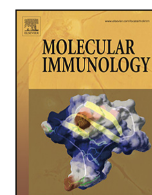
Molecular Immunology 86 (2017) 16–22

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm



# Intercellular communication for innate immunity

Tan A. Nguyen[a,b,*], Ken C. Pang[a,c,d,e,1], Seth L. Masters[a,b,1]

[a] *Inflammation Division, The Walter and Eliza Hall Institute of Medical Research, Parkville 3052, Australia*
[b] *Department of Medical Biology, The University of Melbourne, Parkville 3010, Australia*
[c] *Murdoch Children's Research Institute, Parkville, VIC, Australia*
[d] *Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia*
[e] *Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia*

ARTICLE INFO

*Article history:*
Received 17 August 2016
Received in revised form 6 October 2016
Accepted 11 October 2016
Available online 18 October 2016

*Keywords:*
Innate immunity
Intercellular transfer
Inflammasome
Exosomes
STING
Type I interferon

ABSTRACT

An effective innate immune response relies on the detection of pathogen associated molecular patterns (PAMPs) by various host pattern recognition receptors (PRRs) that result in the production of pro-inflammatory cytokines and chemokines. Viruses and bacteria have co-evolved with the immune system and developed multiple strategies to usurp or circumvent host machinery and blunt the innate immune response in infected cells. Recently, it has become apparent that infected or dying cells can transmit PAMPs and host PRR signalling proteins to uninfected bystander cells to thereby bypass pathogen evasion strategies, and potentiate innate immune signalling. This bystander activation of innate immunity represents an alternative method by which the host can control infections via cell-to-cell communication. In this review, we discuss what is currently known about the intercellular transfer of pathogen- or host-derived RNA, DNA and proteins from infected cells to neighbouring cells and how this impacts on host innate immunity.

© 2016 Elsevier Ltd. All rights reserved.

## 1. Introduction

During infection, the initiation of the innate immune response is a critical step to control the spread of invading pathogens and to direct the adaptive immune response. Viral or bacterial derived nucleic acids and peptides serve as potent pathogen associated molecular patterns (PAMPs) that are sensed by multiple host pattern recognition receptors (PRRs) to activate various adaptor proteins and induce the production of type I interferons (IFNs) as well as other pro-inflammatory cytokines including TNF, IL-6, IL-12 and IL-1ß via NF-κB signalling. To that end, multiple PRRs exist, each one unique in both their ligand specificity and subcellular localisation. For example, endosomal toll like receptors (TLRs) are ideally placed to detect foreign nucleic acid and proteins that have been internalised via endocytosis from the extracellular space, whereas cytoplasmic RIG-I-like receptors (RLR) and NOD-like-receptors (NLRs) are important for the detection of PAMPs within productively infected cells.

Given the importance of these receptors to sense the presence of PAMPs and thus help limit and clear infections, many pathogens have developed mechanisms to inhibit, evade and even hijack these pathogen sensing pathways in order to further their replication and persistence within the infected host (Beachboard and Horner, 2016; Chan and Gack, 2016). In recent years, there is emerging evidence that infected host cells are able to transfer not only PAMPs but also host derived signalling molecules to non-infected cells to facilitate bystander activation of innate immunity, and thus avoid pathogen defences. This newly described form of innate immune intercellular signalling likely represents a host quorum sensing mechanism whereby an initial stimulation from an infected cell results in activation of multiple bystander cells to mount a self-sustaining and even amplified innate immune response. In this review, we discuss the current knowledge regarding the intercellular transfer of pathogen- and host-derived material to neighbouring uninfected cells to overcome inhibition of innate immunity and thus enable the host to regain the upper hand in the ongoing arms race with invading microbes.

* Corresponding author at: The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville 3052, Victoria, Australia.
*E-mail address:* nguyen.t@wehi.edu.au (T.A. Nguyen).

[1] These authors contributed equally.

http://dx.doi.org/10.1016/j.molimm.2016.10.002
0161-5890/© 2016 Elsevier Ltd. All rights reserved.

## 2. Nucleic acids

### 2.1. Exosomal transfer of viral RNAs

Viral RNAs have long been considered an important danger signal in the detection of viral infection (Jensen and Thomsen, 2012; Nellimarla and Mossman, 2014). Single stranded RNAs (ssRNAs) that are internalised from the extracellular space are detected by endosomal toll like receptors 7 and 8 (TLR7 and TLR8) and lead to the activation of the adaptor protein MyD88 (Akira and Takeda, 2004; de Bouteiller et al., 2005; Diebold et al., 2004; Heil et al., 2004). Viral double-stranded RNA (dsRNA) is produced as a by-product of replication and is readily detectable in cells infected with dsDNA, dsRNA and ssRNA viruses (Son et al., 2015; Weber et al., 2006). Internalised dsRNAs are detected via toll like receptor 3 (TLR3) which then signals through the cytoplasmic adaptor protein TRIF (Alexopoulou et al., 2001; Leonard et al., 2008). dsRNAs produced within the cytosol of infected cells during viral replication are sensed via the cytosolic RIG-I-like receptors, consisting of retinoic inducible gene 1 (RIG-I) and melanoma differentiation associated protein 5 (MDA-5) (Bruns and Horvath, 2014; Gitlin et al., 2006; Kato et al., 2006), which in turn trigger the oligimerisation of mitochondrial antiviral signalling protein (MAVS) (Hou et al., 2011; Seth et al., 2005). Upon binding of their respective ligands, all of the aforementioned PRRs culminate in the production of type I IFN. Accordingly, multiple viruses are known to have evolved multiple strategies to inhibit RNA sensing by the infected host cell machinery either by directly binding/sequestering the RNA or by inhibiting the function of the various host machinery (Chan and Gack, 2016; Davis et al., 2014; Ding et al., 2013; Sànchez and Mohr, 2007; Uchida et al., 2014).

Recent evidence has suggested that host cells have developed mechanisms whereby viral RNAs are released by virally infected cells and are transferred to neighbouring uninfected cells resulting in bystander innate immune activation. In particular, there is increasing evidence that the transfer of viral RNAs via exosomes enable host cells to limit and control viral spread (Fig. 1A). Exosomes are membranous vesicles ranging from 40 to 100 nm in diameter that originate in late endosomes following the inward budding of the endosomal membrane to form intracellular multivesicular bodies (MVBs) (van der Pol et al., 2012). These cargo-filled MVBs are then released into the extracellular space upon fusion of the plasma membrane via an endosomal sorting complexes required for transport (ESCRT) mediated mechanism (Janas et al., 2015). Exosomes are readily detectable in a wide range of biological fluids, including blood, cerebrospinal fluid, urine, semen, synovial fluid and breast milk and have been implicated in the regulation of a number of biological processes (Ratajczak and Ratajczak, 2016). In the context of viral infections, exosomes have been shown to contain viral mRNAs and microRNAs (miRNAs) and facilitate the transfer of these molecules to neighbouring uninfected cells to mediate immunity (Kalamvoki and Deschamps, 2016; Ratajczak and Ratajczak, 2016; Schwab et al., 2015). Up until recently it was predominantly believed that the effects of exosomal RNA transfer during viral infections was limited to the regulation of host gene transcription but it has now become apparent that the transfer of viral RNAs can also act as ligands for multiple PRRs and lead to the production type I IFNs as described below.

Hepatitis C virus (HCV) is a ssRNA virus that is able to effectively inhibit the innate immune response in hepatic cell lines in vitro, but in vivo infection induces a potent type I IFN response in the infected liver (Bigger et al., 2004; Su et al., 2002; Tasaka et al., 2007). This observation suggested that type I IFN produced during HCV infection was mediated via bystander activation of surrounding non-hepatic cells within the liver. Indeed, subsequent work showed that HCV infected cells activated plasmacytoid dendritic cells (pDCs) to produce type I IFN via TLR7. Importantly, using HCV sub-genomic replicon (SGR) cells, they demonstrated that this type I IFN production was dependent on active HCV RNA replication but independent of virus-particle assembly and release of free virus particles (Takahashi et al., 2010). This implied a cell-to-cell RNA transfer mechanism in which HCV infected cells were able to induce the production of type I IFNs in uninfected pDCs. Further work revealed that the transfer of HCV RNA from infected hepatocytes to pDCs was mediated by exosomal release in an ESCRT dependent manner (Dreux et al., 2012). They also showed that purified exosomes from HCV infected cells were able to activate pDCs and this process is suppressed by exosome release inhibitors. Taken together, these studies provide evidence for the importance of exosomal RNA transfer in the bystander production of type I IFN during HCV infection.

Epstein Barr virus (EBV) is a large DNA herpesvirus which is able to asymptomatically persist in infected host B cells by minimising transcriptional activity to evade innate immune detection. During latent infection, EBV produces the long noncoding RNAs, EBER1 and EBER2, which form long dsRNAs with an uncapped 5′ triphosphate (5’ppp) that can serve as ligands for TLR3 and RIG-I respectively (Li et al., 2015; Samanta et al., 2006). Recently, it was discovered that latently infected B cells preferentially sort and export 5’ppp EBER1 dsRNAs into exosomes which are then subsequently internalised by neighbouring DCs to produce type I IFN in a RIG-I-dependent manner (Baglio et al., 2016). Importantly, this study demonstrates a host response mechanism that selectively transfers 5’ppp dsRNAs from infected cells to uninfected cells during a latent infection to trigger cytoplasmic RLR signalling in bystander DCs.

Human immunodeficiency virus type 1 (HIV-1) consists of a ssRNA viral genome that comprises 9 different proteins as well as multiple regulatory noncoding RNAs that can regulate host gene expression (Schopman et al., 2012). One of these RNAs is the trans-activating response element (TAR) that forms a 57 base stem loop structure that is abundant in both cell culture supernatants and blood during infection (Sampey et al., 2016). Interestingly, this study also demonstrated that HIV TAR miRNA was incorporated into exosomes within infected cells and exported to uninfected primary macrophages to potently induce the production of pro-inflammatory cytokines such as IL-6 and TNFß in a TLR7-8 and NF-κB dependent manner. Full length TAR RNAs were also isolated in exosomes from infected cells and were able to bind to TLR3 to induce the production of type I IFN. It will be interesting to determine if these RNA species can also activate the cytoplasmic RLRs to enhance type I IFN production in HIV infected cells.

### 2.2. Extracellular transport of dsDNA

Endosomal and cytosolic detection of viral or bacterial dsDNA are also able to induce a potent type I IFN response via the TLR9 and STING/cGAS pathways respectively. TLR9, which is predominantly expressed in pDCs, recognises internalised dsDNA with hypomethylated CpG islands and signals via the adaptor molecular molecule MyD88 culminating in the activation of IRF7 and production of type I IFNs (Akira and Takeda, 2004; Hemmi et al., 2000). Viral or bacterial-derived dsDNA that enters the cytoplasm is sensed by cyclic GMP-AMP synthase (cGAS) (Sun et al., 2013). Upon engagement of dsDNA, cGAS catalyses the production of the second messenger 2’3’-cyclic GMP-AMP (cGAMP) which subsequently activates stimulator of interferon genes (STING) (Ishikawa and Barber, 2008; Ishikawa et al., 2009). Activation of the cGAS/STING axis elicits a robust type I IFN response to initiate an antiviral state.

While innate immune sensing of dsDNA is commonly associated with foreign viral and bacterial DNA, certain human autoimmune diseases, such as systemic lupus erythematous (SLE) have been shown to produce high levels of self dsDNA that are released

Download English Version:

https://daneshyari.com/en/article/5592168

Download Persian Version:

https://daneshyari.com/article/5592168

Daneshyari.com