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Muckle-Wells syndrome

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CONTENTS

Abstract

Muckle-Wells syndrome (MWS) is a rare autosomal dominant autoinflammatory disorder mainly characterized by recurrent fever, associated with urticaria and amyloidosis, as well as sensorineural deafness, arthritis and other inflammatory symptoms. Muckle-Wells disease starts at a very young age and can progress to renal failure due to generalized amyloidosis. Although there is currently no cure for MWS, novel targeted approaches hold promise as future effective therapies.

Introduction

Back in 1962, Muckle and Wells first described an autosomal dominant inherited syndrome characterized by urticaria, deafness and amyloidosis (1). Muckle-Wells syndrome (MWS, OMIM: 191900) was later classified as a type of autoinflammatory disorder within the so-called hereditary periodic fever syndromes, which feature intermittent attacks of inflammatory symptoms (2). The etiology of MWS has been linked to activating mutations in the *CIAS1* (cold-induced autoinflammatory syndrome 1), or *NALP3,* gene encoding the cryopyrin protein (3). In addition to MWS, mutations in the *NALP3* gene give rise to two other autoinflammatory disorders: familial cold autoinflammatory syndrome (FCAS) (3, 4) and neonatal-onset multisystem inflammatory disease (NOMID), also known as CINCA (chronic infantile neurologic, cutaneous articular) syndrome (5). These three related conditions are also known under the term cryopyrin-associated periodic syndromes (CAPS). Although they are distinct clinical entities and differ in disease severity (with FCAS and MWS being relatively mild compared to the potentially fatal CINCA syndrome), all share inflammatory clinical features, such as periodic fever, skin rash and amyloidosis (3-7).

Specifically, MWS starts during childhood with urticaria as the most frequent manifestation, associated with periodic fever and arthralgia. Other typical symptoms are progressive sensorineural deafness and amyloidosis of the kidney or other organs, often of the amyloidosis-associated (AA) type, which can be life-threatening. Amyloidosis has been reported to occur in around one-third of MWS patients (2). Inflammatory eye disease that manifests as conjunctivitis or acute anterior uveitis (8), as well as hyperpigmented sclerodermoid skin lesions (9) and acute visual impairment (10), have also been described in addition to the classic features of the disease. Laboratory findings commonly detected in MWS include leukocytosis and elevation of serum C-reactive protein (CRP) and serum amyloid-associated (SAA) protein (9-12). In particular, SAA protein is a sensitive marker of disease activity and the occurrence of an acute-phase SAA protein response is essential for the development of AA amyloidosis.

There is currently no approved treatment for MWS and steroids and other antiinflammatory drugs have only provided limited success in the management of symptoms. However, recent discoveries on the function of the *CIAS1* gene and the pathogenic role of the potent inflammatory cytokine interleukin-1β (IL-1β) have opened new avenues for the treatment of this condition. A summary of ongoing clinical studies evaluating new therapeutic strategies is presented in the Experimental therapies section.

Genetics

Early genetic studies located the MWS gene in the chromosomal region 1q44 (13), which later on was identified as the *CIAS1* gene (3). The *CIAS1* gene is also called *NALP3* because it contains a central NACHT domain, a *C*-terminal Leucine-rich repeat domain and an amino-terminal Pyrin domain. Mutations associated with MWS, as well as FCAS and CINCA syndrome, are generally missense substitutions affecting exon 3 of the *NALP3* gene, in particular the NACHT domain (3, 4). In MWS, gain-of-function *NALP3* mutations constitutively activate the cryopyrin protein and cause overactivation of

caspase-1, which leads to spontaneous IL-1β production (14). Genotype-phenotype studies have found a certain correlation between different *NALP3* mutations and disease expression. Thus, certain mutations appear to be associated with a more severe disease phenotype (7, 15) or may confer different susceptibility to therapy (see Experimental therapies: anakinra).

Pathogenesis of MWS: the role of IL-1β and the NALP3 inflammasome

IL-1β is a major proinflammatory cytokine and a potent endogenous pyrogen that plays a crucial role in the immune response against infectious pathogens, but which has also been linked to a number of systemic inflammatory disorders, such as MWS (16). The production and release of mature IL-1β by cells of the innate immune system require proteolytic cleavage of its inactive precursor pro-IL-1β by caspase-1 (14). Active IL-1β secreted by monocytes or macrophages binds to IL-1 receptors in the hypothalamus vasculature, which triggers the production of prostaglandin E_2 (PGE_2), which in turn activates the thermoregulatory center to cause fever. In the periphery, active IL-1β is responsible for a broad range of manifestations, from skin rash to thrombocytosis (16) (Fig. 1). The actions of IL-β are mediated via binding to the IL-1 receptor type I (IL-1RI) expressed on endothelial and serosal cell surfaces and complexed with IL-1R accessory protein (IL-1RAcP) (17). IL-1β also stimulates inflammatory responses in adjacent endothelial tissue, such as the production of adhesion molecules, chemokines and IL-6.

But which are the signals that trigger IL-1β production? Bacterial products, such as lipopolysaccharide (LPS), stimulate innate immune cells via binding of Toll-like receptors (TLRs) to activate nuclear factor-κB (NF-κB) and the subsequent generation of pro-IL-1β (18). However, additional signals are required for IL-1β to be produced. *In vitro*, the activation of purinergic $P2X_7$ receptors by ATP is also required to activate the inflammasome (19). Binding of $P2X_7$ receptors by extracellular ATP –which may be elevated upon tissue injury or inflammation– triggers the opening of a pore in the cell membrane mediated by pannexin-1 hemichannels, which is required for subsequent caspase-1 activation (20). However, the physiological effect of ATP as an *in vivo* activator of the inflammasome remains to be determined.

Recently, a TLR-independent pathway dependent on pannexin-1 recognition of bacterial components has also been shown to activate caspase-1 (21). As mentioned earlier, caspase-1 is one of the best-characterized so-called "inflammatory" caspases and key for IL-1β processing and release (14). However, the activation of caspase-1 requires the activation of a cytosolic molecular scaffold called "the inflammasome" complex (22). The NALP proteins are central components of the inflammasome, together with the apoptosis-associated speck-like (ASC) adaptor protein and caspase-1 (Fig. 2).

The assembly of the NALP3 inflammasome components is triggered by pathogens, toxins or bacterial RNA

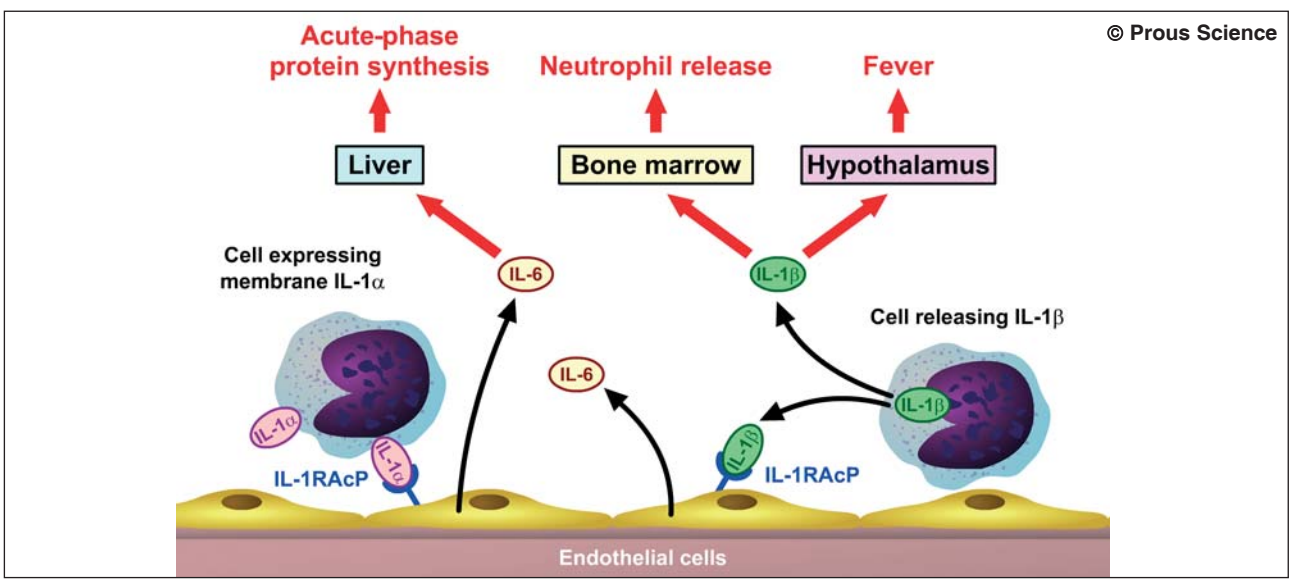

Fig. 1. Role of IL-1 in systemic and local inflammation. Activated monocytes or macrophages adhere to endothelial/serosal surfaces and synthesize inactive pro-IL-1β, which is subsequently cleaved by caspase-1 (or IL-1β-converting enzyme) to form active IL-1β. Active IL-1β enters the circulation and reaches the bone marrow, where it stimulates neutrophil release, and the hypothalamus, where it induces fever. The actions of IL-1β are mediated via binding to the IL-1 receptor type I (IL-1RI) expressed on endothelial and serosal cell surfaces and complexed with the IL-1R accessory protein (IL-1RAcP). IL-1β also stimulates inflammatory responses in adjacent endothelial tissue, including stimulation of the production of adhesion molecules, chemokines and IL-6. IL-6 enters the circulation and eventually reaches the liver, where it stimulates acute-phase protein synthesis. Membrane-bound IL-1α is also shown. It is functionally comparable to IL-1β, binding to and activating the IL-1RI/IL-1RAcP receptor complex to produce similar inflammatory responses (37).

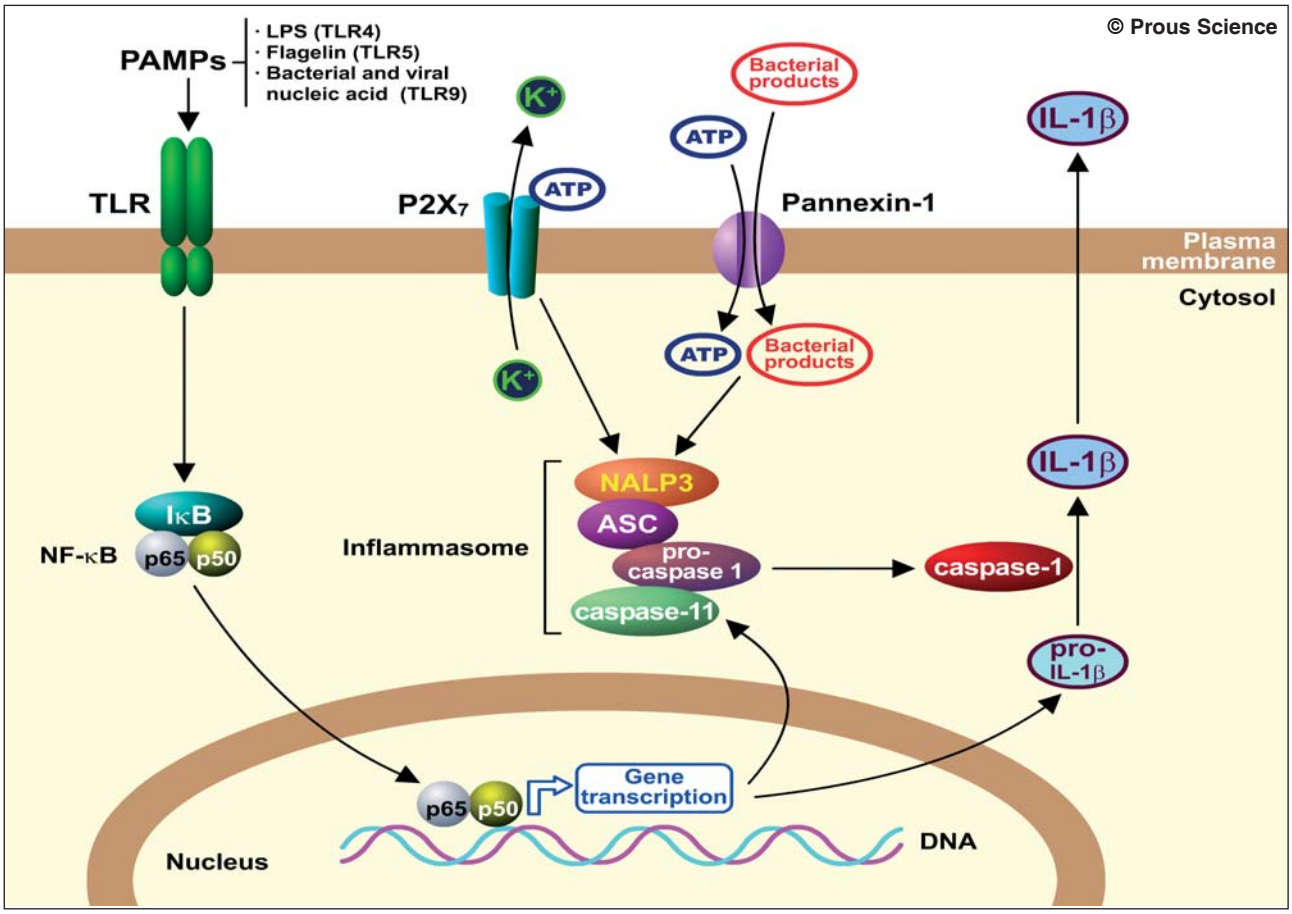

Fig. 2. IL-1β release by activation of the NALP3 inflammasome: Binding of pathogen-associated molecular patterns (PAMPs) to Toll-like receptors (TLRs) triggers the activation of NF-κB and subsequent production of the IL-1β precursor (pro-IL-1β). A second signal for caspase-1 activation is activation of $P2X_7$ receptors by ATP. Bacterial products (LPS = lipopolysaccharide) or tissue injury signals (ATP) have also been hypothesized to enter the cytosol via pannexin-1 hemichannels, which may activate the NALP3 inflammasome. The NALP3 protein together with the apoptosis-associated speck-like (ASC) protein conform the molecular scaffold for caspase-1 activation. Activated caspase-1 cleaves pro-IL-1β to release active IL-1β, which will be secreted to the extracellular space to act on its receptors in the periphery and in the CNS (44).

(23, 24) by inducing a conformational change in NALP3, which exposes the NACHT domain and promotes NALP3 oligomerization and posterior binding to ASC. The ASC protein contains a *C*-terminal CARD (caspase recruitment domain) motif, which binds to the CARD motif of caspase-1, and also a CARD-like pyrin domain that binds to the pyrin domain of NALP3 (or other NALP proteins), thus acting as a connector between the sensor NALP3 and the effector caspase-1. Although, NALP3 is essential for caspase-1-mediated pro-IL-1β processing (25), it cannot directly activate caspase-1 and requires the presence of ASC (26).

In MWS, increased activity of the NALP3 inflammasome has been demonstrated (26). Agostini *et al.* showed that in monocytes isolated from MWS patients, IL-1β levels can be detected prior to stimulation with LPS, indicating spontaneous IL-1β secretion (26). The mechanism by which mutations in the *NALP3* gene ultimately lead to aberrant IL-1β production in MWS are still unknown. However, it has been proposed that mutations in the *NALP3* gene, which generally involve the NACHT domain, may favor an "open state" of the cryopyrin protein, hence exposing this domain and favoring enhanced assembly of the inflammasome components (15). A recent study by Gattorno *et al.* demonstrated that whereas in monocytes from healthy individuals IL-1β secretion requires two signals (LPS and ATP), a single stimulus is sufficient to trigger activation of the inflammasome in patients with cryopyrin mutations (27).

The pattern of NALP3 protein expression also indicates a role for the NALP3 inflammasome in the defense against pathogens, as it is not limited to peripheral blood mononuclear cells (PBMCs), but is also high in epithelial cells from mucosal sites (oral cavity, esophagus, female reproductive tract and urinary tract) (28). Recently, unrelated stimuli, such as gout-associated uric acid crystals (29) and contact sensitizers (30), have been found to activate the NALP3 inflammasome, hence suggesting that it acts like an endogenous sensor of danger signals in different tissues (18).

Experimental therapies

Different approaches involving the blockade of IL-1β activity have shown promising results in MWS patients. Here, we summarize relevant clinical evidence gathered from individual case reports and open and randomized clinical studies (see also Table I).

Anakinra

The role of IL-1β in the pathogenesis of MWS seems clear, as inhibition of the IL-1 receptor (IL-1R) with the IL-1R antagonist anakinra remarkably alleviates the inflammatory symptoms of MWS patients (31). Anakinra is a recombinant IL-1R antagonist launched in the U.S. in 2001 as Kineret® by Amgen for the reduction of signs and symptoms of moderately to severely active rheumatoid arthritis in adult patients who have failed one or more disease-modifying antirheumatic drugs (DMARDs). In 2003, Hawkins first reported the clinical benefit of anakinra in 2 patients with MWS (31). Ever since, substantial evidence has been gathered supporting its further investigation in controlled clinical studies. Two patients presenting with *NALP3* mutations (R260W variant) and characteristic MWS clinical symptoms (fever, rash, conjunctivitis, arthralgia), as well as acute elevations of SAA protein, were treated with a daily s.c. dose of anakinra of 100 mg following treatment failure with various drugs. The inflammatory picture receded within a few hours of the first injection and SAA protein returned to baseline levels persistently for 6 months (31).

An additional report from Hawkins described a substantial response to anakinra treatment in 3 family members with MWS (*NALP3* variant V198M or V200M) (32) who mainly exhibited rash, arthralgia, fever, severe fatigue and deafness, although other features more typical of FCAS and CINCA syndromes were also present. Similarly to previous cases, resolution of clinical symptoms was achieved rapidly in all 3 patients and SAA protein levels remained normal for up to 3 months.

In addition to its potent antiinflammatory activity, anakinra has also been reported to trigger menarche, which is commonly delayed in adolescent girls with MWS (32, 33). Acute visual loss has also been described as an unusual clinical manifestation of MWS that responds to anakinra treatment. A patient suffering from an acute flare of MWS reported, in addition to fever, rash and SAA elevation, visual field constriction of the left eye associated with optic nerve disk edema. Anakinra produced recovery of visual acuity, associated with a marked remission in plasma SAA levels (10).

Although the pathophysiology of sensorineural deafness in MWS is still unclear, anakinra has been shown to ameliorate (34), if not completely restore, hearing loss (35). However, in some cases, hearing impairment does not respond to anakinra treatment, suggesting different patient susceptibility, probably depending on the *NALP3* mutation. Hence, a patient bearing the E311K mutation identified by Mirault *et al*. (35) (which involves the conversion of a glutamic acid into a basic lysine residue) was found to totally recover hearing after anakinra therapy. Hearing improvement has also been recently reported in a patient with a newly identified mutation (I480F) of the *NALP3* gene (36), whereas in other cases featuring the V200M *NALP3* variant anakinra failed to cause any hearing improvement (32). Thus, it appears that IL-1 may not be the only cause of sensorineural deafness in MWS. In fact, IL-6 could also play a role in the pathophysiology of deafness, as elevated IL-6 levels found in MWS may trigger osteoclast activation and subsequent Corti organ destruction (9). However, this hypothesis remains to be confirmed.

Rilonacept (IL-1 Trap)

Rilonacept is an IL-1 trap developed by Regeneron that comprises the extracellular domains of IL-1RAcP and human IL-1RI fused to the Fc portion of human IgG_1 (37). A pilot study carried out by researchers at Regeneron and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) demonstrated that rilonacept therapy (loading regimen of 100 mg/day s.c. for 3 days followed by 100 mg/week for 1 year in an extension phase) immediately improved clinical symptoms and laboratory parameters in patients with *NALP3* mutations and MWS/FCAS symptoms. A maximum response to therapy was seen on day 9, with flares occurring in all patients at a median of 21 days. After rilonacept onset, daily diary scores were significantly reduced, but increased after flare, which could be rapidly controlled with a second loading regimen. Significant reductions were also observed in CRP and erythrocyte sedimentation rate. Rilonacept also improved patient's overall well-being. No significant adverse events or injection-site reactions were reported (38). A clinical trial sponsored by NIAMS is currently evaluating the utility of IL-1 Trap in treating patients with MWS and other autoinflammatory diseases (39).

Furthermore, the safety and efficacy of rilonacept (160 mg/week s.c.) were examined in a randomized, double-blind, placebo-controlled phase III study in 47 patients with FCAS/MWS. The study involved a 6-week treatment comparison phase and a second phase of single-blind

Table I: Experimental therapies in Muckle-Wells syndrome (MWS) (from Prous Science Integrity®).

Drug	Mechanism of action	Source	Phase/Indication	Ref.
Anakinra	IL-1 receptor antagonist (recombinant human)	Amgen	L-2001/Rheumatoid arthritis	10,31-36
Rilonacept	IL-1 inhibitor (fusion protein)	Regeneron	Prereg./CAPS	38,40
ACZ-885	Anti-IL-1β (monoclonal antibody)	Novartis/Medarex	III/MWS	41

CAPS: Cryopirin-associated periodic syndromes

rilonacept treatment followed by a 9-week randomized withdrawal comparison phase. During the first phase, rilonacept significantly improved signs and symptoms associated with disease activity (rash, fever, joint pain, eye redness/pain and fatigue) and normalized SAA levels compared to placebo. Although no serious adverse events were reported, more injection-site reactions, the majority of which were mild, and mild to moderate upper respiratory tract infections were observed with rilonacept treatment. During the second withdrawal phase, patients treated with placebo had a gradual return of disease activity (40).

ACZ-885

ACZ-885, or canakinumab, is a monoclonal antibody specific for human IL-1β in phase II/III development at Novartis for the treatment of rheumatoid arthritis. Results from a proof-of-concept study in which ACZ-885 was given to patients with MWS and documented *NALP3* mutations were highly promising. Initial improvement of clinical symptoms was observed within 2 days of a single i.v. injection of ACZ-885. Complete clinical remission was achieved after 8 days and persisted during a median of 185 days. After 1 week of treatment, SAA and CRP, as well as IL-6 and IL-1R levels, normalized to baseline values. Downregulation of IL-1β mRNA in peripheral blood was observed within 1 day of ACZ-885. Moreover, ACZ-885 was well tolerated and showed a plasma half-life of 29 days and a minimum effective concentration of about 1 μg/ml (41).

Novartis will further investigate the safety and efficacy of ACZ-885 in a multicenter, randomized, double-blind, placebo-controlled phase III clinical study that is expected to enroll 20 patients with MWS and identified *NALP3* mutations. In fact, the study will be divided into two parts: part I will be an 8-week, open-label, active treatment period to identify ACZ-885 responders and double-blind part II will compare the efficacy of ACZ-885 with that of placebo (42). Additionally, an open phase I/II clinical trial is currently recruiting patients to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of ACZ-885 in patients with *NALP3* mutations (43).

Conclusions

Evidence collected from basic research and clinical studies in the last few years has helped to elucidate the complexity of NALP3-mediated cryopyrinopathies. The role of the NALP3 inflammasome as an intracellular regulator of infection and inflammation may provide new clues to understand the pathogenesis of these varied disorders. In MWS, the discovery of associated *NALP3* mutations that cause abnormal IL-1β signaling has changed the therapeutic strategy to tackle this disease from palliative to targeted medicines. MWS patients have begun to benefit from therapies that, although they remain to be tested in controlled clinical studies, have shown promising results.

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