Genetic and Molecular Basis of Inflammasome-mediated Disease*

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The central function of IL-1β in fever regulation was recognized with its discovery >30 years ago (1). It was an attractive candidate as a master regulator in the pathogenesis of the hereditary fever syndromes; however, definitive proof was elusive. The mechanisms enabling maturation and release of active IL-1β are complex, and it was difficult to detect the cytokine in patient serum. Validation of its central role in these rare autoimmune inflammatory conditions was achieved in the last decade with the convergence of three major developments in translational medicine research: 1) advances in the techniques used to identify human disease-causing genes, 2) innovations in genomic analysis, and 3) progress in effective targeted biologic therapeutics. Recent years have seen the explosion of exciting research elucidating the principal role of IL-1β in fever disorders and expanding the autoimmune inflammatory disease family beyond rare Mendelian syndromes to include common conditions such as gout and occupational lung disease (2). Concurrently, there have been significant advances in understanding the complexity of the innate immune system; the mechanisms regulating IL-1β release; and the host response to pathogens, internal danger signals, and nonpathogenic inflammatory stimuli. With the advent of IL-1-targeted therapy, unprovoked inflammation due to excess IL-1β can be managed and sequela avoided. New research will continue to unravel the innate immune system’s arsenal of sensory proteins and fully reveal the many pathways comprising IL-1β function.

Genetics of Inherited Recurrent Fevers

The hereditary fever syndromes are a family of inflammatory diseases characterized by recurrent episodes of fever, joint symptoms, and rash. The clear Mendelian inheritance of these conditions combined with improved genetic mapping methods allowed the identification of the underlying genes, beginning with the MEFV gene for familial Mediterranean fever (FMF)2 in 1997 following an international effort (3, 4). In the next 2 years, heterozygous mutations in TNFRSF1A, encoding the TNF receptor, were linked to the autosomal dominant disease previously known as familial Hibernian fever, now called the TNF receptor-associated periodic syndrome (5). Homozygous mutations in the gene for mevalonate kinase were shown to cause hyperimmunoglobulinemia D with periodic fever syndrome (6, 7). Although these conditions are clinically related, a unifying underlying mechanism did not become clear until researchers mapped the genetic basis for two unusual fever syndromes, familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), in 2001 (8).

FCAS and MWS are autosomal dominant conditions; however, further similarities between the two were not immediately recognized, and initially, they were not classified as fever disorders. FCAS is characterized by day-long attacks of rash and joint pain precipitated by exposure to cold temperatures, which, although debilitating, do not generally lead to long-term morbidity (9). MWS consists of febrile episodes without the association with cold. In addition, MWS patients develop progressive hearing loss and end-stage renal disease due to amyloidosis (10). Patients with both syndromes exhibit a distinctive urticaria-like rash associated with fever, suggesting these two seemingly disparate conditions have a common root. Genetic linkage of both FCAS and MWS to chromosome 1q44 indeed indicated that these diseases are genetically related, and the final identification of heterozygous mutations in the NLRP3 (CIAS1) gene in patients with both disorders was definitive proof (8, 11). As more patients were identified with phenotypes falling between FCAS and MWS, it became clear that these syndromes are part of a single disease continuum that was further enlarged by the genetic mapping of a third disorder known as neonatal onset multisystem inflammatory disease (NOMID). In addition to almost daily fevers and an urticaria-like rash, patients with NOMID exhibit a characteristic arthropathy and significant central nervous system involvement (12, 13). To reflect the cold-induced febrile episodes characteristic of FCAS, the NLRP3 gene product was called cryopyrin (“ice fire”; also called NALP3 and NLRC3), and these diseases are collectively known as the cryopyrin-associated periodic syndromes (CAPS).

Genomics of Inflammation

The Human Genome Project provided an avalanche of raw genomic DNA and cDNA sequences that could be rapidly classified based on homology to proteins of known function. Recognition of conserved domains suggested a commonality of function among wide groups of seemingly distantly related proteins. Researchers studying inflammation and apoptosis mined databases using APAF-1, a scaffold protein that nucleates a caspase-activating complex called the apoptosome, and CIITA, the MHC Class II transactivator (14, 15). Dozens of novel intracellular protein candidates were identified, and this family became collectively known as NLR, for nucleotide-binding domain (NBD) and leucine-rich repeats (LRRs). NLR proteins have a central NBD (also known as NOD for nucleotide oligomerization domain) and, like the cell-surface Toll-like recep-

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‡ The abbreviations used are: FMF, familial Mediterranean fever; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID, neonatal onset multisystem inflammatory disease; CAPS, cryopyrin-associated periodic syndromes; NBD, nucleotide-binding domain; LRR, leucine-rich repeat; TLR, Toll-like receptor; CARD, caspase activation and recruitment domain; PYD, pyrin domain; ROS, reactive oxygen species.
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NLR Inflammasomes: Structure and Function

The primary function of CARDs is the activation of caspases, but in addition, CARDs, as well as PYDs, NBDs, and LRRs, serve as protein-protein interaction domains in a scaffold for a complex similar to the apoptosome. However, instead of activating caspases mainly involved in apoptosis (such as caspase-3, -8, and -9), NLR-related inflammasome complexes activate caspase-1, also known as the IL-1-converting enzyme. These inflammasomes consist of NLR proteins (NLRP3, NLRP1, and NLRC4), adaptor proteins (PYCARD and possibly CARDINAL), chaperone proteins (heat shock protein 90 and SGT1), and caspases (1 and/or 5) (17–19). NLR proteins are predicted to form a hexameric or heptameric scaffold allowing adaptors or chaperones to interact based on inter- and intraprotein domain-domain interactions (20). Multiple molecules of caspase-1 are recruited and concentrated, resulting in proximity-induced cleavage and activation. Mature caspase-1 then cleaves pro-IL-1β and pro-IL-18. Active IL-1β and IL-18 are secreted and initiate multiple inflammatory processes. The inflammasome therefore serves a crucial regulatory role by controlling the release of potent mediators (Fig. 2).

The NLR proteins are thought to function as innate immune sensors of intracellular pathogens that escape the extracellular or membrane-associated TLR armament. Inflammasomes have been implicated in the host response to various Gram-negative and Gram-positive bacteria, including pore-forming and toxin-producing organisms such as *Bacillus anthracis* (21), *Listeria monocytogenes* (22, 23), and *Staphylococcus aureus* (23–25), as well as *Neisseria gonorrhoeae* (26), virulence factor-producing *Shigella flexneri* (27, 28), and flagellated bacteria such as *Pseudomonas aeruginosa* (28, 29), *Salmonella typhimurium* (28), and *Legionella pneumophila* (30, 31). Studies also suggest that inflammasomes sense DNA and RNA viruses such as vaccinia and influenza (32–36), fungal products such as yeast zymosan and mannan (37) and *Candida albicans* hyphae (38–40), and hemozoin pigment produced by the malaria parasite (41–43) (see inflammasome activators in Table 1). Although there is some degree of specificity of inflammasomes for particular pathogens, clearly each NLR protein, particularly NLRP3, can recognize multiple pathogen-associated molecular pattern-activating signals. The mechanisms underlying this impressive list of microorganism targets are under active study (44).

Invading host cells to avoid the immune system is a well known tactic employed by many different microbes, thus necessitating the evolution of an arsenal of cytosolic sensory proteins such as the NLR family. Recently, however, a new class of innate immune activation signals derived from the host itself, so called “danger-associated molecular patterns,” have also been shown to activate the inflammasome. Extracellular ATP, perhaps released by dying cells, is a prerequisite to NLRP3-mediated IL-1β release (23, 45, 46), demonstrating that bacterial products alone are not sufficient to trigger the inflammasome. Activation of the purine receptor (P2X7) and subsequent potassium efflux were shown to be necessary for this process (47). Pore-forming toxins mimic these effects, whereas incubating cells *ex vivo* in medium containing a high concentration of potassium prevents inflammasome activation (23, 48). Additional danger-associated molecular patterns include particles such as monosodium urate, the crystalline salt of endogenously produced uric acid, and calcium pyrophosphate, a metabolic byproduct (49). Components of the extracellular matrix such as hyaluronin and biglycan also signal via the inflammasome (50, 51). These host-derived activators may contribute to a sterile inflammatory response in the absence of microbial infection.

NLR Inflammasomes and Disease

Given the susceptibility of the inflammasome to minute amounts of activators encountered during normal cellular processes, it is perhaps not surprising that excess IL-1 production has been linked to several common conditions. Experimental data from recombinant mice deficient in specific inflam-
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Although the mouse and *in vitro* cell line data are compelling, little evidence exists confirming similar pathways in humans or primary human cells.

**CAPS and Inflammasome Activation**

A wealth of genetic and functional data demonstrate direct involvement of the inflammasome in the pathogenesis of CAPS.
A total of 82 unique coding heterozygous mutations in NLRP3 have been reported in patients with the three CAPS phenotypes that are not observed in matched population control samples (65). There is limited genotype-phenotype correlation, with certain mutations often associated with specific phenotypes; however, some mutations have been linked to more than one phenotype, and many CAPS patients fall between diagnoses (20). Most mutations are missense changes in the NBD, with a few variants described in the LRR domain (66). Protein modeling of the NLRP3 NBD maps most disease variants on one surface of the hexameric protein complex, suggesting interference with inter- or intraprotein domain-domain interactions (Fig. 3). A common model proposes that CAPS mutations result in a gain-of-function phenotype leading to a constitutively active or

| Class/inflammasome activator | Clinical relevance | Mechanism | Refs. |
|-----------------------------|-------------------|-----------|-------|
| **G**                      |                   |           |       |
| *Listeria monocytogenes*    | Food-borne disease | Listeriolysin O-induced K⁺ efflux | 22, 23 |
| *Streptococcus pyogenes*    | Skin infection, pharyngitis, rheumatic fever | Streptolysin O- and NFκB-dependent | 74 |
| *Staphylococcus aureus*     | Skin infection, pneumonia, meningitis | Hemolysin-induced K⁺ efflux | 23–25 |
| *Bacillus anthracis*        | Anthrax           | Lethal toxin NLRP1 inflammasome activation | 21 |
| **G⁻**                     |                   |           |       |
| *Legionella pneumophila*    | Legionnaires' pneumonia | Flagellin-induced NLRC4 inflammasome activation | 30, 31 |
| *Shigella flexneri*         | Food-borne disease | Type 3 secretion system protein-induced NLRC4 inflammasome activation | 27, 28 |
| *Salmonella typhimurium*    | Food-borne disease | Flagellin- and type 3 secretion system protein-induced NLRC4 inflammasome activation | 28 |
| *Escherichia coli*          | Food-borne disease, opportunistic and nosocomial disease, sepsis, meningitis | Flagellin- and type 3 secretion system protein-induced NLRC4 inflammasome activation | 28 |
| *Burkholderia pseudomallei* | Melioidosis       | Type 3 secretion system protein-induced NLRC4 inflammasome activation | 28 |
| *Pseudomonas aeruginosa*    | Opportunistic and nosocomial infections | Membrane disruption- and type 3 secretion system protein-induced NLRC4 inflammasome activation | 28, 29 |
| *Neisseria gonorrhoeae*     | Sexually transmitted infection, pelvic inflammatory disease | Cathepsin B release from lysosomes | 26 |
| *Vibrio spp.*               | Cholera, wound infections | Hemolysin and NFκB activation | 75 |
| *Porphyromonas gingivalis*  | Periodontal disease | ? | 76 |
| *Borrelia burgdorferi*      | Lyme disease      | ? | 77 |
| *Mycobacterium tuberculosis*| Lung disease      | Bacterial secretion system detection and membrane disruption | 78 |
| *Chlamydia trachomatis*     | Sexually transmitted infection, pelvic inflammatory disease, eye infection | K⁺ efflux, type 3 secretion system bacterial protein detection, ROS | 79 |
| **Fungal products**         |                   |           |       |
| *Aspergillus fumigatus*     | Opportunistic infections | K⁺ efflux, ROS, Syk kinase activation | 80 |
| *Candida albicans*          | Candidiasis, opportunistic infections | K⁺ efflux, ROS, Syk kinase activation, hypha formation | 38–40 |
| Zymosan mannan              |                   | Pannexin-1 hemichannel protein activation | 37 |
| *β- Glucan*                |                   | K⁺ efflux, ROS, Syk kinase activation | 81 |
| **Viruses**                 |                   |           |       |
| DNA/vaccinia                | Vaccines          | Viral endocytosis | 33, 35 |
| RNA/influenza               | Influenza         | RNA sensing, lysosomal acidification, ROS, RIG-1 RNA helicase activation | 32, 34, 36 |
| **Parasites**               |                   |           |       |
| Hemozoin                    | Malaria           | K⁺ efflux, ROS, uric acid generation, endocytosis, Syk kinase activation | 41–43 |
| **Particles**               |                   |           |       |
| Alum                        | Vaccines          | K⁺ efflux, lysosomal damage with cathepsin B release, endocytosis | 54, 82–85 |
| Asbestos                    | Occupational lung disease | K⁺ efflux, ROS, endocytosis | 53 |
| Silica                      | Occupational lung disease | K⁺ efflux, ROS, endocytosis, cathepsin B release, TNF | 46, 52, 53, 83 |
| **Danger signals**          |                   |           |       |
| Amyloid β                   | Alzheimer disease | Lysosomal damage with cathepsin B release | 55 |
| Monosodium urate-phosphate  | Gout, lung fibrosis | Particle endocytosis | 49, 86 |
| Calcium pyrophosphate       | Pseudogout        | Particle endocytosis | 49 |
| Biglycan                    | Tissue injury     | ROS | 50 |
| Hyaluronin                  | Trauma            | Endocytosis, lysosomal digestion of hyaluronin | 51 |
| Necrotic cells              | Cancer therapy    | Mitochondrial release of ATP from dying cells | 87–89 |
| ATP                         | Sterile inflammatory response | K⁺ efflux | 23, 45, 46 |
| RNA                         |                   | Double-stranded RNA sensing | 90, 91 |
| **Other**                   |                   |           |       |
| UVB light                   | Sun exposure      | Increase in cytoplasmic Ca²⁺ | 92 |
| Implant metals              | Orthopedic implants | Metal ion sensing, ROS | 93 |
hyperactive inflammasome. During steady-state conditions, NLRP3 may assume an inactive or “closed” conformation with the LRR domain and NBD in a folded position. CAPS mutations may disrupt the binding between the two domains, resulting in a labile “open” conformation (20). This hyperactive state is dependent on nucleotide binding because disruption of the Walker A nucleotide-binding motifs has been shown to prevent in vitro IL-1β secretion from recombinant mutant monocytic cells (45). Although the above theory is compelling, true experimental evidence is lacking, and the exact mechanism underlying the increased inflammasome activation in CAPS patients is still unclear.

Ex vivo studies of peripheral blood mononuclear cells from CAPS patients provide clear evidence of increased inflammasome activation. These cells demonstrate either constitutive IL-1β release or increased production compared with control cells in response to various doses of a proinflammatory stimulus such as LPS (67). Low concentrations of crude LPS preparations stimulate maximal secretion of mature IL-1β from CAPS cells, whereas control cells require much higher concentrations, likely because trace amounts of contaminating ATP are needed as a second signal for inflammasome activation. Indeed, CAPS peripheral blood mononuclear cells release IL-1β when treated with pure preparations of LPS in the absence of ATP, whereas control cells have increased pro-IL-1β transcription but require ATP for mature IL-1β to be released. Pharmacologic inhibition of caspase-1 at least partially abrogates release from control and CAPS cells; thus, this process is inflammasome-dependent (68).

The development of recombinant mice with CAPS-associated mutations in the murine Nlrp3 gene has provided further functional data to support the central role of the inflammasome in CAPS pathology. Mice expressing MWS-associated mutations devised by two independent groups show evidence of systemic inflammation, including neutrophilic infiltration and tissue cytokine expression involving the skin, lymphoid organs, joints, muscle, and conjunctiva, that is consistent with the clinical picture of CAPS patients. In addition, significantly elevated serum levels of IL-1β and IL-18 were observed in mutant MWS pups. Bone marrow-derived myeloid cells from these mice release increased IL-1β in response to crude LPS and do not require ATP for IL-1β release in response to pure LPS, similar to mononuclear cells from CAPS patients (69, 70). Interestingly, although complete phenotypic rescue occurred when the mutation was expressed on a PYCARD-null background, breeding onto an IL-1 receptor-null background only partially aborted the CAPS phenotype, and treating with high doses of a mouse form of the IL-1 Trap molecule (rilonacept) extended life by 3 days on average (69). Taken together, these findings indicate that murine CAPS is inflammasome-dependent, but other mediators besides IL-1β play a significant role in pathology. Given patients’ dramatic response to IL-1-targeted therapy, it is perhaps surprising that the mouse model had such significant disease in the absence of IL-1 signaling; however, some CAPS patients continue to have underlying inflammation despite adequate treatment, and the arthropathy characteristic of NOMID is completely nonresponsive. It is thus likely that cytokines besides IL-1β, such as IL-18, play roles in both human and murine CAPS.

**Cold-induced Inflammation in FCAS**

Patients with FCAS, the mildest CAPS phenotype, consistently report development of fever, rash, and joint pain after a generalized cold exposure. Although patients show some evidence of chronic systemic inflammation, these cold-induced episodes are self-limited. Symptoms associated with these episodes can be consistently reproduced in a controlled environmental cold room challenge by exposing patients to 4°C for ~30 min, followed by natural warming to room temperature. Within 1 h of challenge, a urticaria-like rash develops on exposed and unexposed areas, and fever and joint pain develop within the first 2–3 h. Symptoms peak at ~8 h, coinciding with
blood neutrophilia, and both resolve within 12–18 h. Serum IL-1β levels are undetectable throughout the cold-induced episodes; however, serum IL-6, often used as a surrogate for IL-1β, increases within 1 h and peaks at 4 h post-challenge, preceding the peak of symptoms. Tissue expression of IL-1β and IL-6 is associated with neutrophil infiltrate in the dermis of affected skin, but not in adjacent unaffected areas. All symptoms and laboratory features are completely abrogated by pretreatment with recombinant IL-1 receptor antagonist (anakinra), demonstrating the central role of IL-1β in the pathogenesis of this disorder (71).

The mechanisms underlying this unusual inflammatory response to temperature are still unclear. It is known that cultured adherent monocytes from patients with FCAS, but not normal controls, release IL-1β when exposed to temperatures similar to that of human skin (32 °C), but not at core body temperature (37 °C) (72). A similar cold-induced response is observed in bone marrow-derived dendritic cells isolated from mice with a common FCAS mutation, but not in the same cells generated from a mouse with a MWS mutation (69). This phenomenon suggests that specific inflammatory cells of myeloid origin have the ability to sense minor temperature changes. The transient receptor potential ion channels used by neurons to detect temperature change have also been identified on myeloid cells.3 Another known mechanism underlying responses to temperature involves heat and cold shock proteins, chaperones that interact with and stabilize protein complexes. It is known that HSP90 interacts with the inflammasome, but whether this protein plays a role in the response to temperature observed in FCAS remains to be seen (73). Finally, small changes in temperature can have significant effects on protein structure, so it is likely that specific FCAS-associated mutations in the gene encoding NLRP3 change the protein dynamics and affect the inter- and intraprotein domain-domain interactions. Further study is required to determine whether one or more of these mechanisms are involved in the FCAS response and whether this response plays a role in other temperature-related diseases.

Conclusion

The inflammasome is a master regulator of inflammation, translating a variety of microbe- and host-derived distress signals into IL-1β activation. As new research elucidates the roles of NLR proteins and the autoinflammatory disease family further expands, it is likely that new clinical uses for IL-1 inhibitors will be recognized. As a clear example of the direct effects of inflammasome dysregulation, CAPS-related research will be invaluable to the study of more complex disorders and the application of targeted therapies.

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