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REVIEW ARTICLE

Respiratory Syncytial Virus (RSV) Modulation at the Virus-Host Interface Affects Immune Outcome and Disease Pathogenesis

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The dynamics of the virus-host interface in the response to respiratory virus infection is not well-understood; however, it is at this juncture that host immunity to infection evolves. Respiratory viruses have been shown to modulate the host response to gain a replication advantage through a variety of mechanisms. Viruses are parasites and must co-opt host genes for replication, and must interface with host cellular machinery to achieve an optimal balance between viral and cellular gene expression. Host cells have numerous strategies to resist infection, replication and virus spread, and only recently are we beginning to understand the network and pathways affected. The following is a short review article covering some of the studies associated with the Tripp laboratory that have addressed how respiratory syncytial virus (RSV) operates at the virus-host interface to affects immune outcome and disease pathogenesis.
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INTRODUCTION

People of all ages experience viral respiratory tract infections each year, with young children, the elderly, and immune compromised most severely afflicted (1). Epidemiological surveys of diagnostic studies have identified common agents that include respiratory syncytial virus (RSV), influenza viruses (flu), human metapneumovirus (HMPV), rhinoviruses (RV) parainfluenza virus (PIV), adenovirus (Ad), and human coronavirus (hCoV) (2-4). Common to these viruses are their ability to infect airway epithelial cells, co-opt host cell proteins to facilitate infection, modulate both innate and adaptive immune responses, and to mediate proinflammatory responses which contribute to disease pathogenesis. Despite the airways constantly being challenged, airway defense mechanisms generally protect from disease with minimal clinical consequences.

VIRUS-HOST INTERACTION

It is well-understood that airway epithelial cells possess innate immune functions that control infection and replication, and recruit, activate and facilitate expansion of adaptive immune responses to facilitate clearance of infected epithelial cells (5-7). This response is in part mediated by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) that act as viral sensors of infection (8,9). The distribution of TLRs has been shown to depend on the type of cells and their localization (10,11). TLR4 has been shown to be important in sensing RSV infection and its expression is linked to dis-

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Abbreviations: Ad, adenovirus; flu, influenza virus; hCoV, human coronavirus; HMPV, human metapneumovirus; MDA5, melanoma differentiation-associated protein 5; PIV, parainfluenza virus; PRRs, pattern recognition receptors; RIG-I, retinoic acid-inducible gene 1; RSV, respiratory syncytial virus; RV, rhinovirus; SOCS, suppressor of cytokine signaling protein

ease outcome (12-14), however all viruses are sensed via PRRs. RNA from viruses such as influenza and RSV is rapidly detected during replication by intracellular PRRS such as RIG-I and MDA5 (15). These viruses induce activation of the IFN-promoter via RIG-I signaling, and this signaling has a role in the antiviral response to infection (16,17).

RSV interaction with host airway epithelium leads to the induction cytokines, chemokines and antiviral agents. This response occurs very early, i.e. before the expression of viral proteins (7). For example, TLR4 is expressed on the cell surface of respiratory epithelial cells, and responds to the RSV fusion protein (12,13). TLR4 signals through MyD88 to activate NF-kappa B, and via TRIF, to activate IRF-7, and cytokine, chemokine and IFN expression (18). The resulting cytokine cascade leads to a pro-inflammatory response that must be negatively regulated, primarily through suppressor of cytokine signaling (SOCS) proteins (19-21). Recently, a novel class of antiviral cytokines was discovered and classified as type III IFNs: IFN-lambda1 (IL-29), IFN-lambda2 (IL-28A), and IFN-lambda3 (IL-28B). (22,23). IFN lambdas are potent antivirals affecting RSV and influenza virus replication, a feature that may also affect influenza reassortment in susceptible cells (24).

ROLE FOR RSV G PROTEIN IN MODULATING HOST RESPONSES

Airway epithelial cells are important in recruiting and activating immune cells in the defense of viral infection. These cells express patterns of Th1- and Th-2 type cytokines and chemokines having a wide range of effects on both innate and adaptive processes. RSV interferes with the host antiviral cytokine response (7). Studies have shown that RSV nonstructural proteins, NS1 and NS2 antagonize the IFN response in infected epithelial cells and affect dendritic cell maturation (25-27). The RSV G protein has also been shown to affect the pattern and magnitude of cytokines and chemokines expressed in the lung following infection of mice (28-30), as well as the trafficking of immune cells (30-32). Recent evidence indicates that RSV G protein governance of the host cell response is associated with let-7 microRNA (miRNA) expression mediated by the central conserved (CX3C) region in the G protein (33). Significantly, RSV infection of a human alveolar epithelial cell line (A549) induced five miRNAs (let-7f, miR-24, miR-337-3p, miR-26b and miR-520a-5p) and repressed two miRNAs (miR-198 and miR-595) whose targets included cell-cycle genes (CCND1, DYRK2 and ELF4), a chemokine gene (CCL7) and SOCS3. Modulating let-7 miRNA levels with miRNA mimics and inhibitors affected RSV replication indicating that RSV modulates host miRNA expression to affect the outcome of the antiviral host response, and this was mediated in part through RSV G protein expression.

Numerous mouse and some human studies have revealed that RSV proteins modulate many aspects of the immune response to infection, particularly the RSV G protein (7). A primary contributor to G protein immune modulation and disease pathogenesis is CX3C chemokine mimicry mediated by the CX3C motif in the central conserved region of the G protein (34). The G protein binds to the fractalkine receptor, CX3CR1, and G protein CX3C-CX3CR1 interaction facilitates virus infection, modulates leukocyte chemotaxis, and adversely affects RSV-specific cytotoxic T cell responses, and enhances disease pathogenesis (31,34-37). Several studies have shown that antibodies that block G protein CX3C-CX3CR1 interaction protect against G protein-associated pulmonary inflammation, disease outcome, and that they are neutralizing and protective against RSV challenge (38-42). The importance of having anti-RSV G protein antibody responses were revealed in a human study showing that anti-RSV G protein antibody responses after recent RSV infection or vaccination are associated with inhibition of RSV G protein CX3C-CX3CR1 interaction and RSV G protein-mediated leukocyte chemotaxis (43). These findings suggest a vaccination strategy to target antibodies against the G protein could be efficacious. Indeed, it was shown that G protein vaccination to induce antibodies blocking the G protein CX3C-CX3CR1 interaction reduces pulmonary inflammation and virus replication in mice (38), and that mice immunized with RSV A2 G polypeptides generate antibodies that block binding of RSV A2 and B1 native G proteins to CX3CR1, and that these antibodies effectively cross-neutralize both A and B strains of RSV (44).

DEVELOPMENT OF DISEASE INTERVENTION STRATEGIES

Current disease intervention strategies for RSV are limited and largely ineffective, a feature true for influenza as well (45). Protection via vaccination has been unsuccessful for RSV, and is complicated for influenza by the rapid evolution linked to mutilation (antigenic drift) and reassortment (antigenic shift), features that mediate drug resistance (46). Thus, new disease intervention strategies are urgently required, and an important

first step is to increase our understanding of the virus-host interface. To do this, studies have been performed to harness the power of RNA interference (RNAi) through the use of small interfering RNA (siRNA) to either target the virus genes directly for silencing (47-49), or the host genes required for virus replication (50-53). Controlling RNAi can be used to provide a powerful platform-enabling technology that will allow for the identification and validation of virus-host interactions and pathways (50,51,54,55). The pro- and anti-viral genes discovered by RNAi screening (53,56,57), provides an opportunity to transition the findings toward translational disease intervention approaches such as creation of novel therapeutics, drug repositioning, or create a new generation of vaccine cell lines capable of increased viral production.

FUTURE PERSPECTIVES

The airway epithelium has a central role in defense against respiratory virus infections by expression of antiviral and immune signals mechanisms that contribute to viral resistance and clearance. However, respiratory viruses have evolved strategies to subvert the defense mechanisms leading to cytopathogenesis, increased inflammatory responses, and disease. A thorough understanding of the mechanisms by which viruses modify innate and adaptive immune responses is needed to develop new therapeutic approaches to treat or prevent respiratory diseases caused by important human viral infections mediated by RSV and influenza viruses.

CONFLICTS OF INTEREST

The author has no financial conflict of interest.

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