Autoinflammatory Skin Disease: A Review of Concepts and Applications to General Dermatology

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Abstract
We provide an up-to-date summary of important concepts of autoinflammation as well as describe important but rare monogenic autoinflammatory disorders that may present with cutaneous findings. Finally, of particular interest to a practicing general dermatology audience, we review concepts of autoinflammation as they apply to understanding the disease pathogenesis of common skin disorders.

Introduction to Autoinflammation

Autoinflammation is a newly expanding concept in medicine with substantial relevance in the field of dermatology, as many autoinflammatory disorders present with cutaneous findings. It involves aberrant control of the innate immune response, often through interleukin (IL)-1-mediated pathways. This is distinct from classical autoimmunity in that antibodies, T-cell-mediated or major histocompatibility complex-related processes are not the primary mediators of disease. Rather, autoantibody titers are absent or low and as opposed to lymphocytes, neutrophils, and macrophages are most often the effector cells [1]. However, autoinflammation and autoimmunity are not mutually exclusive, as mediators of autoinflammation likely play a role in a variety of conditions thought of as ‘autoimmune’.

Central to understanding the pathogenesis of autoinflammation is the inflammasome. The inflammasome, like the toll-like receptor, is a critical part of the normal innate immune response to infection and tissue injury. These are cytoplasmic protein complexes involved in the regulation of processing of IL-1β and the progression of the inflammatory cascade. They have been described in myeloid cells as well as epithelial cells including keratinocytes [2, 3]. In normal immune function, microbial and other cytoplasmic toxins such as crystals stimulate specialized receptors in the cytoplasm, which lead to the assembly of inflammasome complexes [4]. A number of these cytosolic receptors have been identified such as the NOD-like receptor (NLR) family of receptors NLRP3, NLRP1, AIM2 and MEFV [5]. Expression of NLRP3, NLRP1 and AIM2 has been identified in keratinocytes [6].

When activated, these cytosolic receptors oligomerize with an adaptor protein called ASC and caspase-1 to form the inflammasome complex. Assembly of the inflammasome complex leads to activation of caspase-1, which activates multiple substrates but most importantly the precursor to IL-1β, leading to production of active IL-1β [5] (fig. 1).
Mutations in the genes encoding components of inflammasomes lead to dysregulation of the IL-1 inflammatory cascade and the resulting monogenic autoinflammatory diseases. Importantly, much of our understanding of autoinflammatory processes in general is a result of studying these rare monogenic diseases.

**Cryopyrin-Associated Periodic Syndrome**

To illustrate the link between inflammasome component mutations and clinical disease, we will discuss the cryopyrin-associated periodic syndrome (CAPS). The term CAPS includes 3 conditions on a spectrum of phenotype severity, starting with familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID). These were previously thought to represent different disease processes but are now thought of as part of a continuum of CAPS disease from mild to severe [6].

CAPS is caused by mutations in the NLRP3 gene encoding for NLRP3 (also known as NALP3, C1AS1 or cryopyrin), which is one of the best-described inflammasome complexes. In CAPS, different gain-of-function mutations in NLRP3 cause abnormal IL-1 activation (fig. 1). Patients have been described with both hereditary germline mutations (heterozygous missense mutations) as well as somatic mosaic mutations in NLRP3 [7]. The complete molecular mechanisms by which this mutation leads to IL-1 inflammation is yet to be fully described but there is evidence that mutated autoinhibitory regions of NLRP3 allow for unregulated inflammasome assembly and IL-1 activation, and that mast cells expressing mutant NLRP3 are critical to IL-1 production [5, 8].

Patients with FCAS, the mildest version of CAPS, present in infancy with cold-induced urticaria, arthralgia, fatigue and fever. Those with MWS also present in infancy with urticarial eruptions, arthralgia and fever but may go on to develop sequelae such as amyloidosis, deafness and conjunctivitis [9]. Individuals with NOMID can present with all of the symptoms described above; however, they are affected earlier in the newborn period and have debilitating CNS involvement as well as severe arthropathy [10]. The urticarial eruption seen in CAPS is distinct from common urticaria as it is characteristically nonpruritic, sometimes painful and has a circadian rhythm (fig. 2).

Laboratory evaluation of patients with CAPS shows elevated acute-phase reactants such as C-reactive protein and serum amyloid A [11]. Histologic evaluation of skin eruptions in patients with CAPS shows perivascular and more specifically perivascular neutrophilic inflammation [12, 13]. In NOMID, there is intense neutrophilic infiltration into multiple organs. Patients with CAPS have a dramatic response to IL-1 blockade with near complete resolution of symptoms with the IL-1 receptor blockers anakinra, canakinumab and rilonacept [14].

CAPS shares many phenotypic features with the multisystem inflammatory diseases such as systemic-onset juvenile idiopathic arthritis, adult-onset Still’s disease,

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**Fig. 1.** Pathogen-derived signals activate the NLRP3 inflammasome, activating caspase-1 and stimulating the formation of IL-1β from its precursor. In cryopyrin-associated periodic syndrome, a mutated domain of NLRP3 leads to autoactivation of the same inflammatory cascade.
and Schnitzler’s syndrome such as febrile attacks, urticarial eruptions, bone pain, and elevated inflammatory markers [15]. As these diseases share phenotypic similarities and all are responsive to IL-1 blockade, they have been termed collectively ‘IL-1opathies’. Several other monogenic autoinflammatory syndromes have been described in Table 1.

**Autoinflammation in Neutrophilic Dermatoses**

Given the importance of neutrophilic mediated processes in the described autoinflammatory conditions, it follows that autoinflammation may play an important role in dermatoses where neutrophils are predominant. In autoinflammatory disorders, innate immunity directly causes tissue inflammation, whereas in autoimmune disorders, the role of innate immunity is less clear although it is possible that innate mechanisms activate the adaptive immune responses that are the primary mediators of disease. Autoinflammation to autoimmunity likely represents a spectrum of disease processes from innate to adaptive, with many common skin conditions with overlapping features [16].

Prime examples of dermatoses closer to the autoinflammatory end of the spectrum are pyoderma gangrenosum and Sweet’s syndrome, both conditions characterized by sterile neutrophilic infiltrates. Firstly, mutations in the inflammasome are important in PAPA syndrome, a genetic syndrome characterized by the triad of pyoderma gangrenosum, arthritis and cystic acne [17]. Specifically, autosomal dominant transmission of mutations in the gene PSTPIP1 leads to defective inhibition of the inflammasome complex and thus the inflammation seen in PAPA syndrome. Additionally, high levels of inflammatory cytokines such as IL-1 have been found in pyoderma gangrenosum lesional skin even in patients without a syndromic inflammatory syndrome [18]. Additionally, in patients with myelodysplastic syndrome who have neutrophilic skin lesions of Sweet’s, mutations in MEFV have been described similar to that in patients with familial Mediterranean fever [19].

**Autoinflammation in Psoriasis**

Evidence also exists for the role of autoinflammation in psoriasis [20]. Firstly, a pustular psoriasis-like rash is the cardinal cutaneous presentation of the autoinflammatory syndromes called deficiency of IL-1 receptor antagonist (DIRA) and deficiency of IL-36 receptor antagonist (DITRA). Children with these syndromes can present with failure to thrive along with flares of generalized pustular psoriasis, fevers, and systemic inflammation. Patients have a favorable clinical response to direct IL-1 blockade with anakinra with resolution of cutaneous and systemic symptoms as well as marked improvement in growth [21].

Autoinflammation very likely has a role in the pathogenesis of classic plaque psoriasis as well, through multiple inflammatory pathways. Inflammatory cytokines, specifically IL-36γ, have been shown to be elevated in skin lesions of psoriasis and are also elevated in the blood of individuals with active disease [22]. As demonstrated by single-nucleotide polymorphism studies, genetic variation in NLRP1 and NLRP3 has been shown to be associated with the earlier onset of disease and psoriasis susceptibility [23]. Through another proinflammatory pathway,
gain-of-function mutations in caspase recruitment domain family member 14 (CARD14), an important mediator of NF-κB, are also associated with psoriasis [24]. In these studies, variants in CARD14 were associated with upregulation of a variety of genes important in the psoriasis phenotype, including cell proliferation and immune cell migration [25]. However, despite the evidence for the role of autoinflammation in psoriasis, treatment with anti-IL-1 therapy has shown mixed success, indicating the complex nature of the disease. Anakinra has been shown to be effective in a series of patients with generalized pustular psoriasis [26]. However, a trial of canakinumab has shown limited efficacy, and anakinra has only shown moderate efficacy in specifically palmoplantar pustular psoriasis, a particularly treatment-recalcitrant form of psoriasis [27, 28]. Furthermore, anti-IL-1 treatment has actually been shown to induce new-onset plaque psoriasis in a patient treated for rheumatoid arthritis in a paradoxical side effect, raising the question of the role of IL-1 as a cytokine regulator in the pathogenesis of psoriasis [29].

### Table 1. Monogenic autoinflammatory syndromes

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Gene</th>
<th>Age at onset</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryopyrin-associated periodic syndrome (CAPS)</td>
<td>NLRP3</td>
<td>Infancy</td>
<td>Cold-induced atypical urticarial eruption, fevers, arthralgias, risk of amyloidosis, neurological disorders</td>
</tr>
<tr>
<td>Familial Mediterranean syndrome (FMF)</td>
<td>MEFV1</td>
<td>Childhood</td>
<td>Variable cutaneous findings including urticarial eruptions, acral erythema, fevers, arthritis, episodes lasting 12–72 h</td>
</tr>
<tr>
<td>Blau syndrome</td>
<td>CARD15/NOD2</td>
<td>Childhood</td>
<td>Granulomatous papular rash, fevers, synovitis, posterior uveitis, iridocyclitis</td>
</tr>
<tr>
<td>TNF receptor-associated periodic syndrome (TRAPS)</td>
<td>TNFRSF1A (TNF receptor 1)</td>
<td>Childhood</td>
<td>Migratory erythematous macules, papules, fevers, abdominal pain, pleurisy</td>
</tr>
<tr>
<td>Hyperimmunoglobulinemia D syndrome with periodic fever (HIDS)</td>
<td>MVK (mevalonate kinase)</td>
<td>Childhood</td>
<td>Morbilliform eruption, arthralgia, abdominal pain, lymphadenopathy</td>
</tr>
<tr>
<td>Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)</td>
<td>CD2BP1/PSTPIP</td>
<td>Childhood to early adulthood</td>
<td>Severe cystic acne, sterile arthritis, pyoderma gangrenosum</td>
</tr>
<tr>
<td>Deficiency of interleukin 1 receptor antagonist (DIRA)</td>
<td>IL1RN</td>
<td>Infancy</td>
<td>Pustular dermatitis, multifocal osteomyelitis, low or absent fevers</td>
</tr>
<tr>
<td>Deficiency of interleukin 36 receptor antagonist (DITRA)</td>
<td>IL36RN</td>
<td>Infancy</td>
<td>Sudden flares of pustular psoriasis or generalized erythematous rash, high fevers</td>
</tr>
<tr>
<td>Majeed syndrome</td>
<td>LPIN2</td>
<td>Infancy</td>
<td>Neutrophilic dermatosis, recurrent multifocal osteomyelitis, congenital dyserythropoietic anemia</td>
</tr>
<tr>
<td>Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)</td>
<td>PSMB8</td>
<td>Childhood</td>
<td>Erythematous plaques, recurrent fevers, lipodystrophy</td>
</tr>
<tr>
<td>Sting-associated vasculopathy with onset in infancy (SAVI)</td>
<td>TMEM173/STING</td>
<td>Infancy</td>
<td>Early-onset vasculitis, microangiopathic thrombosis, ulcerative acral rash</td>
</tr>
<tr>
<td>CARD14-mediated psoriasis (CAMPS)</td>
<td>CARD14</td>
<td>Childhood to adulthood</td>
<td>Pustular psoriasis, plaque psoriasis, pityriasis rubra pilaris, fevers</td>
</tr>
<tr>
<td>Deficiency of adenosine deaminase 2 (DADA2)</td>
<td>DADA2</td>
<td>Infancy and childhood</td>
<td>Fevers, stroke, livedoid rash +/- small vessel vasculitis, low cell counts</td>
</tr>
<tr>
<td>PLCγ2-associated antibody deficiency and immune dysregulation (PLAID)</td>
<td>PLCγ2</td>
<td>Infancy</td>
<td>Cold-induced urticaria, atopy, low immunoglobulins, infections</td>
</tr>
</tbody>
</table>
Autoinflammation in Eczematous Processes

Innate immunity and the inflammasome also clearly play a role in eczematous processes. The activation of innate immunity has been shown to be critical in the development of the adaptive immune response in allergic contact dermatitis [30]. Specifically, the NLRP3 inflammasome in keratinocytes is able to sense different contact sensitizers and is involved in the sensitization phase of contact hypersensitivity. Using a mouse model, Watanabe et al. [31] show that mice deficient in the inflammasome components ASC and NLRP3 are unable to develop the early phase of contact hypersensitivity when exposed to trinitrochlorobenzene, a known contact sensitizer.

In contrast to the role of autoinflammation in contact dermatitis, in atopic dermatitis, there is evidence for impaired NLRP3 expression as well as function that could be partially responsible for susceptibility of skin to colonization by Staphylococcus aureus [32]. Although multiple cytokines are known to play a role in atopic dermatitis, the evidence for specific anticytokine therapy in atopic dermatitis is limited. Elevated IL-6 is produced by T cells present in blood and lesional skin of patients with atopic dermatitis and is thought to play a role in T-cell differentiation. A small case series of patients treated with anti-IL-6 receptor therapy (tocilizumab) has been shown to improve clinical atopic dermatitis symptoms by 50% but was also associated with bacterial superinfection [33].

Autoinflammation in Acne and Other Conditions

Acne is a multifactorial disorder, with inflammation, comedone formation, sebum production and Propionibacterium acnes all important to pathogenesis although the exact sequence of these events is uncertain [34]. Most directly, the role of innate inflammation in acne is demonstrated by PAPA syndrome [35]. Similarly, in classic acne vulgaris, aberrant innate inflammation likely plays a role specifically through interactions with P. acnes [34]. It has been shown that P. acnes activates the NLRP3 inflammasome and induces release of IL-1β from human seocytes as well as antigen-presenting cells [36, 37]. IL-1β is abundantly found in inflammatory acne lesions and along with other proinflammatory cytokines contributes to the process of follicular hyperkeratosis and inflammatory acne lesions [38].

Hidradenitis suppurativa (HS) is a disease characterized by follicular occlusion, rupture and subsequent inflammatory response. The pathophysiology of this disease is complex with theories of both immune deficiency causing microbial overgrowth and immune overactivity proposed [39]. Comprehensive review of the microflora of HS lesions concluded that HS lesions are typically nonsterile and tend to contain opportunistic pathogens from skin microflora or other body sites [40]. The combination of this bacteriologic data and investigations showing decreased expression of innate immune markers in HS skin lesions supports the idea that HS is a result of poor control of bacterial flora on the skin. Alternatively, some studies have shown upregulated amounts of TNF-α, IL-1β and IL-10 in lesional HS skin, which would support an autoinflammatory pathway in HS. In addition, the inflammasome NLRP3 is upregulated in lesional skin of HS [41]. The most likely scenario is that of an overall ‘altered’ immune response to bacteria on the skin leading to chronic inflammatory skin disorders seen clinically [40]. In addition to long-term antibiotic therapies, there is now evidence for safety and success of TNF-α blockers in HS [42]. Initial studies also show promising evidence for the efficacy of anakinra in treating HS, with improvement in disease severity as well as quality of life [43, 44].

Diseases categorized as polygenic autoimmune conditions such as systemic lupus erythematosus (SLE) and systemic sclerosis also have interplay with innate immune processes. First described in a Brazilian cohort, polymorphisms in NLRP1 were associated with development of SLE and specifically rash, nephritis and arthritis. Mechanistically, the authors propose that variation of NLRP1 receptor properties could lead to increase the sensitivity to self-antigens and influence the development of autoimmunity [45]. Also, a recent meta-analysis of IL-1 polymorphisms in SLE showed an associated overall susceptibility to SLE in Europeans and Asians with certain IL-1α polymorphisms [46]. Additionally supporting the role of innate immune activation in SLE is that neutrophilic dermatoses have been described in patients with SLE [47].

Systemic sclerosis is a fibrosing disease of unclear etiology characterized by persistently activated fibroblasts, collagen formation and restrictive skin and visceral disease. There is limited research on autoinflammation in this disease, but overexpression of the NLRP3 and AIM2 inflammasome genes has been described in dermal fibroblasts in skin of patients with systemic sclerosis [48]. Skin thickness in these patients has also been correlated with the level of NLRP3 expression [49].

It is important for dermatologists to consider the category of autoinflammation in patients with recurrent febrile attacks, cutaneous eruptions, multisystemic manifestations and negative autoimmune workups. Addition-
ally, research is showing now the role of autoinflammation and innate immune processes in many classically ‘autoimmune’ skin diseases. With this improved understanding of the autoinflammatory component of the pathogenesis of disease, we will hopefully be able to modify and improve the course of many skin conditions.

References


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Disclosure Statement

The authors have no conflicts of interest to declare.


