Autoinflammation: From monogenic syndromes to common skin diseases

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Autoinflammation is characterized by aberrant regulation of the innate immune system and often manifests as periodic fevers and systemic inflammation involving multiple organs, including the skin. Mutations leading to abnormal behavior or activity of the interleukin 1 beta (IL-1ß)-processing inflammasome complex have been found in several rare autoinflammatory syndromes, for which anticytokine therapy such as IL-1 or tumor necrosis factor-alfa inhibition may be effective. It is becoming clear that features of autoinflammation also affect common dermatoses, some of which were previously thought to be solely autoimmune in origin (eg, vitiligo, systemic lupus erythematosus). Recognizing the pathogenetic role of autoinflammation can open up new avenues for the targeted treatment of complex, inflammatory dermatoses. (J Am Acad Dermatol 2013;68:834-53.)

Key words: anakinra; autoinflammation; common dermatoses; inflammasomes; interleukin-1 beta; periodic fevers.

The discovery of monogenic origins for seemingly unprovoked inflammatory episodes in patients with periodic fever syndromes has led to a new disease pathogenesis model known as autoinflammation. This concept is distinct from autoimmunity, in which lymphocyte-mediated immune responses are directed against specific self-antigens. Autoinflammation, by contrast, is characterized by aberrant regulation of the innate immune system. As a more complete understanding of autoinflammation emerges, it is also becoming clear that these pathways may play an important role in common dermatologic disease, leading to the possibility of new therapeutic approaches for these conditions.

A family of genes known as the nucleotide-binding domain leucine-rich repeat-containing (*NLR*) genes are integral to autoinflammation.[1] Thus far 22 human *NLR* genes have been identified.[2] Most *NLR*s include a caspase-recruiting domain (*CARD*) or a pyrin domain at the N-terminal, a central nucleotide-binding domain (*NACHT*), and a C-terminal leucine-rich repeat domain (Fig 1). Each *NLR* encodes a NLR protein (NLRP), which interacts with the apoptosis-associated speck-like protein and the precursor form of caspase-1 to form a multiprotein structure known as an inflammasome. Upon formation of the inflammasome, caspase-1 becomes activated and hydrolyzes the interleukin (IL)-1 family

Abbreviations used:

CAPS:	cryopyrin-associated periodic syndrome
CARD:	caspase-recruiting domain
CRP:	C-reactive protein
DIRA:	deficiency of the interleukin-1 receptor antagonist
ESR:	erythrocyte sedimentation rate
FMF:	familial Mediterranean fever
HIDS:	hyper-IgD syndrome
IL:	interleukin
NLR:	nucleotide-binding domain leucine-rich repeat-containing
NLRP:	nucleotide-binding domain leucine-rich repeat-containing protein
PAPA:	pyogenic arthritis, pyoderma gangrenosum, and acne
PG:	pyoderma gangrenosum
PRR:	pattern recognition receptor
RA:	receptor antagonist
SLE:	systemic lupus erythematosus
SNPs:	single nucleotide polymorphisms
TLR:	Toll-like receptor
TNF:	tumor necrosis factor
TRAPS:	tumor necrosis factor receptor–associated periodic syndrome

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Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication November 1, 2012.

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Published online March 4, 2013.
0190-9622/$36.00

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http://dx.doi.org/10.1016/j.jaad.2012.11.002

precursors into their active cytokine counterparts.[3] Caspase-1 can also mediate secretion of IL-1 alpha (IL-1α) and fibroblast growth factor 2.[4]

NLR mutations may lead to inappropriate activation of or failure to inhibit inflammasomes,[5] resulting in abnormal secretion of inflammatory cytokines (primarily IL-1ß, IL-6, and IL-18). Although incompletely understood, active IL-1ß appears to prime the production of its precursor pro-IL-1ß, thereby perpetuating autoinflammatory responses that further damage affected tissues.[6,7] Alternative pathways of autoinflammation have also been suggested, including inflammasome activation by mitochondria-derived reactive oxygen species in response to exogenous pathogens or endogenous danger signals.[8]

Both infectious and noninfectious stimuli are capable of triggering innate immune responses through membrane-bound pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) or cytosolic PRRs such as the aforementioned NLRPs.[9] Binding of TLRs to pathogen- or danger-associated molecular patterns activates expression of inflammatory cytokines via nuclear gene transcription factors (Fig 1). Independent of the role of TLRs, NLRPs in the cytosol function as innate sensors of intracellular pathogen- and danger-associated molecular patterns. Their direct binding is responsible for the formation of inflammasomes, activation and secretion of inflammatory cytokines, and the subsequent cascade of extracellular downstream effects of inflammation (Fig 1). See Tables I and II for a summary of autoinflammatory syndromes and their therapies.

CAPSULE SUMMARY

- Autoinflammation is characterized by aberrant regulation of the innate immune system.
- Pathways mediating innate immunity, many of which are related to the interleukin-1ß-processing inflammasome, are common targets in monogenic autoinflammatory syndromes.
- Several common dermatoses have been found to be affected by features of autoinflammatory disease, leading to the possibility of new, targeted therapies.

MONOGENIC AUTOINFLAMMATORY SYNDROMES

Cryopyrin-associated periodic syndrome

Cryopyrin-associated period syndrome (CAPS) is a rare childhood-onset disorder that presents with a wide spectrum of severity. In fact, CAPS encompasses 3 distinct phenotypes, listed in the order of increasing severity: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disorder. As the name suggests, episodes of familial cold autoinflammatory syndrome may follow exposure to low ambient temperatures.[10,11] The hallmarks of CAPS episodes are evanescent, nonpruritic, urticaria-like papules and confluent geographic plaques on the trunk and extremities, periodic fevers, and distal arthralgia (Fig 2).[10,12,13] Skin histology reveals a sparse interstitial, perivascular, or perieccrine neutrophilic infiltrate.

Less common features of CAPS are ocular involvement, including conjunctivitis, episcleritis, and uveitis, and neurologic manifestations, which encompass headaches, sensorineural hearing loss, and chronic meningitis.[14,15] Secondary amyloid A amyloidosis most frequently affects the kidney and can lead to nephrotic syndrome. One case series reported 6 cases of reactive amyloidosis out of 22 patients.[14] Leukocytosis and elevation of C-reactive protein (CRP) and serum protein amyloid A are almost always present, whereas the erythrocyte sedimentation rate (ESR) is variably elevated.[16] IL-1ß expression is upregulated in tissues of patients with CAPS.[7,14,17] There are no known susceptibility markers in patients with CAPS for the development of amyloidosis.

Mutations in the *NLRP3* gene [also referred to as the *CIAS1* (cold-induced autoinflammatory syndrome 1) or *NALP3* (nacht domain-, leucine-rich repeat-, and PYD-containing protein 3) gene], which codes for the cryopyrin NLRP, are dominantly inherited; however, de novo *NLRP3* mutations have been reported.[18-20] Targeted inhibition of IL-1ß has revolutionized the treatment of patients with CAPS. Treatment with anakinra, a recombinant-DNA analog of the human IL-1 receptor antagonist (RA), typically leads to rapid clearance of skin lesions and improvement of amyloidosis-induced nephrotic syndrome.[21-25] Rilonacept, a "cytokine trap" antibody with high affinity for anti-IL-1, is also effective,[26-28] and canakinumab, a fully human monoclonal antibody against IL-1ß, demonstrated a 97% complete response rate in a recent clinical trial.[29]

Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a dominantly inherited disorder characterized by pyoderma gangrenosum (PG), acne vulgaris, and pyogenic arthritis

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