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Feature Review

Integration of Innate Immune Signaling

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The last decades of research in innate immunology have revealed a multitude of sensing receptors that evaluate the presence of microorganisms or cellular damage in tissues. In the context of a complex tissue, many such sensing events occur simultaneously. Thus, the downstream pathways need to be integrated to launch an appropriate cellular response, to tailor the magnitude of the reaction to the inciting event, and to terminate it in a manner that avoids immunopathology. Here, we provide a conceptual overview of the crosstalk between innate immune receptors in the initiation of a concerted immune reaction to microbial and endogenous triggers. We classify the known interactions into categories of communication and provide examples of their importance in pathogenic infection.

Trends

Coordination of innate immune receptor signaling in response to simultaneous stimuli in a complex tissue occurs at the levels of ligands, signaling transducers, and immune effector mechanisms.

Cross-activation between innate immune receptors involves all families of PRRs and serves as an important means of signal amplification in the initiation of an antimicrobial effector response.

Cross-inhibition between innate immune receptors, predominantly involving members of the NLR family, provides a means of signal prioritization, immune effector hierarchy, and regulated immune response termination.

PRR cooperation and cross-activation is an essential strategy of antipathogen defense.

Cell type- and tissue-specific expression patterns of innate immune sensors determine the biogeographical pattern of immune receptor crosstalk.

Introduction

Twenty-five years after the formulation of the theory of pattern recognition in innate immune sensing [1], research in the field of innate immunity has led to the discovery of several families of innate immune receptors, their intracellular signaling pathways, and the immune effector mechanisms that are triggered upon receptor engagement [2]. Defined microbial and non-microbial ligands as specific triggers of single pattern recognition receptors (PRRs) have been instrumental in delineating receptor specificities and downstream intracellular response circuitries. The field has now progressed to a state in which predictions can be made about the engagement of certain immune effector mechanisms, for example changes in transcription or phagocytic activity, in response to specific microbial ligands. However, innate immune sensing in a complex tissue in the *in vivo* setting involves a multitude of simultaneously triggered responses, interaction between signaling pathways, and concurrently-active effector mechanisms. As such, tissue-level innate immune sensing needs to integrate not only stimuli derived from different ligands of the triggering agent but at the same time must balance concomitantly-active signaling pathways to generate an appropriate, concerted, and self-limiting effector response. The mechanisms are only beginning to be understood, but recent studies have revealed multiple innate immune receptor interactions that provide insight into the principles of concerted tissue-level integration of innate immune signaling [3]. We discuss here several categories of PRR interaction in the coordination of the immune response, and focus on some of the most outstanding questions in the field, including the need to further delineate the cellular, tissue-level, and whole-organism facets orchestrating the compartmentalization of local and systemic innate immunity.

Integrated Components of Innate Immune Signaling

Recognition of microorganisms, including viruses, bacteria, and fungi, by the host immune system is based on the detection of conserved molecular structures that are shared by a large number of pathogens, termed pathogen-associated molecular patterns (PAMPs), as well as

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damage-associated molecular patterns (DAMPs). According to protein structure and domain function, six families of PRRs can be distinguished:

(i) Toll-like receptors (TLRs) are a family of membrane-bound proteins that initiate innate immune responses through signaling pathways mediated by NF-κB and interferon (IFN)-regulatory factors (IRFs) [4]. With the exception of TLR3, all TLRs elicit signaling through MyD88 and the transcription factors NF-κB and IRF5 to induce the expression of proinflammatory cytokines such as IL-6, IL-12, and TNF [5]. In addition, some TLRs initiate signaling through MyD88 and IRF7 (TLR7, TLR8, and TLR9), or through TRIF/TRAM and IRF3 (TLR3 and TLR4) to induce type I IFNs [6].

(ii) C-type lectins (CTLs) are membrane-bound carbohydrate receptors that consist of two types: type I CTLs (such as DEC-205 and MMR) that contain multiple carbohydrate recognition domains (CRDs), and type II CTLs (including dectin 1, dectin 2, Mincle, DC-SIGN, DNGR-1) that contain a single CRD [7,8]. An additional member of the CTL family is the soluble carbohydrate receptor mannose-binding lectin (MBL). Intracellularly, CTLs trigger a pathway that is dependent on the kinase SYK and phospholipase C (PLC).

(iii) NOD-like receptors (NLRs) are cytoplasmic receptors of various microbial and non-microbial stimuli. While NOD1 and NOD2, upon stimulation, lead to the activation of NF-κB signaling and changes in gene expression, other members of this family do not directly alter transcription but initiate the formation of the inflammasome complex. The inflammasome recruits and activates caspase 1, which in turn activates proinflammatory cytokines by post-translational cleavage [9,10].

(iv) RIG-I-like receptors (RLRs), such as RIG-I, MDA5, and LGP2, are cytoplasmic sensors of RNA. Upon activation, they signal to the mitochondrial adapter MAVS to induce an IRF3- and IRF7-mediated type I IFN response [11].

(v) AIM2-like receptors (ALRs) are cytoplasmic DNA sensors. Some of these sensors, including IFI16 and DAI, signal through the endoplasmic reticulum-associated adapter STING to initiate downstream signal transduction. Others, such as AIM2, are capable of forming an inflammasome [12].

(vi) OAS-like receptors (OLRs) are a recently identified group of cytoplasmic innate sensors of nucleic acids. Members of this family are the oligoadenylate synthase (OAS) proteins and cyclic GMP-AMP synthase (cGAS). These PRRs are unique in their signal transduction mechanisms because they produce 2′–5′-linked second messenger molecules that initiate downstream antiviral immune responses [13].

Conceptually, PRRs can therefore be classified based on the type of their microbial or endogenous ligands (e.g., cell wall components, nucleic acids, metabolites), the signaling pathways they trigger (e.g., MAP kinase, NF-κB, IRFs, inflammasome), and the downstream immune effector modules they initiate (e.g., cytokine production, antimicrobial peptides, phagocytosis, antibodies) (Figure 1). As detailed below, some receptors can be activated by similar ligands, and initiate the same signaling and effector modules, thereby inducing a complex and multifaceted immune response.

Shared Ligands

Multiple PAMPs trigger more than one receptor (Figure 1A). The recognition of identical microbial ligands by more than one PRR likely provides an opportunity for the host to develop ‘back-up’ mechanisms for compensatory microbial sensing, and creates the possibility to sequentially add additional information to the recognition event, resulting in a continuum of signaling ranges instead of a ‘digital’ output denoting only the presence or absence of an inflammatory trigger. However, activation of several innate immune pathways by the same shared signals also poses the conceptual challenge of understanding the code determining which receptors are to be engaged in a given situation, and at which priority, signaling strength, and temporal and spatial