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SARS coronavirus and innate immunity

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Abstract

The emergence of the highly pathogenic SARS coronavirus (SARS-CoV) has reignited interest in coronavirus biology and pathogenesis. An emerging theme in coronavirus pathogenesis is that the interaction between specific viral genes and the host immune system, specifically the innate immune system, functions as a key determinant in regulating virulence and disease outcomes. Using SARS-CoV as a model, we will review the current knowledge of the interplay between coronavirus infection and the host innate immune system in vivo, and then discuss the mechanisms by which specific gene products antagonize the host innate immune response in cell culture models. Our data suggests that the SARS-CoV uses specific strategies to evade and antagonize the sensing and signaling arms of the interferon pathway. We summarize by identifying future points of consideration that will contribute greatly to our understanding of the molecular mechanisms governing coronavirus pathogenesis and virulence, and the development of severe disease in humans and animals.

Keywords: SARS coronavirus; Innate immunity; Interferon; RNA virus

1. Introduction

Viral interactions with the innate immune system play a central role in determining the outcome of infection. Early control of viral replication by type I interferons (IFN), complement proteins, and other innate immune mediators limit viral spread within the host during the early phases of the disease (Katze et al., 2002). The early innate response also plays an important role in shaping the downstream adaptive immune response, however an overactive innate immune response can also result in immune pathology and subsequent tissue damage (reviewed in Garcia-Sastre and Biron, 2006). Within the last decade, it is clear that many viruses encode specific gene products that antagonize both the innate and acquired arms of the immune response (Andrejeva et al., 2004; Basler et al., 2000; Cruz et al., 2006; Gale et al., 1997; Meylan et al., 2005; Parisien et al., 2001; Park et al., 2003; Symons et al., 1995; Xiang et al., 2002; Ye et al., 2007). Therefore, a detailed knowledge of how specific viruses interact with the host innate immune system is essential for understanding the molecular mechanisms regulating virulence, pathogenesis and disease outcomes.

Coronavirus interactions with the adaptive immune system have been studied in great detail, however, surprisingly little is known about how these viruses interact with the innate immune system (La Bonnardiere and Laude, 1983). Although early studies indicated that mutations in the M glycoprotein of transmissible gastroenteritis virus (TGEV) modulated type I IFN responses, suggesting that coronaviruses may encode a novel set of gene functions that interface with the host innate immune response, little effort focused on unraveling the details of coronavirus innate immune interactions (Charley and Laude, 1988; La Bonnardiere and Laude, 1983). Early experiments showed that variants of mouse hepatitis virus (MHV) are differentially susceptible to IFN. This may contribute to different pathogenic outcomes, however little additional experimentation was performed (Taguchi and Siddell, 1985). The SARS coronavirus (SARS-CoV) epidemic of 2003 rekindled a high level of interest in how coronaviruses interact with the host and whether interactions with the host innate immune system are important in both the control of viral infection or if these interactions lead to virus-induced disease.

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In this article, we will discuss two components of the innate immune response that are clearly important for SARS-CoV induced disease: (1) interactions with macrophages (MP) and dendritic cells (DC), which shape the early innate and adaptive immune responses within the lung, while also potentially contributing to virus-induced immune pathology, and (2) the type I IFN system, an essential component of the early innate response to viral infections that appears to be blocked or evaded by SARS-CoV and other coronaviruses.

2. Dendritic cells and macrophages

Dendritic cells and macrophages are first line components of the innate immune network. DCs, which can be grouped into plasmacytoid (pDC) and myeloid types (mDC), play important roles in driving both innate and adaptive immune responses to viral pathogens (Akira and Hemmi, 2003; Ito et al., 2005; Nakano et al., 2001). pDCs rapidly respond to viruses or their derivatives to produce large amounts of type I IFN, which can induce direct antiviral responses and also modulate other components of the innate and adaptive immune response, such as natural killer cells and CD8 T cells (Colonna et al., 2004; Diebold et al., 2003; Cella et al., 1999; Siegal et al., 1999). Though less robust than pDCs, mDCs can also secrete large amounts of type I IFN (Laiosa et al., 2006). However, mDCs also play a major role in stimulating acquired immune responses through their capacity as antigen presenting cells and producers of a wide array of immuno-modulatory cytokines (Laiosa et al., 2006). MPs are potent producers of type I IFNs and other pro-inflammatory cytokines that induce antiviral protection while also potentially contributing to immune pathology associated with viral infections (Diamond et al., 2003). Analysis of the impact of DCs and MPs on SARS-CoV infection will be discussed below.

3. The type I IFN system

Since its discovery 50 years ago by Isaacs and Lindemann, the IFN system has come to be recognized as a crucial frontline defense against viral infection (Isaacs and Lindenmann, 1957). IFNs mediate direct antiviral effects that limit viral replication by activating/up-regulating several well defined antiviral effectors, including PKR and RNaseL, while also modulating other aspects of the innate and adaptive immune responses through the induction of a wide array of IFN inducible genes (ISGs) (Stark et al., 1998; Takaoka and Yanai, 2006). The number of pathogens that neutralize IFN, or other key components of the IFN system, illustrate that this system is essential for the control of a diverse array of viruses and bacteria. Perhaps the clearest indicator of how important this pathway is to antivi-

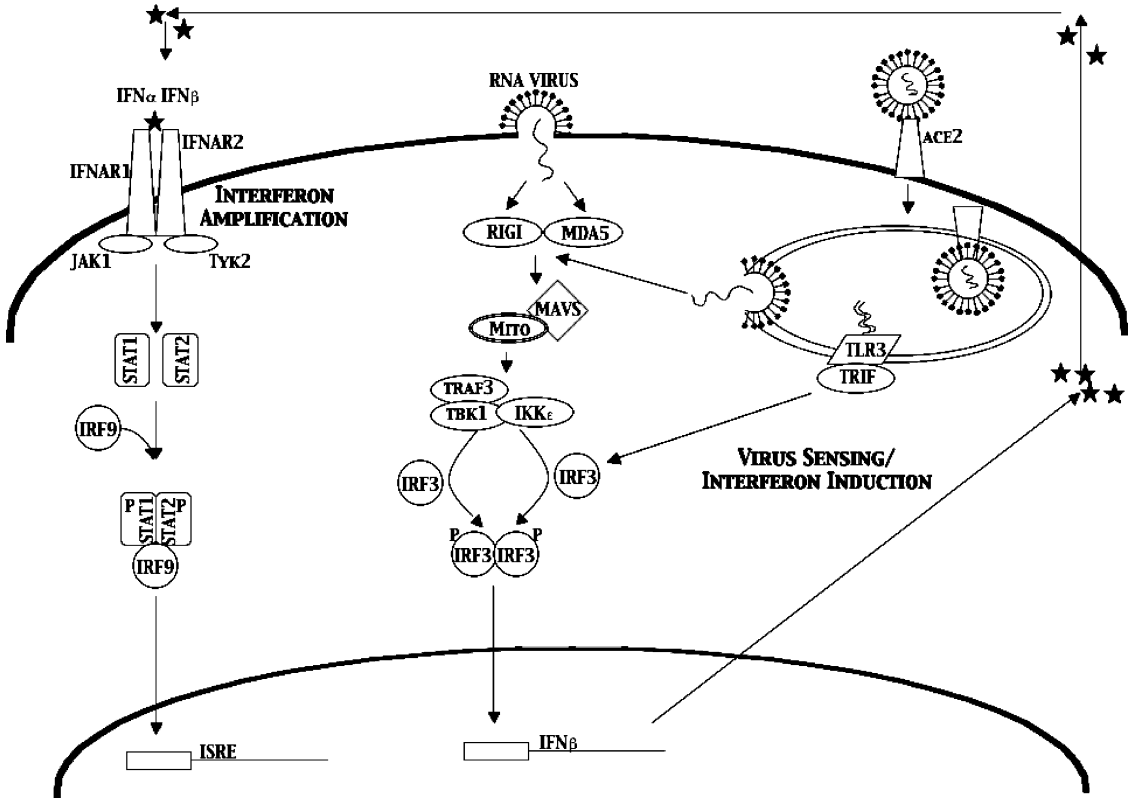

Fig. 1. IFN sensing and signaling pathway. RNA viruses are internalized through several mechanisms, either fusion with the plasma membrane or binding to a surface receptor (ACE2 for SARS-CoV, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) for MHV). That internalization exposes the genomic RNA to the dsRNA sensing machinery in the cell; TLR3, RIGI and MDA5. These proteins signal the IRF-3 cascade leading to induction of IFNb and production of secreted IFNβ protein. That IFNβ protein can then bind IFNα/β receptors (INFAR1) on the surface of the same cell or surrounding cells. This activates the Stat1 signaling pathway to activate the many anti-viral genes found with ISRE promoter elements.