Sensing infection and tissue damage

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Innate and adaptive immunity work hand-in-hand across vertebrates to protect against invasions by pathogens before they become established as disease. The sensors that monitor the environment and transduce a signal to the immune system are often molecular circuits that can be activated by a variety of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). These patterns are recognised by Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), cytosolic sensors of DNA, RNA, and protein and other pattern recognition receptors (PRRs) that activate the innate immune system. This innate immune response is crucial to control the early growth of pathogens and limits their spread. Once the immune system becomes activated, it can mount a coordinated, specific attack that is targeted against the invading pathogen. The coordinated effort of innate and adaptive immunity allows the body to respond to a wide range of pathogens and their different mechanisms of entry and spread.

Cell-intrinsic immunity to RNA viruses

The ability of all nucleated vertebrate cells to respond to virus invasion has been recognised since the discovery of interferons, virus-induced cytokines produced by both immune and non-immune cells. However, only recently have the relevant sensors and transducers been identified. RNA viruses such as influenza virus replicate using a primer-independent mechanism that leaves a tri-phosphorylated end of the genome. The 5′ppp mark is absent from cellular RNAs, which are capped (mRNA) or otherwise processed (tRNA and rRNA). 5′ppp and, for some viruses, 5′pp, therefore acts as a tell-tale sign of RNA virus presence in the cytosol that is recognised, together with elements of RNA secondary structure, by a cytoplasmic protein sensor named RIG-I (Pichlmair et al., 2006; Goubau et al., 2014). A related sensor, MDA5, recognises double stranded (ds) or highly base-paired RNA, which is also often a product of viral replication and is absent from uninfected cells. Following activation by viral RNA, RIG-I and MDA5 engage the mitochondrial adapter protein MAVS initiating a signal transduction pathway that culminates in activation of transcription factors of the IRF and NF-κB families to induce type I and type III IFN gene expression (Fig 1). Interestingly, IFNs are not themselves antiviral effectors. Rather, they are secreted by virally infected cells and act in an autocrine and paracrine amplification loop, binding to IFN receptors that signal to induce interferon-stimulated genes (ISGs; Fig 1). ISGs include the RIG-I and MDA5 sensors themselves, providing a positive feedback loop for innate virus sensing. ISGs also encode a variety of effector proteins that restrict virus propagation by shutting down cell translation, cleaving cellular and viral RNAs and blocking virion replication, assembly and/or release. As such, ISGs encode effectors of antiviral immunity elicited by a simple cell-intrinsic sensing and transducing immune circuit, albeit one involving IFN-mediated amplification and spread (Fig 1).

Interestingly, the IFN response is absent in invertebrates and plants, which, instead, defend themselves from viruses using RNA interference (RNAi). In those organisms, Dicer enzymes process viral dsRNA to generate small interfering RNA (siRNA) that is loaded onto a complex containing Argonaute proteins that can “slice” viral RNAs bearing complementary sequences. This sequence-specific antiviral RNAi response was thought to have been lost during vertebrate evolution of the IFN response even though the RNAi machinery itself has been preserved and is used for miRNAs generation and action. In fact, sequence-specific antiviral RNAi is not absent in mammals and was recently found to be masked or suppressed by the sequence-unspecific actions of ISG proteins (Maillard et al., 2016). Therefore, RNAi is an antiviral strategy that is preserved from plants to humans and may be important in cellular niches in which the IFN response is attenuated.

Dendritic cells as sensors of viruses and microbes

Viruses have evolved measures to block cell-intrinsic immunity; in vertebrates, innate defences are not sufficient to prevent their spread. We have a sophisticated system of adaptive immune defence that makes use of T and B cells to specifically recognise viruses and other pathogens, as well as commensals, at any body barrier that might be colonised. The T and B cells need to be primed by virus-sensing DCs and RNA viruses present in extracellular spaces can be detected by specialised plasmacytoid DCs using transmembrane receptors of the Toll-like receptor (TLR) family such as TLR7 (Diebold et al., 2004). The ligand-binding domain of TLR7 faces the lumen of endosomes and detects the presence of RNA carried by influenza and other RNA viruses that are taken up into those compartments prior to low pH-induced fusion and cytoplasmic entry (Diebold et al., 2004). TLR7 signalling in plasmacytoid DCs results, among others, in the production of type I IFNs that favour priming of antiviral effector T cells.
Interestingly, TLR7 recognition, unlike that of RIG-I, does not rely on virus-specific RNA marks and the receptor can be triggered by self RNA artificially delivered to endosomal compartments (Diebold et al., 2004). This argues that pathogen detection can ensue, in some instances, from recognition of molecules shared between invader and host but that become mislocalised in an infectious setting (Diebold et al., 2004). Nevertheless, many TLRs and other innate immune sensing receptors specifically detect molecular signatures of microbes that are qualitatively distinct from those of self. Such receptors include Dectin-1, a transmembrane protein member of the C-type lectin receptor (CLR) family that binds to fungal and bacterial β-1,3-glucans in the extracellular space and endosomes. Dectin-1 possesses a tyrosine-based hemITAM signalling motif in its cytoplasmic tail that becomes phosphorylated by Src family kinases after ligand engagement and serves as a platform for recruiting Syk, a non-receptor tyrosine kinase (Rogers et al., 2004).
Dectin-1 and DNGR-1 can both be expressed by DCs. Dectin-1 is monomeric but can oligomerise upon binding to β-glucans exposed by fungal cells. Src family kinases (SFKs) phosphorylate the tyrosine in the VxL hemITAM motif and allow for docking and activation of Syk, which then signals to NF-κB, MAPK and NFAT resulting in DC activation. In contrast, DNGR-1 is a homodimer stabilised by a disulphide bond in its neck region. Binding of DNGR-1 to F-actin on dead cells also leads to SFK-dependent hemITAM phosphorylation and Syk activation, but this does not transmit to NF-κB and does not induce DC activation. Rather, DNGR-1 signalling appears to regulate endosomal maturation to favour presentation of dead cell-associated antigens by MHC class I molecules, a process known as cross-presentation.

Figure 2. Role of the Syk-coupled CLRs, Dectin-1 and DNGR-1, in DCs.

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fate mapping is a powerful means of genetically tracing the DC lineage in vivo (Schraml et al., 2013). However, the receptor is also expressed at much higher levels by a particular sub-type of fully differentiated DCs known as DC1 that is key for inducing antiviral and antitumour CD8+ T-cell responses. Interestingly, pre-clinical studies suggest that targeting antigens to DC1 via antibodies to DNGR-1 is a promising approach for inducing or boosting antitumour immunity. Therefore, receptors utilised by DCs to sense cell damage or pathogens can be useful targets for manipulating the cells in the context of vaccination or immunotherapy. Thus, study of the mechanisms utilised by the immune system to detect pathogens and cell damage not only can lead to basic discoveries but can also have translational application.

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Conflict of interest
The author declares that he has no conflict of interest.

References

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Caetano Reis e Sousa is awarded the 2017 Louis-Jeantet Prize for Medicine for his contribution to our understanding of the mechanisms by which the immune system senses pathogen invasion and tissue damage. He is a Senior Group Leader at The Francis Crick Institute, Professor of Medicine at Imperial College London and Honorary Professor at both University College London and King’s College London.