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REVIEW ARTICLE

Autoinflammatory Disorders: A Review and Update on Pathogenesis and Treatment

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Abstract
The autoinflammatory diseases comprise a broad spectrum of disorders characterized by unchecked activation of the innate immune system. Whereas aberrations in adaptive immunity have long been identified in 'autoimmune' disorders, the concept of 'autoinflammation' emerged relatively recently, first describing a group of clinical disorders characterized by spontaneous episodes of systemic inflammation without manifestations typical of autoimmune disorders. Improved knowledge of innate immune mechanisms, coupled with remarkable progress in genomics and an expanding number of clinical cases, has since led to an increasing number of disorders classified as autoinflammatory or containing an autoinflammatory component. Biologic therapies targeting specific components of the innate immune system have provided immense clinical benefit, and have further elucidated the role of innate immunity in autoinflammatory disorders. This article reviews the basic mechanisms of autoinflammation, followed by an update on the pathophysiology and treatment of the monogenic and multifactorial autoinflammatory diseases, and the common dermatologic conditions in which autoinflammation plays a major role.

Key Points

Autoinflammation is characterized by an aberrant innate immune response.

Recent research has begun to delineate the complex pathways of innate immunity, which has increasingly led to the identification of autoinflammatory components in a number of diseases.

Advances in targeted therapies have led to dramatic improvements in outcomes among patients with autoinflammatory disorders.

1 Introduction

Autoinflammatory syndromes are a group of conditions characterized by an exaggerated innate immune system response leading to episodes of spontaneous inflammation involving multiple organ systems. First proposed in 1999, the concept of autoinflammation was used to describe a group of syndromes characterized by recurrent fevers and various forms of systemic inflammation, without typical manifestations of autoimmune diseases such as antigen-specific T lymphocytes or high-titer autoantibodies. Since then, remarkable progress in genomics and an increasing number of clinical reports have led to recognition of autoinflammatory diseases as a distinct entity, while a fundamental role of the innate immune system has been increasingly identified in the physiopathogenesis of other chronic diseases as well. This improved understanding of innate immunity and disorders of autoinflammation has contributed to a growing arsenal of targeted therapies, not only drastically improving patients' lives but also confirming hypotheses on the complex role of the innate immune system in autoinflammation.

In this review, the basic concepts of autoinflammation will be discussed, followed by a review of the pathophysiology and treatments of the monogenic and multifactorial autoinflammatory diseases, and the common dermatologic conditions in which autoinflammation plays a major role.

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2 Mechanisms of Autoinflammation

2.1 Autoinflammation Versus Autoimmunity

The innate immune system is the non-specific, germline-encoded arm of immunity that responds rapidly to danger signals through specialized receptors known as pattern recognition receptors (PRRs). Activation of innate immune system cells, predominantly those of myeloid lineage, triggers the production of pro-inflammatory cytokines including interleukin (IL)-1, IL-18, tumor necrosis factor alpha (TNF-α), and type-1 interferons (IFNs), and leads to a host of downstream immunologic pathways. This sequence of events is a critical first-line defense against a number of pathogenic assaults, and becomes exaggerated in 'autoinflammation,' a term that has evolved to denote diseases in which innate immunity plays the primary pathophysiologic role. The result of autoinflammation is episodic spontaneous inflammation affecting multiple organ systems and often leading to host tissue damage. In contrast, the term 'autoimmunity' typically describes disorders of the adaptive immune system, which is primarily mediated by lymphocytes and characterized by elevated serum autoantibody titers with variable activation of ILs. Though autoimmune and autoinflammatory disorders often comprise distinct clinical entities, a growing body of evidence suggests that inappropriate signaling through innate mechanisms may be necessary for initiating and/or maintaining systemic autoimmune processes [1]. Continued research into the complex pathways of innate immunity has led to the reclassification of a number of autoimmune or unclassified diseases as autoinflammatory or containing an autoinflammatory component.

2.2 Inflammasomes

First described in 2002 [2], inflammasomes are large intracellular signaling complexes that are vital to the innate immune response. Formation of inflammasomes occurs through activation of various cytosolic receptors, including absent in melanoma 2 (AIM2), recombination activating gene 1 (RAG1), pyrin, and those of the NOD-like receptor (NLR) family, of which NLRP3 is the best characterized [3]. Recognition of stimuli by cytosolic receptors promotes their oligomerization with adaptor protein apoptosis-associated speck-like protein containing CARD (ASC), a protein common to all inflammasomes. This step organizes the inflammasome complex, which subsequently promotes cleavage of procaspase-1 into its active form, caspase-1, and leads to the production and cleavage of the pro-inflammatory cytokines pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18. Activation of inflammasomes is thus critical to the innate immune system, and genetic mutations in inflammasome pathways that permit unchecked activation have been implicated in a number of inflammatory disorders.

A variety of stimuli, both exogenous and endogenous, have been shown to activate inflammasomes, including pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). The prototypical PAMPs are lipopolysaccharides on gram-negative bacterial cell walls, though lipoteichoic acid (gram-positive bacteria), double-stranded RNA (viruses), peptidoglycan, and flagellin also contain PAMPs. Endogenous stimuli are also involved in inflammasome activation: during cell death, nuclear and cytosolic proteins are broken down which form non-pathogenic danger signals, or DAMPs, which activate inflammasomes to remove cellular debris or react to potential neoplasia. While recent research has found that the inflammatory milieu may be helpful in promoting autophagy of cancer cells [4–6], the relationship between inflammasomes and tumorigenesis is complicated: an inflammatory environment can also promote stress-related protein activation that causes cancer cells to exhibit greater resistance to apoptosis [7].

2.3 Interleukin (IL)-1β and IL-18

Discovery of IL-1β occurred throughout the twentieth century, long before the inflammasome was identified as a key component in innate immunity. A 1948 study described a substance isolated from rabbit leukocytes that was capable of inducing fever [8], later identified in the 1970s as IL-1β. Over the next few decades its role as a robust pro-inflammatory cytokine was characterized, and the cells responsible for its secretion identified as both immune (e.g., monocytes, macrophages, lymphocytes, neutrophils) and non-immune (e.g., keratinocytes). IL-1β is an acute phase reactant and pyrogen. Following its action on multiple receptor types, including the IL-1 receptor type I (IL-1RI), IL-1β activates nuclear factor kappa light-chain-enhancer of activated B cells (NFκB), which subsequently upregulates expression of cyclooxygenase-2 (COX-2), leading to fever. IL-1β also induces the upregulation of pro-inflammatory cytokines, notably IL-6 and TNF-α. Despite its critical role in mediating fever and the response to infection, unchecked upregulation of IL-1β can lead to a deleterious pro-inflammatory cascade as seen in many of the autoinflammatory conditions. In contrast, IL-1α, which also acts on the IL-1RI, is constitutively present in the cells of healthy individuals and plays a lesser role in autoinflammation [9].

Whereas much is known about IL-1β, the role of IL-18 is less clear, although significant attention is now focused on characterizing its function in the inflammatory milieu. IL-18 exhibits characteristics of other pro-inflammatory cytokines,

including upregulation of IFN-γ and chemokines, though unlike IL-1β, the induction of fever as well as acute phase proteins is not a significant property. IL-18 plays a role in the inflammatory components of inflammatory bowel disease (IBD), heart disease, and metabolic syndrome, and also mediates certain pathways in tumorigenesis. For instance, inhibition of IL-18 reduces expression of vascular cell adhesion molecule-1 (VCAM-1), decreasing metastases in a mouse model of melanoma [10]. Hence, inhibition of IL-18 activity has become an attractive therapeutic target in both inflammatory disorders and certain types of cancer.

2.4 IL-1 Inhibitor Therapy

Given its pivotal role in the inflammasome response and innate immunity, a growing body of research has targeted IL-1β in the treatment of autoinflammatory disorders. Among the IL-1 inhibitors that have shown considerable success are anakinra, a competitive inhibitor of both IL-1β and IL-1α which binds to the IL-1RI [11]; rilonacept, a soluble fusion decoy IL-1R [12]; and canakinumab, a selective anti-IL-1β monoclonal antibody [13]. Despite marked success in quelling the innate immune response and improving clinical symptoms across a spectrum of disorders, anakinra causes a relatively high incidence of injection site reactions and requires daily injections due to its short half-life, limiting its use among certain patient populations. Rilonacept and canakinumab can be administered weekly [12] and bimonthly [13], respectively, facilitating greater ease of use and oftentimes providing viable alternatives for those in whom anakinra is infeasible or intolerable. While the IL-1 inhibitors are frequently used off-label, an expanding body of high-quality studies over the last 2 decades has led to United States (US) Food and Drug Administration (FDA) approval for certain indications. In 2001, anakinra was approved for the treatment of rheumatoid arthritis (RA) and the cryoporin-associated periodic syndromes (CAPS) [11]; canakinumab has been approved for CAPS, systemic juvenile idiopathic arthritis (SJIA), TNF receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), and familial Mediterranean fever (FMF) [13]; and rilonacept has been approved for CAPS [12]. IL-1 inhibitors have thus opened new channels in the management of autoinflammatory disorders, providing more targeted treatment and marked improvement over conventional therapies, though considerable progress is yet to be made.

2.5 Proteasome and Immunoproteasome

Whereas dysregulation of the inflammasome and IL-1 have been implicated in a number of autoinflammatory diseases, mutations in proteasome-immunoproteasome components have recently been identified in several autoinflammatory diseases unresponsive to IL-1 inhibitor therapy. Proteasomes and immunoproteasomes are multiprotein structures responsible for the removal of intracellular and foreign waste proteins, respectively [14]. Following recognition of type 1 IFNs by cell surface receptors, activation of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways stimulates transcription of type 1 IFNs, producing reactive oxygen and nitrogen species that damage cell proteins. These damaged proteins require increased proteolytic degradation by the proteasome-immunoproteasome to maintain cell viability [15]. In certain autoinflammatory conditions such as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, mutations in the proteasome-immunoproteasome are unable to remove waste proteins, causing their accumulation and leading to increased production of type 1 IFNs with subsequent recruitment of inflammatory cells and collateral tissue damage [14].

3 Monogenic Autoinflammatory Diseases

The monogenic autoinflammatory diseases constitute a group of rare disorders that are often hereditary and characterized by childhood onset, episodic fever, skin manifestations, and disease-specific patterns of organ inflammation. Genetic analysis remains critical in diagnosing these conditions as the specific mutations underlining them have largely been identified (Table 1).

3.1 Familial Mediterranean Fever (FMF)

FMF is the most common systemic autoinflammatory disease, primarily affecting patients of Jewish, Arab, Armenian, Turkish, and Italian lineage. Inheritance is autosomal recessive, and carrier frequency in Middle Eastern populations is as high as one in three [16], suggesting a possible heterozygote advantage [17, 18]. By age 20, almost all patients experience at least one episode [19], which typically manifests as fever lasting several hours to 3 days; monoarthritis with effusions, often involving large joints of the lower limbs; scrotal pain or swelling; pleuritis causing chest pain; or peritonitis causing abdominal pain. Erysipelas-like lesions on the dorsal foot and anterior leg are a distinguishing clinical finding in up to half of patients [19]. Dermal infiltrates of neutrophils and nuclear dust are often found on histopathologic examination [20]. Additional cutaneous manifestations can include angioedema, palmoplantar erythema, and Raynaud-like phenomena [21]. Patients with FMF also have a higher likelihood of developing vasculitides such as Henoch–Schönlein purpura (HSP) and polyarteritis nodosa (PAN) [22, 23]. Elevated levels of the acute phase

Table 1 Summary of the genetic and clinical features of monogenic autoinflammatory conditions

Monogenic autoinflammatory conditions	Gene (protein)	Cutaneous manifestations	Treatment
Familial Mediterranean fever (FMF)	*MEFV* (pyrin)	Erysipelas-like lesions on lower extremities; vasculitis	Colchicine, canakinumab, anakinra, rilonacept, TNF inhibitors
Cryoporin-associated periodic syndromes (CAPS)	*NLRP3* (cryoporin)	Urticarial lesions, can be induced by cold exposure	Anakinra, rilonacept, canakinumab, corticosteroids, NSAIDs
Mevalonate kinase deficiency (MKD)	*MVK* (mevalonate kinase)	Erythematous macules, papules, and nodules; urticarial lesions	Corticosteroids, NSAIDs, anakinra, canakinumab, TNF inhibitors
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	*TNFRSF1A* (TNF receptor type 1)	Serpiginous or annular patches and plaques overlying local areas of myalgia	Corticosteroids, NSAIDs, canakinumab, anakinra, etanercept
Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome	*PSTPIP1* (proline/serine/threonine/phosphatase-interacting protein)	Severe nodulo-cystic acne; erythematous papulopustules evolving into necrotic ulcers	Corticosteroids, anakinra, canakinumab, infliximab, adalimumab
Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)	*MEFV* (pyrin)	Severe acne; sterile skin abscesses; pyoderma gangrenosum; vasculitis	Anakinra, infliximab, adalimumab
Blau's syndrome (familial juvenile systemic granulomatosis)	*NOD2* (nucleotide-binding oligomerization domain-containing protein 2)	Erythematous micropapular dermatitis; later brownish-red, papulonodular scaly lesions on trunk and extremities	Corticosteroids, methotrexate, cyclosporin, TNF inhibitors, anakinra
Deficiency of the IL-1 receptor antagonist (DIRA)	*IL1RN* (IL-1 receptor antagonist)	Diffuse pustular dermatitis	Anakinra, canakinumab, rilonacept
Deficiency of the IL-36 receptor antagonist (DITRA)	*IL36RN* (IL-36 receptor antagonist)	Generalized pustular psoriasis, often without psoriasis vulgaris	Acitretin, corticosteroids, TNF inhibitors, methotrexate, cyclosporine, phototherapy
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome	*PSMA3*, *PSMB4*, *PSMB8*, *PSMB9* (proteasome subunits)	Periorbital discoloration and edema; facial lipoatrophy; annular purpuric plaques	JAK inhibition with baricitinib, methotrexate, corticosteroids, cyclosporine, azathioprine, IVIG
STING-associated vasculopathy with onset in infancy (SAVI)	*TMEM173* (STING)	Vasculitic ulcers or plaques; telangiectasias; pustular blistering rashes; lesions worse with cold	Baricitinib, tofacitinib, ruxolitinib, corticosteroids

IL interleukin, *IVIG* intravenous immunoglobulin, *JAK* Janus kinase, *NSAID* nonsteroidal anti-inflammatory drug, *STING* stimulator of interferon genes, *TNF* tumor necrosis factor

reactant serum amyloid A (AA) can lead to amyloidosis, a rare but severe complication of FMF. If left untreated, AA amyloidosis can progress to potentially fatal organ involvement, particularly of the kidneys.

Though incompletely understood, the pathogenesis of FMF involves mutations in the *MEFV* gene encoding pyrin. While the role of pyrin in IL-1 activation remains controversial, one hypothesis is that it suppresses activation of pro-caspase-1, thereby inhibiting inflammasome activation [24]. Thus, defective pyrin in FMF may exhibit less of an inhibitory effect on the inflammasome, leading to unchecked production of IL-1β [25].

Since the early 1970s, continuous daily colchicine has been the mainstay of treatment for FMF as it not only reduces the frequency and severity of attacks, but also prevents the development of amyloidosis and leads to remission in the majority of cases [26]. The anti-inflammatory effect of colchicine in FMF was traditionally thought to result from microtubule disruption and altered cell adhesion molecules, preventing the migration of neutrophils in response to chemotactic factors [27]. More recent evidence has suggested that colchicine-induced depolymerization of microtubules leads to activation of the GTPase RhoA, with subsequent phosphorylation of the 14-3-3 protein and inhibition of pyrin-induced inflammasome formation [28]. Other evidence suggests that colchicine may mediate pathways beyond those affecting microtubule depolymerization; one study found that short-term incubation of vascular endothelial cells with colchicine affected expression of genes involved in cell cycle regulation, whereas longer incubation periods were needed before colchicine altered expression of genes involved in neutrophil migration [29]. The mechanism of colchicine in the treatment of FMF remains controversial, however. Resistance to colchicine or intolerance to its side effects occurs in approximately 10–15% of patients [30], and additional therapies are indicated in these cases.

A number of recent studies on the treatment of colchicine-unresponsive or colchicine-intolerant FMF have examined biologic agents, and prognosis is now excellent, due largely to the effects of IL-1 inhibitors. Results from a recent randomized controlled trial of 25 colchicine-resistant FMF patients showed that daily 100 mg anakinra injections led to significantly fewer attacks per month (1.7 vs 3.5 in the placebo group) [31]. This effect was particularly prominent in joints (0.8 joint attacks per month vs 2.1 in the placebo group), suggesting that anakinra may be a complementary treatment to colchicine, a medication that often fails to prevent joint attacks. A recent systematic review reported complete response in 76.5% of patients during treatment with anakinra, and an additional 18.8% of patients had a decrease in attack frequency and inflammation [32]. Anakinra also decreased proteinuria in patients with nephrotic syndrome, and there was no recurrence of AA amyloidosis in renal transplant patients [32]. A large observational study published in 2018 found that treatment with either anakinra or canakinumab for at least 6 months significantly reduced yearly attack frequency in colchicine-resistant FMF patients, from 16.8 attacks to 2.4 attacks per year [33]. Despite mounting evidence supporting the efficacy of anakinra in controlling colchicine-resistant FMF, evidence-based guidelines published by the European League Against Rheumatism (EULAR) recommend concomitant administration of colchicine due to limited long-term data on the efficacy of IL-1 inhibitors in preventing AA amyloidosis [34, 35].

Canakinumab is the only biologic agent approved by the FDA for the treatment of FMF. A recent phase III clinical trial found that 71% of colchicine-resistant FMF patients had a complete response following monthly 150–300 mg canakinumab injections, versus 6% in the placebo group [36]. A recent systematic review reported complete response in 67.5% of colchicine-resistant or intolerant FMF patients treated with canakinumab, while the remaining 32.5% of patients achieved partial response with reduced attack frequency and inflammation [32]. In a 2017 retrospective study of 14 patients resistant to colchicine or both colchicine and anakinra, all participants responded to canakinumab [37]. Although four patients relapsed during follow-up, reducing the canakinumab administration interval from 8 or 6 weeks to 4 weeks led to suppression of disease activity [37].

Rilonacept has also been evaluated in the treatment of colchicine-resistant FMF patients. A small randomized controlled alternating treatment study found that 2.2 mg/kg weekly rilonacept reduced attack frequency to 0.77 per month (versus 2 per month in the placebo group) [38]. Eight patients responded to treatment with rilonacept, while four did not [38].

Anti-TNF agents (etanercept, infliximab, adalimumab) are beneficial in controlling attacks, particularly among FMF patients with articular involvement. A 2011 literature review identified several case reports in which TNF inhibitors were effective in controlling FMF attacks [39]. In a case series of four patients with FMF-related amyloidosis, arthritic symptoms and nephrotic syndrome were effectively controlled with long-term infliximab [40]. A retrospective cohort of ten FMF patients with chronic arthritis and/or sacroiliitis found that musculoskeletal symptoms improved or disappeared in all patients after anti-TNF treatment, and seven patients experienced no attacks [41]. Thus, in recalcitrant or difficult-to-treat cases, TNF inhibition might be a reasonable alternative treatment for FMF.

3.2 Cryoporin-Associated Periodic Syndromes (CAPS)

The CAPS encompass a continuous spectrum of severity of a single condition previously classified as three distinct

subtypes: familial cold-associated syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular syndrome (CINCA) [42]. In 2001, FCAS and MWS were found to share mutations in the *NLRP3* gene encoding cryopyrin [43], a key component of the inflammasome that regulates processing of IL-1β and IL-18. Shortly thereafter, mutations in *NLRP3* were also found to underlie NOMID/CINCA [44]. To date, over 180 gain-of-function mutations in the *NLRP3* gene have been reported [45], arising either de novo or through autosomal dominant inheritance and resulting in defective interaction between NLRP3 and the IL-1β maturation inhibitor cyclic adenosine monophosphate (cAMP) [46] or its negative regulator caspase recruitment domain-containing protein 8 (CARD8) [47].

Common across the CAPS spectrum are episodes of recurring fever, conjunctivitis, and arthralgia. Almost all CAPS patients experience recurrent urticarial rash, which must be differentiated from the wheals present in chronic spontaneous urticaria or urticarial vasculitis [48]. In contrast to the predominant dermal edema and sparse inflammatory infiltrates seen in true urticaria, the urticarial lesions in CAPS—and many autoinflammatory diseases in general—often contain dense neutrophil-rich perivascular and interstitial infiltrates with limited dermal edema [48]. Further, the urticarial-like rash in CAPS is often characterized by burning or painful non-pruritic erythematous patches that lack the classic wheal-and-flare seen in chronic urticaria [48].

FCAS constitutes the mildest end of the spectrum and is characterized by cold-induced inflammatory episodes. Urticarial lesions present several hours after cold exposure and can last up to 12 h. In MWS, the intermediate subtype, urticarial lesions are also seen but may persist for longer than those in FCAS. Progressive sensorineural hearing loss, coxitis, and osteitis leading to limb pain are characteristic features of MWS, and over 25% of patients develop amyloidosis, which can be fatal [49].

NOMID/CINCA constitutes the most severe and earliest-onset of the CAPS subtypes. The majority of patients present with urticaria-like eruptions at birth, and almost all develop these lesions by 6 months of age. Unlike the lesions in FCAS and MWS, urticarial lesions in NOMID/CINCA tend to be persistent. Hearing loss, hypertrophic arthropathy, and dysmorphic features including frontal bossing and midface hypoplasia are common manifestations. Central nervous system inflammation is often the most devastating feature and can lead to chronic aseptic meningitis, cognitive impairment, and epilepsy [50].

A revolution in the treatment of CAPS began with the introduction of anakinra in the early 2000s. Since then, a number of studies have demonstrated remarkable response to IL-1 blockers, and IL-1 inhibition is currently recommended for the entire CAPS spectrum at any age [51]. Observational studies and open-label clinical trials have reported marked symptomatic improvement and prevention of disease progression following anakinra treatment in patients with NOMID/CINCA [52–55], MWS [54–57], and FCAS [54, 58]. Similarly, observational studies and clinical trials have reported long-term safety and sustained response of rilonacept in patients with MWS and FCAS [54, 59, 60], and a randomized controlled trial reported significant improvement in the clinical signs and symptoms of FCAS and MWS with weekly rilonacept [61]. The efficacy of canakinumab has been demonstrated in randomized controlled trials in patients with MWS and NOMID/CINCA-MWS overlap [62, 63], as well as in multiple observational studies and clinical trials of patients across the CAPS spectrum [54, 57, 64–67]. Of note, the real-life effectiveness of canakinumab may be significantly lower than that in clinical trials—a 2016 study showed a real-life complete response rate of 72% [68], versus up to 97% reported in clinical trials [63], reflecting the importance of a treat-to-target approach and dose escalation based on individual responses. Nevertheless, IL-1 inhibition can partially halt or improve organ damage and should be initiated early on in the disease course. Nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids can be used for symptomatic relief during episodes [69], but should not be used without concomitant IL-1 inhibition due to insufficient evidence on preventing organ damage if used alone [51].

3.3 Mevalonate Kinase Deficiency (MKD)

MKD is an autosomal recessive disorder resulting from loss-of-function mutations in the gene encoding mevalonate kinase (MVK), an enzyme involved in the synthesis of cholesterol and isoprenoids. Mutations in *MVK* lead to decreased production of nonsterol isoprenoids, which results in activation of the pyrin inflammasome and increased secretion of IL-1β [28, 70, 71]. The disorder encompasses a continuous spectrum of two phenotypes. The milder form, hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), manifests as sporadic episodes of fever, severe abdominal pain, diarrhea, arthralgias, lymphadenopathy, splenomegaly, and rash. Common skin findings include erythematous macules, papules, nodules, and urticarial lesions [72]. Skin biopsy may show vasculitic lesions [72, 73], and almost half of patients develop aphthous ulcerations in the mouth, often along with genital ulceration [21]. A small percentage of patients develop AA amyloidosis with consequent kidney dysfunction. Onset occurs within the first few months of life, and the frequency of attacks tends to decrease with age. Whereas a partial deficiency in MVK causes the HIDS phenotype, nearly absent enzymatic activity causes the more severe mevalonic aciduria (MA) [74, 75]. Patients

with this phenotype have typical characteristics of HIDS, though symptoms are more chronic. Psychomotor retardation, dysmorphic features, and failure to thrive are also seen in MA [76].

NSAIDs provide moderate benefit in attenuating symptoms during episodes but rarely provide complete response [69]. Glucocorticoids provide therapeutic benefit in most patients, particularly when given at the beginning of an attack [69, 77], whereas colchicine, statins, antibiotics, thalidomide, and cyclosporine have not been shown to be effective [51, 69, 77, 78].

Observational studies and clinical trials with canakinumab and anakinra have shown efficacy in preventing febrile attacks and erosive polyarthritis in MKD [78–81]. A recent randomized controlled trial reported complete response in 35% of MKD patients treated with 150 mg canakinumab, and complete response in 57% when the dose was increased to 300 mg [36]. Given the relatively long asymptomatic intervals (2–8 weeks) [82] and burden of daily injections, on-demand treatment with anakinra may be a reasonable approach to management in cases where anakinra is preferred [80]. However, in cases characterized by frequent attacks or ongoing subclinical inflammation, chronic maintenance therapy is recommended [51]. Variable results have been reported in the small number of patients treated with TNF-α inhibitors [69, 77, 78, 83], and patients who do not respond to etanercept may benefit from switching to other biologics [84]. Despite recent advances in biologic therapies, treatment of MKD remains challenging. The response to IL-1 inhibition is less dramatic than in the other periodic fever syndromes [69, 83], and off-label use of TNF inhibitors and corticosteroids appears to provide only modest benefit. In severe cases refractory to all other therapies, allogeneic hematopoietic stem cell transplantation has been suggested as an option [51].

3.4 Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

TRAPS is an autosomal dominant disorder due to heterozygous mutations in the TNF receptor superfamily 1A (*TNFRSF1A*) gene which encodes for the TNF-α receptor [85]. Mutations produce a misfolded receptor that accumulates in the cell cytoplasm, leading to enhanced NFκB activation, reactive oxygen species (ROS) production and impaired autophagy, ultimately triggering the innate immune response and chronic inflammation. The syndrome presents clinically with acute inflammatory episodes of 1–3 weeks, with long-lasting fever, migratory myalgias, abdominal pain, skin lesions, and ocular involvement including periorbital edema and conjunctivitis [86]. Various types of skin lesions are seen in TRAPS, including erythematous macules and papules which expand and coalesce into serpiginous or annular patches and plaques overlying local areas of myalgia [87]. These 'painful erythemas,' as they were originally described [88], commonly affect the arms and migrate to the distal extremities, resolving in some cases with ecchymoses [87]. The longer duration of attacks as well as skin and eye manifestations distinguish TRAPS from FMF.

Short-term corticosteroids and NSAIDs are useful in aborting attacks and providing symptomatic relief during episodes [69], though the efficacy of corticosteroids may decline over time [89]. TNF-α blockade with etanercept is also beneficial: most patients have a favorable yet incomplete response [69, 90, 91]. In some cases, declining efficacy over time [91, 92] necessitates a switch from etanercept to other therapies. Paradoxical inflammatory attacks have been observed following administration of infliximab and adalimumab [93, 94], and these agents should be avoided in treatment [51]. The IL-1 inhibitors are the most promising therapeutic options; in 2016, canakinumab became the first FDA-approved therapy for TRAPS, and ongoing studies with IL-1 inhibitors are encouraging. A recent large randomized controlled trial found that 45% of patients had a complete response to 150 mg canakinumab, and 73% experienced complete response when the dose was increased to 300 mg [36]. Observational studies and case reports have also reported high rates of clinical remission following treatment with canakinumab [95, 96]. Both on-demand and maintenance therapy with anakinra has led to significant clinical improvements in patients with TRAPS [97–99]. In the Eurofever Registry, anakinra induced a complete response in 79% of TRAPS patients and a partial response in 16% [69]. Case reports of IL-6 inhibition with tocilizumab have also shown rapid improvement in symptoms and prevention of attacks [100, 101].

3.5 Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is associated with mutations in the *PSTPIP1* gene [102], leading to reduced pyrin inhibition of inflammasome activation and subsequent upregulation of IL-1β. The pathogenesis of the syndrome is not fully understood, however. Patients with PAPA experience childhood-onset sterile erosive arthritis which tends to regress with age. Skin manifestations are varied and include severe nodulocystic acne presenting in adolescence and often continuing into adulthood. Pyoderma gangrenosum (PG)—characterized by painful, erythematous papulopustules that evolve to necrotic ulcers with overhanging borders—usually develops on the distal lower extremities but can also occur multifocally on the entire skin [21]. Treatment depends on the dominant clinical manifestation. In general, TNF inhibitors (infliximab, adalimumab) have been considered more effective

in treating skin manifestations [103], while IL-1 inhibition may be more effective in improving arthritis; however, due to the extreme rarity and clinical heterogeneity of the disease [104], there is no standard treatment. In several case reports, anakinra resulted in prompt resolution of arthritis [105, 106], and another case report described complete resolution of PG, arthritis, and acne with anakinra [107]. Treatment with canakinumab led to complete resolution of PG and acne in one case report [108], and a small observational study reported long-term efficacy with anakinra or canakinumab [109].

3.6 Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND)

Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) is a recently identified disorder caused by a dominantly inherited heterozygous mutation in the *MEFV* gene leading to disrupted pyrin-14-3-3 binding and subsequent activation of the pyrin inflammasome [110]. Excessive IL-1β and activation of inflammatory pathways cause a clinical picture characterized by childhood-onset episodic fever, arthralgia, myalgia, and myositis [110]. Severe recurrent neutrophilic dermatosis—characterized by severe acne, sterile skin abscesses, PG, and neutrophilic small vessel vasculitis [110]—differentiates the disorder from FMF. Given the novelty of the disorder and the paucity of case reports, evidence regarding therapeutic options is currently limited. One patient treated with anakinra experienced resolution of clinical symptoms [110]; another patient refractory to corticosteroids and anakinra experienced several years of clinical improvement with infliximab, although eventual loss of efficacy necessitated a switch to adalimumab [111].

3.7 Blau's Syndrome

Blau's syndrome (also known as familial juvenile systemic granulomatosis) is a rare autosomal dominant disorder caused by a mutation in the PRR *NOD2* gene (also known as *CARD15*) [112], leading to elevated NFκB signaling [113]. Disease onset occurs during the first years of life and involves non-caseating granulomatous inflammation affecting the joints, eyes, and skin. Cutaneous manifestations include generalized erythematous micropapular dermatitis which may later develop into tender, brownish-red, papulonodular scaly lesions that affect the trunk and extremities symmetrically, and may contain features of a sarcoidal granulomatous dermatitis [21, 114]. Symmetrical granulomatous tenosynovitis results in a characteristic 'boggy' appearance of the joints. Uveitis is usually the last feature to develop and can be complicated by glaucoma, cataract, and blindness. Of note, mutations in the *NOD2* gene have also been implicated in familial Crohn's disease and early-onset sarcoidosis [115, 116].

Treatment of Blau's syndrome is challenging due to its rarity and heterogeneity. Systemic corticosteroids, methotrexate, cyclosporin, anakinra, and TNF inhibitors have been used with variable success. A small case series and case report showed complete remission in patients treated with TNF inhibitors [117, 118], but response can be inconsistent and adverse outcomes have been reported [119]. Anakinra may improve inflammatory symptoms in some patients [120, 121], though other patients do not benefit [122]. Rapid remission of uveitis following treatment with canakinumab or tocilizumab has been reported in two cases [123, 124]. Despite the use of current therapies, an estimated 60–70% of patients have active arthritis and severe ocular involvement at baseline [125], highlighting the ongoing need for improvements in treatment options.

3.8 Deficiency of the IL-1 Receptor Antagonist (DIRA)

Loss-of-function mutations in the *IL1RN* gene have been implicated in deficiency of the IL-1 receptor antagonist (DIRA), a rare autosomal recessive condition in which unopposed signaling of the pro-inflammatory cytokines IL-1α and IL-1β through the IL-1 receptor [126, 127] leads to severe systemic inflammation. Patients with DIRA present with neonatal-onset sterile osteomyelitis, periostitis, and pustular dermatitis that can be generalized or limited to one area [114]. Ichthyosiform changes may be present, and nail manifestations can include pitting and onychomadesis [128]. The condition can escalate to systemic inflammatory response syndrome (SIRS) and organ failure [126]. Mortality is approximately 30% in early infancy [129].

The IL-1 inhibitors have profoundly altered the prognosis of DIRA, in many cases eliminating the characteristic prolonged hospitalizations and severe clinical manifestations. Several case reports and case series have described rapid clinical improvement and complete recovery following treatment with anakinra, the recombinant replacement for the deficient protein in DIRA [126, 127, 130]. In a 12-year-old patient, complete remission was achieved following administration of canakinumab every 6 weeks [131]. A small open-label study reported long-term disease remission among six patients receiving weekly rilonacept who had previously been treated successfully with anakinra [129]. Given that DIRA requires lifelong therapy, these results are particularly exciting; less frequent injections—either weekly, with rilonacept, or monthly, with canakinumab—may offer significant improvement in quality of life over daily anakinra injections.

3.9 Deficiency of the IL-36 Receptor Antagonist (DITRA)

Deficiency of the IL-36 receptor antagonist (DITRA) is considered a monogenic form of pustular psoriasis caused by inactivating mutations in the *IL-36RN* gene encoding the IL-36 receptor antagonist (IL-36RA). Expression of IL-36 regulates IL-23/IL-17/IL-22 pathways [132] and leads to activation of NFκB. Deficiency of the IL-36RA thus leads to an exaggerated inflammatory response [133] characterized by sudden-onset recurrent episodes of high-grade fever, asthenia, neutrophilia, and severe generalized pustular psoriasis (GPP), often without psoriasis vulgaris [114]. Generalized scaly erythematous pustular eruptions often precede desquamation of the scalp and leg [114]. Histopathology reveals spongiform pustules, acanthosis with elongation of rete ridges, and parakeratosis, consistent with pustular psoriasis [133]. Though cutaneous lesions in DIRA are often similar to those of DITRA, the latter usually involves fewer organ systems and manifests primarily in the skin, a finding which may be attributable to the localization of IL-36 receptors to epithelial cells [134]. In contrast, the IL-1 receptor is expressed ubiquitously. Treatment of DITRA remains challenging and involves acitretin, topical and oral steroids, adalimumab, etanercept, infliximab, methotrexate, cyclosporine, and phototherapy, all of which have shown varying rates of success [114].

3.10 Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

CANDLE syndrome is characterized by infant-onset recurrent fevers, progressive facial lipoatrophy, and chronic characteristic skin manifestations including periorbital discoloration and edema, annular purpuric plaques, violaceous lesions on the heels and toes, and discrete erythematous nodules on the trunk and extremities. Histopathology of skin lesions may display an infiltration of immature, myeloid, mononuclear cells, with some maturation into polymorphonuclears and karyorrhexis [135]. The disorder is caused by mutations in a number of proteasome-associated genes including *PSMA3*, *PSMB4*, *PSMB8*, and *PSMB9* [136, 137], leading to defective proteasome assembly and accumulation of ubiquitinated proteins in the cytoplasm [138]. The result is sustained production of type-1 IFN [136, 137].

No therapies for CANDLE have been consistently effective to date, spanning methotrexate, corticosteroids, cyclosporine, azathioprine, and intravenous immunoglobulin (IVIG). Preliminary data from a compassionate use treatment protocol are encouraging, however: patients treated with the selective JAK1/2 kinase inhibitor baricitinib have experienced clinical improvement and decreased dependence on corticosteroids [139]. IFN signaling through JAK1/2 inhibition is thus a promising therapeutic target.

3.11 Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset in Infancy (SAVI)

Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) is caused by a gain-of-function mutation in the *TMEM173* gene encoding the STING protein, leading to dysregulated signaling of type 1 IFNs [140, 141]. The disease is characterized by neonatal-onset cold-induced acral vasculitis resulting in loss of digits. Telangiectasias, pustular blistering rashes, ulcers, and plaques present mainly on the cheeks, nose, fingers, and toes. Dystrophic nail changes may also be seen. In addition to cutaneous manifestations, many patients have interstitial lung disease of varying severity [141]. Therapies are currently limited. Blockade of IFN signaling with JAK inhibitors may offer a viable therapeutic strategy [141]; in four patients, baricitinib significantly improved cutaneous vasculitis flares and prevented the progression of spontaneous amputations and the development of gangrene [142]. Interstitial lung disease also stabilized on baricitinib, although levels of inflammatory markers and IFN remained elevated [142]. Treatment with the JAK inhibitors tofacitinib [143] and ruxolitinib have also provided therapeutic benefit in a small number of patients [143, 144].

4 Autoinflammatory Keratinization Diseases (AIKD)

Autoinflammatory keratinization diseases (AIKD) is a recently proposed disease concept encompassing a group of disorders triggered by genetic factors and characterized by inflammation in the dermis and epidermis with hyperkeratosis [145, 146]. Though the term initially included GPP, impetigo herpetiformis, acrodermatitis continua, palmoplantar pustular psoriasis (PPPP), pityriasis rubra pilaris type V, and keratosis lichenoides chronica [145], an increasing number of diseases have been classified as AIKD, including hidradenitis suppurativa (HS) and porokeratosis [147, 148]. We describe a number of these diseases below (see Table 2).

4.1 Hidradenitis Suppurativa (HS)

HS is an inflammatory disease restricted primarily to the intertriginous areas and characterized initially by follicular occlusion due to infundibular hyperkeratinization and hyperplasia of the follicular epithelium, as well as psoriasiform hyperplasia of the interfollicular epidermis [149]. Dilatation and rupture of follicles occurs later in the disease

Table 2 Summary of the genetic and clinical features of multifactorial autoinflammatory conditions

Multifactorial autoinflammatory conditions	Genes	Cutaneous manifestations	Treatment
Hidradenitis suppurativa (HS)	Unknown	Nodules with ulceration, abscesses, and fistulas; evolve into hypertrophic scars	Adalimumab, infliximab, ustekinumab, anakinra, antibiotics, corticosteroids
Generalized pustular psoriasis (GPP)	*CARD14*, *IL36RN*	Widespread subcorneal pustules overlying erythematous plaques	Retinoids, cyclosporine, methotrexate, infliximab, gevokizumab, canakinumab, IL-17A inhibitors
Palmoplantar pustular psoriasis (PPPP)	*CARD14*	Sterile pustules on palms and soles; hyperkeratosis and fissuring	PUVA, UVB, acitretin, methotrexate, corticosteroids, cyclosporine, ustekinumab
Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO)	*PSTPIP2*, *LPIN2*, *NOD2*, *IL1RN*, unknown	Palmoplantar pustulosis, severe acne, pustular psoriasis, psoriasis vulgaris, hidradenitis suppurativa	NSAIDs, methotrexate, sulfasalazine, bisphosphonates, TNF inhibitors, ustekinumab, secukinumab, anakinra
Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)	*PSTPIP1*, *NLRP3*, *MEFV*, *NOD2*, *PSMB8*, *NCSTN*	Suppurative hidradenitis; acne; pyoderma gangrenosum later	Anakinra, infliximab, adalimumab
Behcet's disease (BD)	*MEFV*, *HLA-B51*, *TNFAIP3*, complex	Oral aphthous ulcers; genital ulcers; erythema nodosum	Colchicine, corticosteroids, azathioprine, thalidomide, cyclosporine, cyclophosphamide, TNF inhibitors, anakinra, canakinumab, tocilizumab
Systemic juvenile idiopathic arthritis (SJIA)	Complex	Evanescent salmon-colored maculopapular rash	Corticosteroids, NSAIDs, canakinumab, anakinra, tocilizumab
Adult-onset Still's disease (AOSD)	Complex	Evanescent salmon-colored maculopapular rash	Corticosteroids, DMARDs, TNF inhibitors, anakinra, canakinumab, tocilizumab
Schnitzler's syndrome	Unknown	Urticarial-like lesions with neutrophilic infiltrates	Corticosteroids, anakinra, canakinumab, rilonacept
Sweet's syndrome (acute febrile neutrophilic dermatosis)	*HLA-B54*, *PTPN6*, *IDH1*, *MEFV*, unknown	Erythematous papules, nodules, and plaques	Corticosteroids, colchicine, dapsone, potassium iodide, anakinra, TNF inhibitors
Pyoderma gangrenosum (PG)	*MEFV*, *NLRP3*, *NLRP12*, *NOD2*, *LPIN2*, *PSTPIP1*, *JAK2*, *MTHFR*, complex	Sterile pustules evolve into ulcers with undermined borders	Corticosteroids, antibiotics, IVIG, thalidomide, infliximab, ustekinumab, canakinumab, anakinra
Psoriasis	*CARD14*, *IL36RN*, *TNFAIP3*, *TNIP1*, unknown	Papules and plaques with silver scale, typically on extensor surfaces; sterile pustules; hyperkeratosis	Corticosteroids, retinoids, phototherapy, methotrexate, cyclosporine, TNF inhibitors, ustekinumab, secukinumab, ixekizumab, apremilast
Acne vulgaris	Complex	Comedones; papules; pustules; nodules; cysts	Antibiotics, retinoids, salicylic acid, spironolactone, nitric oxide-releasing agents

DMARD disease-modifying antirheumatic drug, *IL* interleukin, *IVIG* intravenous immunoglobulin, *NSAID* nonsteroidal anti-inflammatory drug, *PUVA* psoralen and ultraviolet A, *TNF* tumor necrosis factor, *UVB* ultraviolet B

process [149]. Clinically, the disease manifests as painful nodules, often with ulceration, abscesses, and fistulas which evolve into retracting or hypertrophic scars [42]. The pathogenesis may involve the initiation of inflammation through IL-17 + cells, promoting the release of IL-1β from keratinocytes and leading to activation of the NLRP3 inflammasome and upregulation of the pro-inflammatory DAMPs S100A8/A9 [150]. Infiltrating neutrophils may perpetuate the process through secretion of IL-17 [150], resulting in a positive-feedback loop. Several studies have reported upregulation of IL-1β, IL-17, inflammasome activation, and S100A8/A9 in lesional skin of HS [151–153].

Despite a controversial role of bacteria in the pathogenesis of HS [154], antibiotics have long been considered a first-line therapy [155], although their efficacy is often transient. Corticosteroids are frequently used in cases of systemic disease, but no randomized controlled trials have demonstrated their efficacy in treating HS. Wide local excision therapy is indicated in severe cases.

Widespread evidence now exists for the efficacy of infliximab and adalimumab in the treatment of HS, and the latter has been FDA-approved for moderate to severe cases. TNF-α inhibition with etanercept has been less promising: a randomized double-blind trial showed no significant improvement in patients who received etanercept versus placebo [156]. Recent reports of the IL-12/IL-23 inhibitor ustekinumab have been encouraging: in an open-label study, almost half of the 12 patients who completed the study protocol achieved Hidradenitis Suppurativa Clinical Response 50, a corollary to the Psoriasis Area and Severity Index (PASI)-50 [157]. For recalcitrant cases of HS, IL-1 inhibition with anakinra may be an option: successful treatment was reported in a patient who had failed oral antibiotics, azathioprine, cyclosporine, adalimumab, and infliximab [158], although there have also been several case reports of failure with anakinra therapy [159, 160]. In a randomized controlled trial of 20 patients, anakinra led to significant improvements in disease activity and HS clinical response [161].

4.2 Generalized Pustular Psoriasis (GPP)

GPP is an uncommon subtype of pustular psoriasis characterized by recurrent eruptions of widespread subcorneal pustules. The disorder commonly presents with 2- to 3-mm sterile pustules overlying areas of painful, expanding erythematous plaques or over erythematous skin [162], and patients often appear dramatically ill. Kogoj spongiform pustules, which show neutrophil accumulation beneath the stratum corneum and damaged keratinocytes, are a characteristic finding on histopathologic exam [163]. Additional epidermal features include parakeratosis, an absent granular layer, Munro's microabscesses, supra-papillary thinning, and psoriasiform hyperplasia, though notably the edema and cell infiltration in GPP are more pronounced than in psoriasis vulgaris [163].

GPP is associated with mutations in *CARD14*, particularly in the setting of preceding or concurrent psoriasis vulgaris lesions [164, 165]. Caspase recruitment domain-containing protein 14 (CARD14) is mainly localized to keratinocytes [164], and *CARD14* mutations likely enhance NFκB activation and a subset of psoriasis-associated genes in keratinocytes [164, 166], leading to clinical manifestations of the disease. In many cases of sporadic GPP without preceding or concurrent psoriasis vulgaris, DITRA (IL-36RA) due to mutations in *IL36RN* [167] leads to uncontrolled disinhibition of IL-1 [133] and subsequent activation of NFκB, similar to the pathophysiologic mechanism underlying DITRA.

First-line treatment for GPP includes retinoids, cyclosporine, and methotrexate. In patients with severe, acute GPP, infliximab is considered a first-line option due to its rapid onset of action [168]. The IL-1β inhibitors gevokizumab and canakinumab have been effective in individual cases [169, 170], although prospective randomized controlled trials have not been conducted. Anakinra has provided benefit in some cases [171, 172], and trials involving IL-17A inhibition with ixekizumab, secukinumab, and brodalumab have shown promising results [173–175].

4.3 Palmoplantar Pustular Psoriasis (PPPP)

PPPP is a type of localized pustular psoriasis characterized by painful sterile pustules on the palms and soles that lead to hyperkeratosis and skin fissuring [176, 177]. Nail lesions are common and include pitting, onycholysis, subungual pustules, and nail dystrophy [178]. Histopathology of cutaneous lesions is similar to that of GPP, although PPPP often features eosinophils and mast cells in the upper dermis [179]. In European patients, variants in *CARD14* have been implicated in disease pathogenesis [180]. PPPP is refractory to treatment in many cases; psoralen and ultraviolet A (PUVA), narrow-band ultraviolet B (UVB), acitretin, methotrexate, topical corticosteroids, and cyclosporine have been used with variable success [181]. In two patients with severe refractory PPPP, anakinra led to only mild clinical improvement [182]. One patient responded well to treatment with tocilizumab [183], and another patient experienced significant clinical improvement following treatment with etanercept combined with phototherapy [184]. Ustekinumab has shown partial success and may be an option in patients refractory to first- or second-line treatments [185, 186]. By and large, though, current therapies seem to provide only modest benefit [181].

5 Multifactorial Autoinflammatory Diseases

In this section, diseases with a clear autoinflammatory etiology but no specified monogenic cause identified will be reviewed (see Table 2).

5.1 Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO)

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) is a rare disorder residing clinically on a spectrum with chronic recurrent multifocal osteomyelitis (CRMO), although skin involvement plays a larger role in SAPHO. Patients with SAPHO also share clinical features with the seronegative spondyloarthropathies and often have a personal or family history of other inflammatory skin diseases [187]. A wide range of musculoskeletal and dermatologic manifestations can be seen. Bone pain caused by hyperostosis or osteitis [188] is a common initial symptom and typically worsens at night, usually accompanied by fever. Skin involvement includes palmoplantar pustulosis, severe acne, pustular psoriasis, psoriasis vulgaris, and HS. Dysregulation of the adenosine triphosphate (ATP) receptor $P2X_7$ in peripheral blood mononuclear cells and subsequent upregulation of IL-1β may play a role in pathogenesis [189], though the exact mechanism is unclear.

NSAIDs are usually first-line treatment, followed in refractory cases by disease-modifying antirheumatic drugs (DMARDs) (e.g., methotrexate, sulfasalazine) or bisphosphonates [190]. Intra-articular corticosteroids are transiently effective in the majority of patients [191], but are associated with long-term complications and relapses following withdrawal. In patients unresponsive to conventional therapy, TNF inhibitors are the most widely used biologic and exhibit clinical efficacy across the disease spectrum [190, 192], although data are derived exclusively from case series and case reports [190]. Reports of IL-1 inhibition are encouraging, albeit limited: in one patient, anakinra treatment resulted in resolution of symptoms within 3 months [189], and a small open-label study reported clinical response in five out of six patients receiving anakinra [193]. Biologics targeting the Il-17/IL-23 axis have also been shown to be beneficial: in a patient with treatment-resistant disease, IL-17 inhibition with secukinumab led to complete resolution of symptoms [190]. The successful use of ustekinumab (anti-IL-12/IL-23) for SAPHO syndrome was first described in a 2014 report of a case resistant to anakinra and TNF inhibitors [194]. Subsequently, a case series of six patients unresponsive to previous treatments showed moderate improvement in skin symptoms with ustekinumab or secukinumab, although musculoskeletal symptoms persisted [195]. One patient experienced complete resolution of interstitial granulomatous dermatitis following treatment with ustekinumab [196].

5.2 Pyoderma Gangrenosum, Acne, and Suppurative Hidradenitis (PASH) Syndrome

A mutation in the *PSTPIP1* gene has been reported in a case of pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) syndrome [197], an autoinflammatory disorder similar to but distinct from PAPA. Mutations in *NLRP3*, *MEFV*, *NOD2*, *PSMB8*, and *NCSTN*—known to play a role in other autoinflammatory diseases—have also been identified in PASH syndrome [198–200], although the molecular pathogenesis is poorly understood. The disorder is characterized by suppurative hidradenitis and acne presenting in adolescence, with onset of PG later in life. Symptoms tend to be less episodic than in PAPA, and the absence of pyogenic arthritis distinguishes PASH from pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH), a recently described disorder also associated with a mutation in *PSTPIP1* [201]. There is no established treatment regimen. Anakinra led to partial remission in one patient [202] and control of severe arthritis in another [198], implying a role of IL-1β in disease pathogenesis. A recalcitrant case of PASH responded remarkably well to infliximab in combination with dapsone and cyclosporine [203], suggesting involvement of other signaling pathways beyond IL-1β. Three patients treated with infliximab had almost complete resolution of both PG and acne lesions, though suppurative hidradenitis persisted [198]. In one patient, treatment with adalimumab for underlying Crohn's disease led to improvement in PASH-associated cutaneous lesions [198]. Several other case reports have also described successful treatment with adalimumab [204–207].

5.3 Behcet's Disease

Behcet's disease (BD) is a systemic inflammatory condition that features ocular lesions, arthritis, gastrointestinal symptoms, neurologic complications, and large vessel vasculitis that can lead to aneurysm or thrombosis. The most common cutaneous manifestations include erythema nodosum, papulopustular lesions, superficial thrombophlebitis, and cutaneous pathergy [208]. Recurrent oral aphthous ulcers usually begin as vesiculopustules, evolving into oval ulcers with rolled borders and a necrotic base surrounded by an erythematous halo [209]. Genital ulcers are also seen. Long considered a T-helper 1 (Th1)-type autoimmune disease due in part to its association with human leukocyte antigen (HLA)-B51, mutations in the *MEFV* gene (also associated

with FMF) have been identified more recently in certain populations with BD [210, 211], though the exact association between *MEFV* and BD remains unclear [212]. Increased levels of neutrophils and IL-1β suggest an autoinflammatory component, and the association with *Streptococcus* species further suggests involvement of innate immune pathways [213]; the extrinsic factor heat shock protein from *Streptococcus* species [214] may promote activation of PRRs and a subsequent inflammatory reaction [215]. A loss of function mutation in *TNFAIP3* causes the disorder haploinsufficiency of A20 (HA20), a condition considered a monogenic form of BD, clinically indistinguishable from BD. An ubiquitylation defect leads to impaired regulatory function of A20 and upregulation of NFκB [216]. By and large, though, the etiology of BD remains unclear.

Treatment of BD is tailored according to the type and severity of clinical manifestations. Despite contradictory results from clinical trials [217], colchicine is widely used in the treatment of BD, particularly for controlling mucocutaneous symptoms. Corticosteroids are also used frequently, either as monotherapy or in combination with immunomodulatory or immunosuppressive agents (e.g., azathioprine, thalidomide, IFN-α, TNF-α inhibitors, apremilast, cyclosporine, and cyclophosphamide) [218]. IL-1 inhibitors can be effective, supporting a possible role for IL-1 in disease pathogenesis. A case series found that patients refractory to TNF-α inhibitors and conventional therapies experienced prompt response to anakinra, though most relapsed over time [219]. In an open-label pilot study, anakinra was partially effective in treating resistant oral and genital ulcers [220]. Complete remission and no long-term relapse were reported in a case series of three patients treated with 150 mg canakinumab every 6 weeks [221]. A retrospective study reported complete disease remission in 13 patients treated with a minimum 12-month course of canakinumab or anakinra [222]. A few case reports have described complete remission with the IL-6 inhibitor tocilizumab, either as monotherapy or in combination with high-dose corticosteroids [223–226], although loss of efficacy with tocilizumab has also been reported [227].

5.4 Systemic Juvenile Idiopathic Arthritis (SJIA); Adult-Onset Still's Disease (AOSD)

SJIA and adult-onset Still's disease (AOSD) represent variants of the same clinical entity with different ages of onset [228, 229]. Polyarticular arthritis, evanescent salmon-colored maculopapular rash, daily spiking fevers, serositis, and hepatosplenomegaly are typical features of SJIA. The pathogenesis is thought to involve IL-1, IL-6, IL-18, neutrophils, and monocytes/macrophages [230], distinguishing the disorder from other JIA subtypes wherein adaptive immunity plays the predominant role. Conventional treatment involves corticosteroids and NSAIDs, and widespread evidence now exists for the efficacy of canakinumab and tocilizumab [231–234], both of which have been FDA approved for SJIA in children over 2 years of age. Randomized controlled trials have also shown improvement with anakinra and rilonacept [235–237], although the latter may provide less benefit [238] and is seldom used in clinical practice [239].

AOSD is rare and shares symptoms with SJIA, although onset occurs in adulthood. First-line therapy involves corticosteroids, followed by conventional DMARDs such as methotrexate. A growing body of research has suggested a benefit of the newer biologics in corticosteroid- and DMARD-refractory cases. However, the rarity of the disease has precluded many prospective, double-blind, randomized clinical trials to determine the efficacy of biologics in AOSD [240]. TNF inhibitors have been shown to control symptoms in only a subset of patients, and the effects are often incomplete or short-lived [241, 242]. Based on small studies, anakinra seems to produce rapid and sustained improvement in symptoms [243–245]. Open-label trials with anakinra have reported superior efficacy over DMARDs [246] and improvement in cutaneous and systemic symptoms, although joint manifestations may be more refractory to therapy [247]. Treatment with canakinumab has led to improvement in systemic symptoms in some case reports, with variable effects on joint manifestations [248, 249]. A recent randomized, double-blind, placebo-controlled, phase III trial of 27 glucocorticoid-refractory patients reported improved systemic symptoms with the IL-6 inhibitor tocilizumab, although the primary endpoint of American College of Rheumatology (ACR) 50 response was not met [250].

5.5 Schnitzler's Syndrome

Schnitzler's syndrome is a rare sporadic acquired autoinflammatory disorder which presents in mid-adulthood with recurrent fever, arthritis, lymphadenopathy and IgM gammopathy. A chronic or recurrent non-pruritic urticaria-like rash with neutrophilic infiltrates is the hallmark feature of the disease [21, 251]. Clinically, the phenotype resembles that of CAPS. While the etiology and pathogenesis remain unclear, several cases have been associated with a p.V198 M variant in *NLRP3* [252, 253]. However, a recent study failed to show mutations in *NLRP3* underlying disease pathogenesis; rather, a number of variants of unknown significance were identified [254]. Aberrations in the ASC inflammasome component and $P2X_7$ receptor have also been identified [255], and reports of increased IL-1 secretion from peripheral blood mononuclear cells further imply a role of dysregulated innate immunity in disease pathogenesis [256].

Until recently, treatment options for Schnitzler's syndrome were largely inadequate and included systemic corticosteroids, immunosuppressants, and NSAIDs [251].

Fortunately, the introduction of IL-1 blockers has led to dramatic improvements in treatment outcomes. A number of case reports have shown improvement in clinical symptoms and inflammation with anakinra [257–260], and a cohort of 21 patients found that 95% achieved a complete response to anakinra [254]. Rilonacept and canakinumab have also shown benefit in two open-label studies [261, 262]. A recent randomized controlled trial demonstrated complete clinical response with canakinumab in five out of seven patients [263].

6 Common Dermatologic Conditions with an Autoinflammatory Component

In addition to the classical monogenic autoinflammatory diseases and conditions strongly linked to autoinflammation as a central cause, there are numerous common dermatologic conditions that likely feature autoinflammation in the disease process.

6.1 Sweet's Syndrome (Acute Febrile Neutrophilic Dermatosis)

Sweet's syndrome (SS) is a neutrophilic dermatosis accompanied by fever and leukocytosis. Skin eruptions are typically abrupt in onset [264] and appear as tender erythematous papules, nodules, and plaques, predominantly located on the face, neck, upper trunk, and limbs [265]. Targetoid and subcutaneous lesions have been reported [266]. Clinical variants of SS include pustular and bullous [267], giant cellulitis-like [268], necrotizing [269], and neutrophilic dermatosis of the dorsal hands (NDDH) [270]. Patients often appear dramatically ill. Aberrant neutrophil function, genetic mutations, and altered expression of cytokines have been linked to SS, and overexpression of IL-1β in lesional skin has been identified in several cases [271, 272]. However, the etiology remains to be clarified. The disorder is frequently associated with leukemia, connective tissue diseases, medications, and other autoimmune and autoinflammatory disorders. First-line treatment for SS is with corticosteroids, which characteristically results in rapid resolution of symptoms. In cases refractory to corticosteroids, colchicine, dapsone, and potassium iodide may be used. Anakinra has led to symptom resolution in several patients [273, 274], and various case reports have described favorable responses with adalimumab [275, 276], etanercept [277, 278], and infliximab [276, 279].

6.2 Pyoderma Gangrenosum (PG)

Persistent activation of innate immune pathways (e.g., through DAMPs or PAMPs) may be implicated in the prolonged and deleterious inflammation seen in PG. Indeed, upregulation of IL-1β has been identified in lesional skin of PG [280], although the etiology of the disorder is unclear. The association of PG with systemic diseases—namely IBD, arthritis, and lymphoproliferative disorders—as well as the presence of PG in numerous autoinflammatory syndromes (e.g., PAPA, PASH, SAPHO) [281] suggests involvement of multiple underlying etiologies. Characteristic of PG are sterile pustular skin lesions which rapidly evolve into tender skin ulcers, often with undermined borders exposing underlying muscles or tendons [282].

Currently, no therapies have been FDA-approved for the treatment of PG. Conventional treatments with corticosteroids, immunosuppressants, antimicrobials, IVIG, and thalidomide have shown variable responses. Traditional biologics have also been used, and many case reports [283–285] and a randomized controlled trial [286] have shown success with infliximab. A systematic review found that 29 out of 34 cases healed with infliximab [287], further highlighting its utility in the treatment of PG. In patients with comorbid IBD, infliximab has also been shown to improve symptoms [284, 288, 289]. Results with etanercept and adalimumab have been less consistent; numerous case reports and case series have reported successes [290–292] and failures [293] with both agents. An open-label study of adalimumab is currently underway [294]. A 2011 case report found increased IL-23 expression in a PG lesion and resolution following treatment with ustekinumab [295]. Several cases of successful treatment with ustekinumab for severe recalcitrant PG have subsequently been reported [296–299].

IL-1 inhibitors may represent a good therapeutic option in challenging cases. In a prospective open-label study, canakinumab led to complete clearance in three of five patients with treatment-refractory disease, and partial response in one patient [280]. A patient with PG refractory to systemic steroids, cyclosporine, infliximab, and adalimumab had complete re-epithelialization of lesions following 3 months of treatment with 150 mg canakinumab [300]. Several case reports have described either significant clinical improvement or complete resolution with anakinra [301–303].

6.3 Psoriasis

Psoriasis is a chronic multigenic inflammatory disorder that often arises in response to environmental triggers such as traumatic injury to the skin or physical stress. Traditionally considered an autoimmune disease, the pathogenesis more likely involves a balance between adaptive and innate immune responses. Polymorphisms of *NLRP1*, *NLRP3* and *CARD8*—negative regulators of caspase-1 activity—have been linked to increased psoriasis susceptibility [304, 305], and increased levels of caspase-1 have been identified in psoriatic lesional skin [306]. Furthermore, *CARD14* has

been identified as the gene responsible for the association of the psoriasis susceptibility locus 2 (PSORS2) with psoriasis [164], and multiple familial and sporadic mutations in *CARD14* have been reported in patients with psoriasis [164, 166, 307–311]. The *CARD14* gene mediates IL-17A-induced NFκB and MAPK signaling pathway activation, leading to the expression of pro-inflammatory factors. Infiltration of neutrophils into the epidermis—a hallmark of psoriasis—is mediated by pro-inflammatory cytokines such as IL-36 [312], highlighting the role of dysregulated cytokine production in psoriatic lesions. Taken together, these findings suggest that aberrant innate immune responses and inflammasome activity play an important role in pathogenesis.

Dermatologic manifestations among psoriasis subtypes are broad, including but not limited to localized, erythematous, sharply-demarcated scaly plaques (chronic plaque psoriasis); multiple, small, widespread scaly plaques (guttate psoriasis); painful sterile pustules on the palms and soles with hyperkeratosis and fissuring (PPPP); and widespread rapid eruptions of subcorneal pustules (GPP). Features among subtypes often overlap. Significant systemic involvement is present in some cases, manifesting as RA, cardiovascular disease, or IBD.

Interestingly, despite involvement of the inflammasome and upregulation of IL-1β in both plaque and pustular psoriasis, the IL-1 inhibitors have provided little benefit [313], although some reports have shown improvements in pustular psoriasis [169, 170, 182]. Inhibitors of TNF-α, IL-17A, and IL-12/IL-23 have been effective in controlling and reducing disease progression, and have become the mainstay of therapy in moderate-to-severe cases [313].

6.4 Acne Vulgaris

Acne vulgaris is a chronic inflammatory disorder characterized by excessive sebum secretion, hyperkeratinization leading to obstruction of sebaceous follicles, colonization by *Propionibacterium acnes*, and an intense inflammatory reaction. Cutaneous findings include comedones, papules, pustules, nodules, and cysts, often on the face and upper trunk. While the sequence of pathogenic events is unknown, emerging evidence suggests that *P. acnes* activates the innate immune response through stimulation of toll-like receptors (TLRs) and the NLRP3 inflammasome, with a subsequent increase in IL-1β [314, 315]. In line with these findings, the interim results of a phase II trial suggested mild improvement in acne vulgaris following treatment with gevokizumab [316]. The manufacturer of gevokizumab is no longer pursuing acne as an indication, however, suggesting that the drug failed to meet target outcomes. Nitric oxide-releasing nanoparticles have also been shown to suppress IL-1β, TNF-α, IL-8, and IL-6, and are a promising option in reducing *P. acnes*-induced inflammation [317]. A phase II trial demonstrated statistically significant reductions in both inflammatory and non-inflammatory lesion count with the topical nitric oxide-releasing agent SB204 [318].

7 Conclusion

The 'autoinflammatory diseases' originally comprised a group of hereditary recurrent fever syndromes, but with advances in genomics and the more recent identification of extremely rare clinical syndromes, this term has come to encompass a much broader spectrum of disorders. In tandem with and contributing to these discoveries has been a growing body of research delineating the critical role of the innate immune system, both in normal host defense and in pathologic states involving aberrant and unchecked activation. As the complex interplay between innate and adaptive immunity is increasingly elucidated, diseases that were once considered 'autoimmune' (e.g., psoriasis) are beginning to be understood in a new light. Common multifactorial conditions such as atherosclerosis [319], type II diabetes [320], aging [321], and obesity [322] may also feature an autoinflammatory component, and new syndromes falling within the 'autoinflammatory' spectrum are likely to be identified as our understanding of innate immunity continues to improve.

The newer biologics have provided considerable benefit in certain autoinflammatory diseases, either as monotherapy or in combination with traditional therapeutic regimens. However, owing in large part to the rarity of these disorders, only a few treatment recommendations are backed by high-quality evidence, and most data stems from retrospective registries, case series, and case reports. Relapse and loss of effect are common pitfalls of biologic therapy, and dose escalation is often required to maintain effect. For many patients, early treatment is critical in preventing later sequelae, highlighting the importance of early and accurate diagnosis. Continued improvements in our understanding of innate immunity and autoinflammatory pathways would help guide treatment, opening the door for more targeted and effective management.

Compliance with Ethical Standards

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