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The innate immune system 'puzzle'

Detecting pathogen invasion and regulating homeostatic processes are two essential functions of myriad non–Toll-like innate immune proteins.

One of the more important revolutions in immunology has been the characterization of germline-encoded innate receptors and/or 'sensors' that can respond to host invasion by pathogens. Many of these innate receptors also have important functions in natural host homeostatic processes, such as the maintenance of gut homeostasis. Among the innate receptors are the Toll-like receptors (TLRs) and the intracellular Nod–like receptor (NLRs), both of which are expressed by many phyla. Although the very idea of 'innate' immune responses preceded the discovery of TLRs and non-TLR innate proteins (natural antibodies and complement are two such relatively 'old' innate immune systems), with the arrival of TLRs came the fundamental idea that innate receptors, like pieces of a puzzle, 'fit' with a distinct pattern of a corresponding 'piece' of a pathogen. Hence, the term 'pattern-recognition receptors' (PRRs) was coined to describe the innate molecules that recognize 'pathogen-associated molecular patterns' (PAMPs).

In this issue of *Nature Immunology*, we present a Focus on four families of Non-Toll-like Innate Immune Proteins, many of which are PRRs. We commissioned four review articles that discuss the present understanding of plant nucleotide-binding site–leucine-rich repeat (NBS-LRR) proteins, mammalian NLRs, C-type lectin receptors (CLRs) and 'triggering receptor expressed on myeloid cells' (TREM) proteins in innate responses to pathogens and in homeostatic processes. Philippe Sansonetti provides a provocative overview that introduces the Focus, summarizing key aspects of the four reviews with a 'global' perspective on how innate signaling has been shaped by evolutionary forces such as host-pathogen 'battles'. Among other goals, we hope this Focus will convey the enormous diversity in structure and function among the many non-TLR innate proteins.

The identification of mammalian TLR innate sensors was an outgrowth of previous work in drosophila, in which the original Toll protein was first characterized. The study of plant host-defense systems has also yielded great insight into the various components required for innate immune signaling. For example, analysis of NBS-LRR proteins has demonstrated two ways in which these proteins can 'sense' danger signals. As reviewed by Roger Innes and colleagues, plant NBS-LRRs respond either directly or indirectly to pathogens. Indirect sensing occurs when endogenous 'self' molecules have undergone structural alterations resulting from direct interaction with a pathogen effector protein. The indirect-sensing NBS-LRR protein then directly interacts with the altered self molecule to mediate 'downstream' inflammatory responses. Future work should determine if mammalian NLRs similarly use an indirect mechanism for pathogen recognition, as evidence of direct interaction between mammalian NLRs and their respective PAMPs remains sparse.

Even though much remains to be discovered about the interacting ligands of mammalian NLRs, a great deal has been learned about the importance of NLR responses in antipathogen immunity and in the regulation of immune and/or organ homeostasis. Dana Philpott and Stephen Girardin and colleagues review characteristics of key NLR family members, focusing specifically on the biology and the purported functions of individual NLRs in host defense against intracellular pathogens and in response to endogenous danger signals, such as the deposition of uric acid crystals in joints. Of central interest are the functions of Nod1 and Nod2 and their relevance to issues associated with 'translational' research, such as how these intracellular sensors function in gut homeostasis and human inflammatory disorders such as Crohn disease.

The family of myeloid CLRs, including the cell surface molecules DC-SIGN and dectin-1, is reviewed by Reis e Sousa and colleagues. Although many CLRs are PRRs that promote synergistic immune responses with other innate receptors, some CLRs (such as the activating natural killer cell receptor Ly49) probably bind host-derived molecules only. The carbohydrate-binding receptor dectin-1 is an example of a CLR that can do both. Strong immune responses to fungus-derived β-glucans, a PAMP expressed by fungal pathogens, require dectin-1, as dectin-1 responses act in synergy with TLR signaling to induce inflammatory cytokines. In addition to β-glucans, dectin-1 also recognizes an endogenous T cell ligand. Beyond their ligands, what may prove to be a critical distinguishing feature of the CLRs are their signaling mechanisms, which may allow classification into functional subgroups based on signaling pathways.

Members of the TREM family of innate immune proteins function as 'amplifiers' of innate responses and as regulators of developmental stage– and tissue-specific functions. Colonna and colleagues describe the various features of several TREM proteins, including TREM-1, which can respond to both endogenous and exogenous danger signals and thereby amplify TLR-mediated signaling to induce proinflammatory cytokines; at the extreme, TREM-1-mediated signal amplification can cause acute inflammatory conditions such as life-threatening sepsis. Although TREM-mediated signaling is known to occur via the adaptor protein DAP12, how individual TREM proteins are specifically regulated and the identification of their individual ligands are of particular interest because some, such as TREM-2, have pleiotropic functions in brain and bone homeostasis in addition to sensing PAMPs.

The non-TLR innate immune receptors and/or sensors discussed in this Focus might seem too dissimilar for a 'unified picture' of innate immunity to be painted. An important aim of this Focus is to highlight four families of innate proteins that span diverse organisms, from nematodes to plants to humans, and to show how these molecules variously contribute to innate immunity. The unified picture derives from viewing the innate immune system as a potential 'network' that can distinguish between 'friend' (commensal bacteria) and 'foe' (pathogenic bacteria). Although there is no doubt that the complete picture of the innate signaling network is yet to be fully described, many pieces of the puzzle are falling into place.