

Preface

Innate immunity has been viewed as the first line of defense discriminating “self” (host proteins) from “non-self” (microorganisms). However, emerging literature suggests that innate immunity actually serves as a sophisticated system for sensing signals of “danger” such as pathogenic microbes or host-derived signals of cellular stress, while remaining unresponsive to non-dangerous motifs, such as normal host molecules. The innate immune system engages an array of pattern-recognition receptors (PRRs) to detect invariant microbial motifs. PRRs are expressed by cells at the frontline of defense against infection, including macrophages, monocytes, dendritic cells, neutrophils, and epithelial cells, as well as cells of the adaptive immune system. The discovery of Toll-like receptors (TLRs) provided a class of membrane receptors that sense extracellular microbes and trigger anti-pathogen signaling cascades. More recently, intracellular microbial sensors have been identified, including NOD-like receptors (NLRs). NLRs detect/sense conserved structures of the microorganisms, the pathogen-associated molecular patterns (PAMPs). PRRs activate intracellular signals that collaborate for efficient activation of host defense. One such specific collaboration is the interaction between TLRs and intracellular NLRs that recognize PAMPs, as well as host-derived danger signals danger associated molecular patterns (DAMPs). Importantly, NLR members are involved in the assembly of molecular platforms, the inflammasomes, activated upon cellular infection, or stress that trigger the maturation of pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and IL-18 to engage innate immune defenses.

Inflammasomes are not only involved in cytokine maturation but also in a highly inflammatory form of cell death called pyroptosis. Moreover, the inflammatory response to infection appears to be coupled to cell death as an important mediator of host defence. Occurring in the context of infection, pyroptosis is morphologically, mechanistically, and physiologically distinct from other forms of cell death. The physiological significance of this unique form of cell death is not clear since pyroptosis can favor pathogen elimination on one hand, while contributing to the pathophysiology of disease on the other.

Different inflammasomes are activated by various bacterial and viral activators through different receptors/sensors in particular NLRP1, NLRP3, and NLRC4, as

well as the PYHIN (pyrin and HIN200 domain-containing) family member AIM2 have all been demonstrated to form functional inflammasomes capable of activating caspase-1.

Recent genetic studies using mice deficient in inflammasome components demonstrate the involvement of the inflammasome in the outcome of infection with the fungus *Candida albicans*, the bacteria *Staphylococcus aureus*, *Salmonella typhimurium* and *Legionella pneumophila*, the helminth *Schistosoma mansoni* as well as the malarial parasite *Plasmodium berghei*. Live fungi, schistosomal egg antigen or malarial hemozoin have the ability to activate the inflammasome and induce secretion of mature IL-1 β .

The most fully characterized inflammasome is the Nlrp3 inflammasome, which is activated by various endogenous and exogenous danger signals such as environmental irritants, signals of tissue damage, and pathogens. Danger signals are endogenous host molecules that are *not in place*, such signals include the presence of ATP or uric acid in the extracellular space, the breakdown or release of soluble extracellular matrix components or the presence of DNA in the cytosol of the cell. All these danger signals have been proven to activate the release of mature IL-1 β through caspase-1 activation. The NLRP3 inflammasome is activated by crystals and particles of varied size and structure. These inflammasome-activating particles have a causative role in human diseases such as gout, asbestosis, silicosis, and Alzheimer's, or are useful as vaccine adjuvants, like in the case of alum. The molecular aspects involved in activation of the NLRP3 inflammasome by particles are being rapidly elucidated and emphasize the importance of phagocytosis, K⁺ efflux, and generation of reactive oxygen species in this process. Knowledge of the involvement of inflammasome activation by danger signals in different diseases is increasing every year and has emerged as responsible for the sterile inflammatory response.

The broad spectrum of activators is reflected at the physiological level in its implication in normal and dysregulated immune responses, including various auto-inflammatory diseases, cancer, skin and lung inflammation, and in the defence against pathogens. The skin is constantly subjected to microbial, chemical, and physical insults. Not surprisingly, it is endowed with the capacity to detect these events and respond accordingly, alerting the immune system when needed, often through the inflammasome. Cancer progression is associated with chronic inflammation and the dampening of antitumor immune responses. Although pro-inflammatory cytokines such as IL-1 β have been proposed to be involved in the initial development of cancer, there is emerging evidence that these pro-inflammatory molecules can also act as potent adjuvants of T-cell-mediated immune responses. Strikingly, the activation of the NLRP3 inflammasome was recently shown to be instrumental in the initiation of an immune anti-cancer response that was required for the success of chemotherapy.

Non regulated inflammation in lung often leads to chronic inflammatory diseases such as asthma, chronic obstructive pulmonary disease, and pulmonary fibrosis. Acute cigarette smoke exposure induces inflammasome-dependent maturation of IL-1 β and ASC-associated protein complex is necessary to lung emphysema.

Bleomycin- or crystalline silica particles- induced pulmonary inflammation and fibrosis are dependent on NLRP3 inflammasome. NLRP3-containing inflammasome appears to be an essential mediator for allergic lung inflammation. Pulmonary exposure to nanomaterials may lead to pulmonary inflammation and fibrosis.

The dysregulated secretion of IL-1 that occurs upon the loss of one or more roadblocks is indeed the cause of a number of severe chronic human diseases, characterized by massive inflammation. These disorders, collectively called “Auto-inflammatory diseases,” differ in pathogenesis and clinical manifestations but share a dramatic therapeutic response to IL-1 blocking. The identification of the gene responsible for Familial cold auto-inflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA) shed light on the possible link between this class of monogenic inflammatory disorders and the pivotal role pathogenic role of IL-1 β . Missense mutations of the *NALP3/CIAS1* gene provide a gain of function to the NLRP3 protein resulting in increased secretion of active IL-1 β .

Inflammatory reactions must be well synchronized and controlled, as the dysregulation of inflammatory processes is associated with disease. The dramatic and sometimes devastating clinical consequences of mutations in NLRP3 itself or in other inflammasome-related genes show how an overly active signaling pathway can lead to chronic pathology. Anti-IL-1 therapies have proven to be enormously successful in the treatment of auto-inflammatory diseases, which gives great hope that such therapies can also be effective in other inflammatory conditions that are linked to inflammasome activation. Future work should focus on deciphering the integral mechanisms that lead to NLRP3 inflammasome activation.

We believe that this volume written by several experts in the field will be useful for scientists and medical doctors investigating the mechanisms of inflammation and the physiopathology of inflammatory diseases and developing new potential therapies. Since the first description in 2002, the scientific literature on inflammasome expanded exponentially with more than 600 scientific publications published. This comprehensive review on inflammasome provides a timely state of the art review of literature, describing the multiple involvements of inflammasome in Immunity.

Finally, we wished to thank the authors dedicating their precious time with expert contributions for this main volume in Inflammation Research.

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