-1β release, binding of IL-1β to the IL-1 receptor, IL-1 receptor *(IL-1R)* signaling transduction, and downstream proinflammatory cytokines. *ASC*, apoptosis associated speck-like protein including a caspase 1 activation and recruitment domain (CARD); *Cardinal*, CARD inhibitor of NF-κB activation ligand; *HSP90*, heat shock protein 90; *NF-κB*, nuclear factor κ-light chain enhancer of activated B cells; *SGT1*, suppressor of G2 allele of skp1.

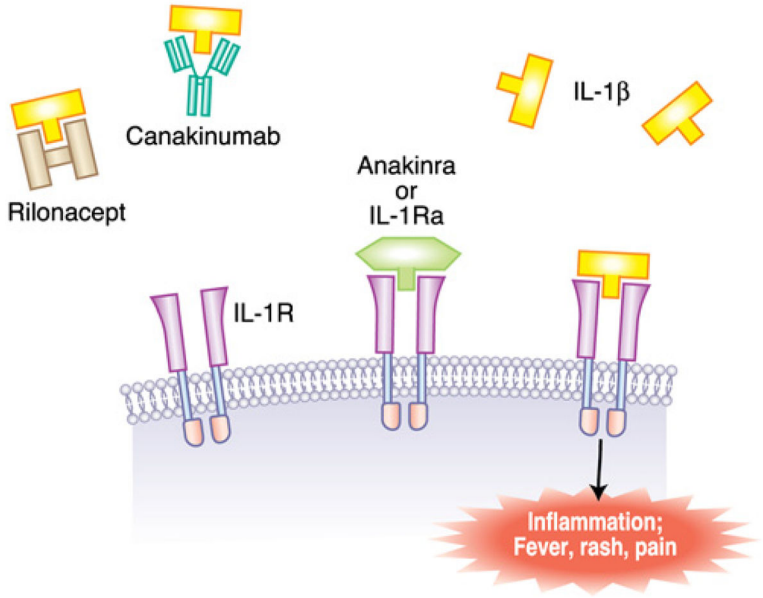

FIG. 3.

Mechanisms of IL-1–targeted therapy. Current therapy is directed at IL-1B, including rilonacept and canakinumab or the IL-1 receptor *(IL-1R)* with anakinra, a recombinant form of IL-1 receptor antagonist *(IL-1Ra)*.

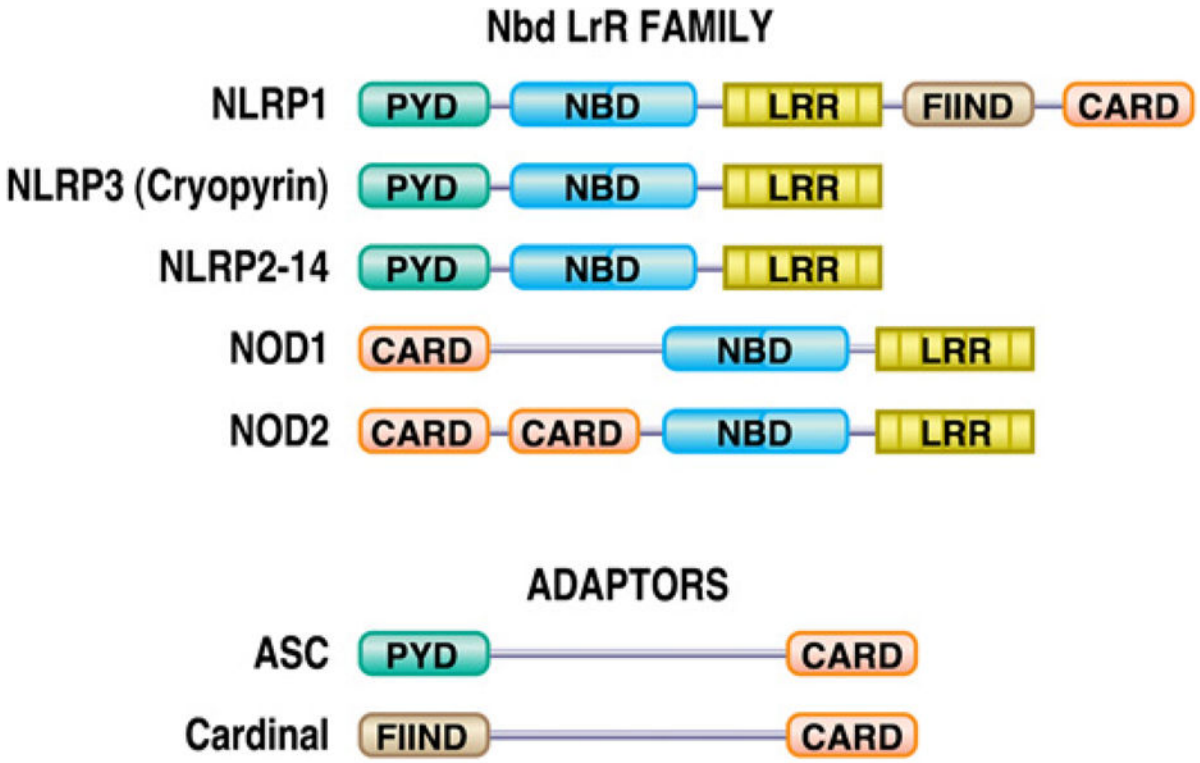

FIG. 4.

Protein domain structure of NLRs, including pyrin domains *(PYD)*, nucleotide-binding domains *(NBD)*, leucine-rich repeat *(LRR)* domains, caspase activation and recruitment domains *(CARD)*, and a domain with function to find *(FIIND)*. *ASC*, apoptosis associated speck-like protein containing a caspase 1 activation and recruitment domain (CARD); *Cardinal*, CARD inhibitor of NF-κB activation ligand; *NLRP*, nucleotide binding domain, leucine rich repeat domain, pyrin domain; *NOD*, nucleotide oligomerization domain.

TABLE I

Autoinflammatory disease therapies

	Clinical studies (adults/children)	No. of patients	Observations
Hereditary fever disorders			
FMF	Colchicine-controlled trials, adults[8–10]	>100	Episode number
	Colchicine open-label trials, children[11,12]	>100	Episode number, inflammatory markers
	Anakinra case reports, both[20–25]	<10	All symptoms, inflammatory markers
	Rilonacept trial in progress		
TRAPS	Etanercept small trials, both[7,13]	>10	Steroid dose, inflammatory markers
	Anakinra case reports, both[14,29,30]	<10	Episode number, inflammatory markers
Hyper-IgD syndrome with periodic fever	Anakinra case reports, both[26–28]	<10	All symptoms, inflammatory markers
CAPS			
FCAS	Anakinra open-label trials, both[16,17]	>10	All symptoms, inflammatory markers
	Rilonacept controlled trials, both[18]	<100	All symptoms, inflammatory markers
	Canakinumab controlled trials, both[19]	<100	All symptoms, inflammatory markers
MWS	Anakinra open-label trials, both[16]	>10	Most symptoms, inflammatory markers
	Rilonacept controlled trials, both[18]	<10	Most symptoms, inflammatory markers
	Canakinumab controlled trials, both[19]	>10	Most symptoms, inflammatory markers
NOMID	Anakinra open-label trial, children[15]	>10	Most symptoms, inflammatory markers
	Canakinumab trials in progress		
Other hereditary disorders			
Pyogenic arthritis, pyoderma gangrenosum, and acne	Anakinra case reports, both[33,34]	<10	Skin symptoms
Blau syndrome	Anakinra case reports, adults[31,32]	<10	Symptoms in 1 patient but not all
Deficiency of IL-1 receptor antagonist	Anakinra case reports, children[5,6]	>10	All symptoms, inflammatory markers
Pseudogout	Anakinra case reports, adults[37,38]	<10	All symptoms
Nonhereditary disorders			
Schnitzler syndrome	Anakinra case reports, adults[39–45]	<10	Skin symptoms
Systemic-onset juvenile idiopathic arthritis	Anakinra trials, children[46–48]	<100	Most symptoms and steroid dose in some
	Rilonacept trials in progress		

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	Clinical studies (adults/children)	No. of patients	Observations
	Canakinumab trials in progress		
Adult-onset Still disease	Anakinra case reports, adults[49–56]	>10	Most symptoms and inflammatory markers
Acute gout	Anakinra small trials, adults[35,36]	>10	Symptoms in most
Chronic gout	Rilonacept controlled trial, adults[57]	>10	Symptoms in most

TABLE II

FDA-approved IL-1–targeted therapies

Compound	Structure	Target	Half-life	Dosing frequency	Other features
Anakinra (Kineret)	Recombinant IL-1 receptor antagonist	IL-1 receptor	4–6 h	Daily	Common painful injection-site reactions
Rilonacept (Arcalyst)	Fusion protein, including IL-1 receptor and IL-1 receptor accessory protein (IL-1 TRAP)	IL-1β (also IL-1α and IL-1Ra)	8.6 d	Weekly	Minor injection-site reactions
Canakinumab (Ilaris)	Humanized mAb to IL-1β	IL-1β	28 d	2 mo	Minimal injection-site reactions