

CLINICAL IMPLICATIONS OF BASIC RESEARCH

The Inflammasome — A Linebacker of Innate Defense

Joost P.H. Drenth, M.D., Ph.D., and Jos W.M. van der Meer, M.D., Ph.D.

Why study hereditary periodic-fever syndromes, which affect fewer than 500 patients worldwide? The discovery of cryopyrin provides an answer. The story begins in 2001, when investigators showed that mutations in the cold-induced auto-inflammatory syndrome 1 (CIAS1) gene, which encodes cryopyrin, causes two hereditary periodic-fever disorders: the Muckle-Wells syndrome and the familial cold autoinflammatory syndrome.¹ The following year, a third periodic-fever syndrome (also referred to as neonatal-onset multisystem inflammatory disease or the chronic infantile neurologic, cutaneous, articular syndrome) was found to be caused by mutant cryopyrin.^{2,3} Three articles recently published in *Nature*⁴⁻⁶ now suggest that by discovering cryopyrin, the researchers stumbled on the Rosetta stone of innate immunity: a highly conserved and specific response system that detects the presence of microorganisms.

Macrophages and neutrophils contain the inflammasome, a complex of proteins that have distinct roles in the innate defense system. Members of the “NALP” family of proteins (which includes cryopyrin) are the main building blocks of the inflammasome. Two types of inflammasome have now been described in detail — the NALP1 inflammasome and the NALP3, or cryopyrin, inflammasome — but there are probably many more variants. The stimulation of cryopyrin within the cryopyrin inflammasome triggers a series of internal reactions that ultimately result in the activation of the proinflammatory cytokine interleukin-1 β . This interleukin is, in turn, secreted by the macrophage and triggers another cascade of molecular events that result in inflammation. The inflammasome was hypothesized to act as an early sensor to detect danger signals threatening the cell and to set the wheels of host defense in motion. Although this hypothesis was attractive, the events critical to the assembly, and hence the activation, of the inflammasome were unknown.

The three recently reported studies by Kanneganti et al.,⁴ Martinon et al.,⁵ and Mariathasan et al.⁶ had similar designs: each group engineered mice in which cryopyrin in the macrophages was knocked out and studied the response of these macrophages to various danger signals. They found that the ability of cryopyrin-deficient macrophages to secrete activated interleukin-1 β was significantly reduced under specific circumstances.

Kanneganti et al.⁴ and Mariathasan et al.⁶ focused on the role of the cryopyrin inflammasome in the detection of infectious agents. Kanneganti et al. showed that macrophages that lack cryopyrin neither produce active interleukin-1 β in response to bacterial RNA nor respond to either of two vaccine adjuvants. Mariathasan et al. showed that cryopyrin-deficient macrophages do not respond efficiently to challenges with *Staphylococcus aureus* or *Listeria monocytogenes*. Both groups demonstrated the specificity of the cryopyrin inflammasome. For example, Mariathasan et al. showed that the recognition of the gram-negative bacteria *Salmonella typhimurium* and *Francisella tularensis* by the macrophage is not dependent on the presence of cryopyrin but requires other common inflammasome components.

Martinon et al.⁵ studied the role of cryopyrin in the detection of urate crystals. It has been known for more than 200 years that the deposition of such crystals causes joint inflammation in patients with gout, but how it does so was unclear. These researchers showed that both monosodium urate (the crystal in gout) and calcium pyrophosphate dehydrate (the crystal in pseudogout) are detected by the cryopyrin inflammasome, which then initiates the inflammatory cascade by activating interleukin-1 β . The inflammasome appears to be key in the initiation: peritoneal macrophages from mice deficient in other components of the cryopyrin inflammasome, such as procaspase-1 (Fig. 1), did not produce interleukin-1 β in response to the injection of

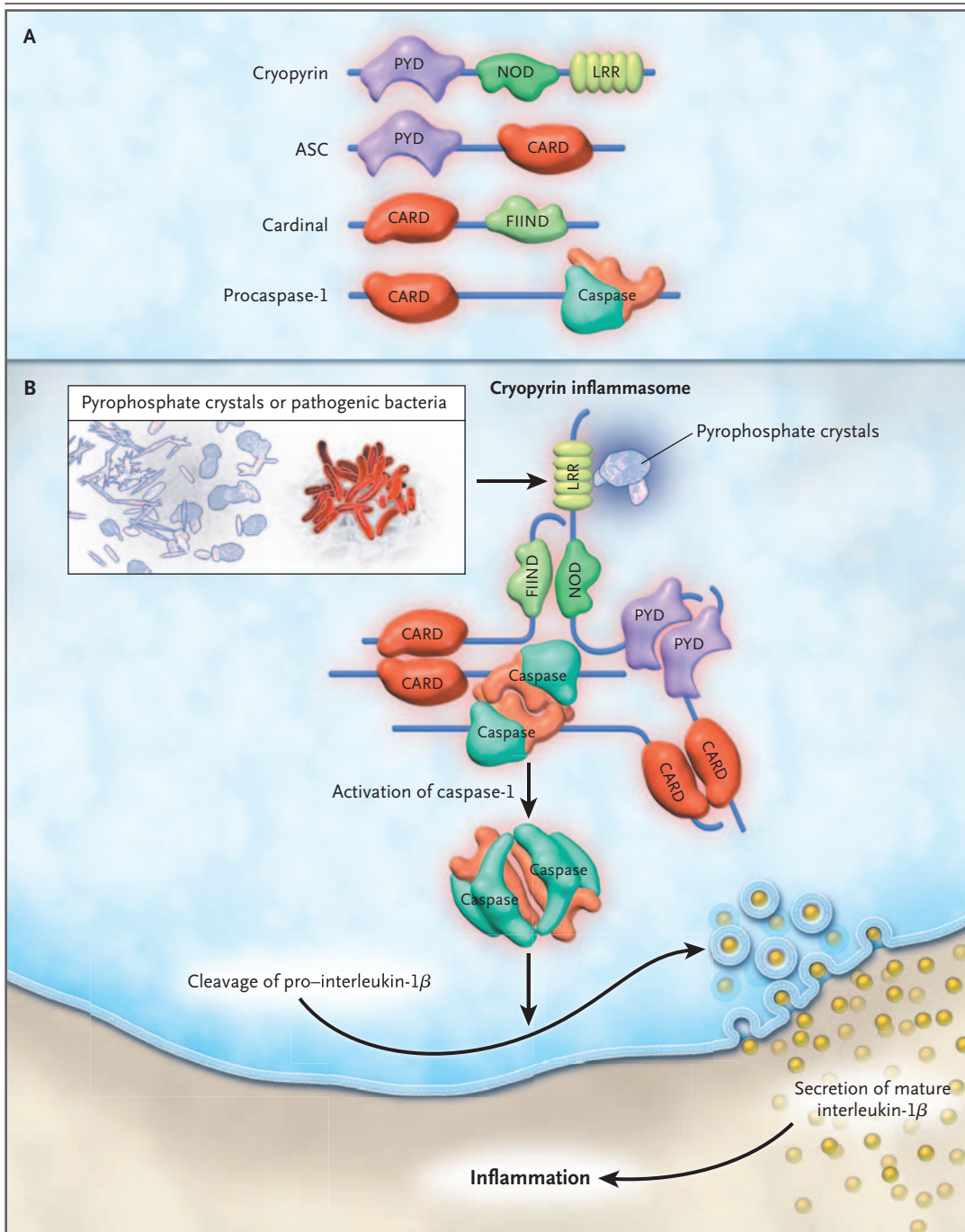


Figure 1. The Cryopyrin Inflammasome.

Cryopyrin, or NALP3, is the central component of the cryopyrin inflammasome. Cryopyrin contains three domains: a pyrin domain (PYD), a nucleoside oligomerization domain (NOD), and a domain of leucine-rich repeats (LRR). The other components of the cryopyrin inflammasome ASC — apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD), cardinal, and procaspase-1 (Panel A) — consist of domains that can be assembled only after cryopyrin is activated through the interaction of its LRR domain with either a crystal (urate or calcium pyrophosphate dehydrate) or certain microbial species (Panel B). The assembly of the domains ultimately leads to the release of active caspase-1, which in turn activates interleukin-1 β through the cleavage of pro-interleukin-1 β . On its secretion into the extracellular milieu, interleukin-1 β sets off a series of events that result in inflammation. FIIND denotes the domain with function to find.

urate crystals. The study⁵ also indicates that cryopyrin is rather choosy: harmless particles such as diamond crystals or aluminum powder do not act as a trigger.

Although the three studies have minor discrepancies that need to be resolved, they catapult cryopyrin from involvement in a rather obscure group of disorders into the realm of common bacterial infections and of gout, which alone affects at least 1 in every 400 persons in the United States.

The cryopyrin inflammasome would seem to be a versatile sentry of the innate immune system, and it is easy to speculate on the possible future therapeutic implications of these findings. In fact, clinical treatment based on the mechanism of disease has already been realized for the three rare diseases that led to the discovery of cryopyrin. Most of the mutations that cause the hereditary periodic-fever syndromes result in a hyperactive cryopyrin, thus leading to the increased secretion of interleukin-1 β . Clinical trials have shown that the interleukin-1 receptor antagonist anakinra effectively ameliorates clinical symptoms in all three syndromes. By modifying the cryopyrin inflammasome, we might protect

against diverse microorganisms, increase the efficacy of vaccines, and ease the inflammatory arthritis characteristic of gout and pseudogout.

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From the Departments of Gastroenterology, Hepatology, and General Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands.

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