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Immune responses in influenza A virus and human coronavirus infections: an ongoing battle between the virus and host

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Respiratory viruses, especially influenza A viruses and coronaviruses such as MERS-CoV, represent continuing global threats to human health. Despite significant advances, much needs to be learned. Recent studies in virology and immunology have improved our understanding of the role of the immune system in protection and in the pathogenesis of these infections and of co-evolution of viruses and their hosts. These findings, together with sophisticated molecular structure analyses, omics tools and computer-based models, have helped delineate the interaction between respiratory viruses and the host immune system, which will facilitate the development of novel treatment strategies and vaccines with enhanced efficacy.

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The structure of the respiratory tract facilitates gas exchange between the exterior environment and interior milieu of the host, while it is a susceptible target and feasible gateway for diverse invasive pathogens. The immune system consists of multiple physical, cellular and molecular components and plays a crucial role in the host defense against microbial invasion. In this mini-review, we will summarize recent findings in respiratory virus immunology research focusing on influenza A virus (IAV) and coronaviruses including SARS (Severe Acute Respiratory Syndrome)-CoV and MERS (Middle East Respiratory Syndrome)-CoV. We will also discuss some key questions that remain to be answered and potential applications of our current knowledge to prevent and treat respiratory virus infection in the clinic.

Immune response: protective or pathogenic?

The host immune system is composed of multiple tissues, cells and molecules and can protect hosts from infectious diseases by recognizing and eliminating pathogens efficiently. In one example, our studies of mice infected with SARS-CoV showed that the severity of SARS correlated with the ability to develop a virus-specific immune response, while inhibitory alveolar macrophages and inefficient activation of dendritic cells (DCs) delayed this process and aggravated disease [1]. In another study, Channappanavar *et al.* further demonstrated that dysregulated type I interferon (IFN) and inflammatory monocyte-macrophage responses led to lethal pneumonia in SARS-CoV-infected mice [2]. In support of these data, inhibition of nuclear factor-kappaB (NF-κB)-mediated inflammation in SARS-CoV-infected mice increased survival [3]. Similar to their pathological roles in coronavirus infections, inappropriate or dysfunctional immune responses such as overactivation of NACHT, LRR and PYD domains-containing protein 3 (NLRP3), high-mobility group box 1 protein (HMGB-1) and interleukin-1beta (IL-1β), have been implicated in host tissue destruction [4–8] and persistent pathological changes in IAV-infected hosts [9]. Expression of the complex of tumor necrosis factor (TNF) superfamily 10 (TNFSF10), histone deacetylase 4 (HDAC4) and HDAC5 negatively correlated with the levels of TNF-α, NF-κB and cyclooxygenase 2 (COX-2) and increases in their expression was correlated with improved prognosis of IAV-infected hosts [10]. In addition to their cell-intrinsic properties, lung macrophage and monocyte heterogeneity in localization in IAV infections also contributed to differences in outcomes [11].

Both adaptive and innate immune responses are required for host protection

The adaptive immune response efficiently recognizes and destroys specific pathogens [12], and thus restricts the spread of pathogens usually without causing significant non-specific inflammation. However, despite intensive investigations and substantial advances in past decades, questions about the initiation, development, regulation, contraction and re-activation of adaptive immune responses upon pathogen challenge remain areas of research [13–16,17•,18–29,30•,31,32••,33] (summarized in Table 1.)

The innate immune system is responsible for initial responses to pathogens and is critical even in the context

Table 1

Recent findings related to adaptive immune responses against IAV and CoV infections

Response type	Virus strain	Major findings	Ref.
B cell/antibody response	IAV	Repertoire diversity is a driving force behind IAV-specific B-cell immunity.	[13]
		Broadly neutralizing antibodies generally target conserved functional regions on HA.	[21]
		Binding of antibody to an epitope masks the epitope and prevents the stimulation and proliferation of specific B cells.	[30]
	MERS-CoV	Recombinant receptor-binding domains of multiple MERS-CoVs induce cross-neutralizing antibodies against divergent human and camel MERS-CoVs.	[28]
T cell response	IAV	Vaccine-generated lung-resident memory CD8 T cells provide heterosubtypic protection to IAV infection.	[31]
		Potential challenges in translating protective memory CD4 T cell responses in experimental animal models to patients.	[19]
	MERS-CoV	MERS-CoV efficiently infects human primary T cells and induces apoptosis.	[14]
	SARS-CoV	Memory T cell responses targeting the SARS coronavirus persist for up to 11 years postinfection.	[23]
Crosstalk between immune components	IAV	Cooperativity between CD8+ T cells, non-neutralizing antibodies, and alveolar macrophages is important for heterosubtypic IAV immunity.	[20]
		Antibody specificity plays an important role in the regulation of ADCC. Cross-talk among antibodies of varying specificities determines the magnitude of Fc receptor-mediated effector functions.	[17]
		IgE cross-linking impairs monocyte antiviral responses and inhibits IAV-driven Th1 differentiation.	[27]
	MERS-CoV	Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses.	[32]
Maintenance of immune memory	IAV	Levels of neutralizing antibodies against previously encountered IAV strains ('original antigenic sin') increase over time.	[22]
		Low levels of circulating CD8+ T effector and central memory cells are associated with IAV infection severity upon re-challenge.	[16]
		Regimen of a CTL-based vaccine/vaccine-component benefits from periodic boosting to prevent clinically evident IAV infection.	[26]
		Multifunctional CD4+ T-cell responses were maintained only in patients with recurrent infections.	[29]
Immunopathology	IAV	IAV-specific CD8+ T cells exacerbate infection following high dose challenge of aged mice.	[25]
		Different subsets of CD8+ T cells interact with subsets of innate cells through costimulatory molecules to balance protection and immunopathology.	[15]
		Identification of protective and pathogenic T cell epitopes in IAV H7N9-infected patients.	[18]
Immunotherapy	IAV, CoV	High titer anti-IAV or CoV sera may be useful prophylactically and therapeutically in exposed and infected patients.	[24,33]

of vaccinated IAV individuals or mice, in which hemagglutinin (HA), neuraminidase (NA) and glycosylation pattern mutations [24], might hinder an effective antibody and T cell response. The contribution of innate immunity to immune defense is not limited in direct anti-viral effects [34]. Innate immune signals such as IFN-I not only interact with other innate immune elements such as monocytes and type-II IFN to limit IAV-caused tissue inflammation [35], but also directly modulated the adaptive immune response. Both IFN-I and toll-like receptor 7 (TLR7) were also found to shape B cell-mediated immune responses against IAV [36], while RIG-I signaling was critical for efficient polyfunctional T cell responses [37]. Moreover, the increased mortality of IAV-infected mice in the absence of mitochondrial antiviral signaling (Mavs) and TLR7 was found to independent of viral load or myeloid differentiation primary response 88 (MYD88)-dependent signaling but dependent on secondary bacterial burden, caspase-1/11, and neutrophil-dependent tissue damage [38••].

As for innate immune cells, a population of lung-resident innate lymphoid cells (ILCs) in mice and humans that expressed CD90, CD25, CD127 and ST2 was found to contribute to airway epithelial integrity and its depletion resulted in diminished lung function and impaired airway remodeling [39]. In other reports, pulmonary endothelial cells [40], lung microvascular endothelial cells [41], neutrophils [42], eosinophils [43], lung mast cells [44], plasmacytoid dendritic cells (pDC) and invariant natural killer cells (iNKT) [45] were all identified as therapeutic targets in severe IAV and CoV infections. However, the involvement of innate immunity in specific populations, such as infants [46•], children [47], the aged [48] and

patients suffering from chronic airway diseases [49] or frequent re-infection with IAV [50•], needs further investigations.

With the increasing accumulation of knowledge of molecular interactions between host cells and viruses, additional host molecules and normal biological processes [51–65,66•,67–69] were found to participate in the viral replication cycle (summarized in Table 2). To clarify the roles of these molecules and processes in virus infection, host genetic determinant screening [70–72], immunomics and Public Health Omics [73], host lipid omics [74••] and characterization of the epigenetic landscape [75] were used to supplement conventional analyses. Moreover, information about interaction between immune and parenchymal cells also facilitated efforts to optimize antiviral response while reducing unwanted side effects [76•,77•]. Computer modeling of host-pathogen interactions is likely to be used more in the future, as additional parameters are identified. Thus, computer modeling helped in prediction of clinical outcomes, demonstrating key roles for the innate immune response and the interval between infections [78]. These novel methodologies are likely to provide additional approaches to identifying targets for novel antiviral therapies.

Immune evasion by respiratory viruses

The IAV non-structural protein NS1, perhaps the best-characterized viral immunoevasive protein, binds double-stranded RNA (dsRNA) to inhibit host innate immune responses [79–81]. Recently, NS1 was also found to bind cellular dsDNA and prevent the loading of transcriptional machinery onto the DNA, thus attenuating expression of antiviral genes [82]. Meanwhile, the C-terminal domain of NS1 blocked IFN-beta production by targeting TNF receptor-associated factor 3 (TRAF-3) [83], while other domains of the protein inhibited interferon regulatory transcription factor 3 (IRF3) [84] and RNA-dependent protein kinase (PKR) activation [85]. Another IAV protein, neuraminidase (NA), was shown to remove sialic

Table 2

Recent findings related to intrinsic molecules and biological processes involved in IAV and CoV infectionss.

Molecules/processes	Virus strain	Major findings	Ref.
Cell cycling proteins	IAV	Competitive inhibition of IAV M1–M2 interaction by cyclin D3 impairs infectious virus packaging, resulting in attenuation	[57]
Apoptosis-related signals	IAV	Apoptosis signaling modulates IAV propagation, innate host defense, and lung injury.	[60]
Sex hormones-related signals	IAV	Progesterone-based contraceptives reduce adaptive immune responses and protection against subsequent IAV infections.	[59]
	SARS-CoV	Male mice were more susceptible to SARS-CoV infection compared with age-matched females, while estrogen receptor signaling played a critical role in protecting females from SARS-CoV-mediated pathogenesis.	[53]
CHD chromatin remodeler	IAV	CHD1 is a proviral regulator of IAV multiplication.	[63]
Nuclear import and export machinery	IAV	IAV have evolved different mechanisms to utilize importin-alpha isoforms, affecting importation on both sides of the nuclear envelope.	[65]
		Activation of the interferon induction cascade by IAV requires viral RNA synthesis and nuclear export.	[61]
		Human heat shock protein 40 promotes IAV replication by assisting in the nuclear import of viral ribonucleoproteins.	[52]
		Preferential usage of importin-alpha7 isoforms by seasonal IAV in the human upper respiratory tract makes it a target of selective pressure.	[64]
Vesicular trafficking	IAV	IAV infection modulates vesicular trafficking and induces Golgi complex disruption.	[68]
		IAV enhances its propagation through modulating Annexin-A1 dependent endosomal trafficking.	[51]
		IAV ribonucleoproteins modulate host recycling by competing with Rab11 effectors.	[67]
	SARS-CoV	A predicted beta-hairpin structural motif in the cytoplasmic tail of the SARS-CoV E protein is sufficient for Golgi complex localization of a reporter protein and functions as a Golgi complex-targeting signal.	[54]
	MERS-CoV	CD9-facilitated condensation of receptors and proteases allows MERS-CoV pseudoviruses to enter cells rapidly and efficiently.	[56]
Exosome secretion	IAV	Exosome deficiency uncoupled chromatin targeting of the viral polymerase complex and the formation of cellular-viral RNA hybrids, which are essential RNA intermediates that license transcription of antisense genomic viral RNAs	[66]
Autophagy	IAV	Autophagy induction regulates IAV replication in a time-dependent manner.	[58]
	SARS-CoV	CoV nsp6 restricts autophagosome expansion.	[55]
Cellular senescence	IAV	Cellular senescence enhances viral replication.	[62]
Coagulation	IAV	Beneficial effects of inflammation-coagulation interactions during IAV infection	[69]

acid residues from NKp46, resulting in reduced recognition of HA and enhancing immune evasion of NK cells [86]. In addition, the IAV M2 protein was shown to reverse bone marrow stromal antigen 2 (BST-2)-mediated restriction of virus release via proteasomal pathways [87]. To evade the host immune system, IAV also inhibits host but not viral mRNA nuclear export [88], without impairing nuclear viral ribonucleoprotein (vRNP) import [89]. In addition, productive viral replication in macrophages resulted in decreased phagocytosis via downregulation of Fc receptors CD16 and CD32, potentially playing a role in IAV pathogenesis [90].

The crucial role of the IFN response makes it a preferred target for viral evasion. Besides NS1, multiple virus-encoded molecules including the nucleoprotein [64], the fusion peptide of HA2 (HA2-FP), HA1 and some variants of polymerase subunits PB1-F2, PB1, PB2, PA all counteract the interferon response [91]. Interestingly, some host cellular molecules are also utilized by IAV to block IFN expression. Using RNA interference, knockdown of a host factor, the double PHD fingers 2 gene (DPF2) [92], resulted in decreased expression of IAV proteins, by releasing IFN-β production from DPF2-mediated suppression [92].

The CoV endonuclease, nsp15, efficiently prevented activation of host cell dsRNA sensors including melanoma differentiation-associated protein 5 (Mda5), 2′–5′ oligoadenylate synthetase (OAS) and PKR [93,94•], while coronavirus-encoded proteases countered innate immunity, including the IFN response, through diverse pathways [95]. A recent investigation further showed that SARS-CoV nucleocapsid inhibited Type I interferon production by interfering with tripartite motif protein 25 (TRIM25)-mediated RIG-I ubiquitination [96].

Modulation of immune responses against respiratory virus infection: novel targets

Recent studies of cellular metabolic processes [97,98] and post-transcriptional protein modification [99,100] identified additional approaches used by viruses to evade host immune responses [101], and to facilitate optimal replication [102].

For example, IAV delayed apoptosis of infected cells by activating a signal transducer and activator of transcription 3 (stat-3)-related pathway, allowing prolonged replication [103]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2), critical for expression of reactive oxygen species (ROS), is often activated in endocytic compartments by RNA and DNA viruses, exacerbating virus-mediated pathogenicity [104•]. In addition to important roles for host proteins [105], the role of lipids [74••] in respiratory virus infections has also drawn increasing attention. Zhao *et al.* reported that age-related increases in prostaglandin D2 (PGD_2) expression in mouse lungs correlated with a progressive impairment in DC migration to DLNs, causing diminished T cell responses upon IAV or SARS-CoV infection [106]. In a subsequent study, Vijay *et al.* demonstrated a critical role for phospholipase A2 group IID (PLA_2G2D) in impaired DC migration to DLN and age-related susceptibility to SARS-CoV infection [107]. PLA_2G2D is upstream of PGD_2 in the prostaglandin synthesis pathway. Both molecules may be useful targets for anti-viral therapies.

As mentioned above, SARS-CoV nucleocapsid protein was reported to interfere with RIG-I ubiquitination [96], while decreased deubiquitination mediated by MERS-CoV nsp3 deubiquitinase also inhibited the host immune response [108]. Recently, Fehr *et al.* found that mutation of the macrodomain of nsp3, important for countering ADP-ribosylation, resulted in virus attenuation [109], while another report demonstrated that binding of the methyl donor S-adenosyl-L-methionine (SAM) to 2′-O-methyltransferase nsp16 enhanced MERS-CoV replication, promoting the recruitment of the allosteric activator nsp10 [110]. On the other hand, IAV induced host histone deacetylase 1 dysregulation in lung epithelial cells, inhibiting IAV infection [111] while NEDDylation (conjugation of a ubiquitin-like protein, neural precursor cell expressed developmentally down-regulated 8 (NEDD8)) of PB2 protein reduced its stability, suppressing IAV replication [112]. Nevertheless, the role of epigenetic modification during respiratory virus infection is not well understood; the application of phosphoproteomics to characterization of the human macrophage response to IAV infection [113] serves as a model for future studies.

Other putative targets for modulating the immune response are carbohydrates present on host and viral proteins. Recently, integrated omics and computational glycobiology revealed the structural basis for IAV glycan microheterogeneity and host interactions [114,115,116]. Glycosylation of the HA protein not only mediated virus entry into host cells [115–117], but also modulated IAV replication and transmission [118], and the immune response against the virus [119–121], thus representing a potential target for vaccine and drug development [122,123•].

Vaccine development update: establishing immune memory

Vaccines remain as the most efficient tools for preventing the occurrence and spread of viral respiratory diseases. Distinct from conventional adjuvants, novel reagents are being used to shape as well as augment the strength of the induced immune responses. Targeting IAV HA to the chemokine receptor, Xcr1, present on some dendritic cells enhanced protective antibody responses against the virus [124]. In addition, knowledge of the microbiota [125], and manipulation of apoptosis [126] and mTOR (mechanistic target of rapamycin) [127]-related signaling

pathways have been used to predict or modulate responsiveness and efficiency of vaccines, respectively. A major goal of IAV and CoV vaccine development is to develop vaccines able to induce broadly acting antibodies; these efforts require more precise definition of useful conserved protective antibody epitopes [128]. Further, monocyte-derived dendritic cells (moDCs) [129] dominated the activation of CD8+ T cells at late times after infection of C57BL/6 mice, triggering a switch in immunodominance from PA to NP-specificity. This differential expression of T cell epitopes has implications for DC-based vaccine design. Additionally, neutrophil-targeting [42] and Th1-targeting strategies [130] might help in establishing tissue-resident memory (TRM) and heterosubtypic immunity.

Inducing effective resident immune memory represents an ideal strategy for protecting the host from respiratory virus infection, especially at very early phases of virus invasion. Recent technical advances have facilitated distinguishing tissue-resident cell populations from those in the periphery. In a recent publication, airway memory CD4(+) T cells induced by a single conserved N protein-specific epitope present in both SARS-CoV and MERS-CoV mediated protection against challenge with either pathogen [131•]. IAV-specific resident memory CD8 cells in the upper respiratory tract or bronchoalveolar fluid provided superior protection compared to those in the lung, although some studies questioned whether these were truly resident memory as opposed to memory cells at these sites [132]. In a recent report, Slutter *et al.* delineated the dynamics of IAV-induced lung-resident memory T cells that underlies waning heterosubtypic immunity [133], illustrating the tight collaboration of resident and peripheral T cell memory in respiratory virus control. In the future, use of sophisticated cell sorting methods and mass spectrometric flow cytometry will provide more precise information about resident memory immune cells.

The IAV-specific antibody response is well known to be a key host factor in protection from subsequent challenge [134,135]. Recent work has identified nasopharyngeal protein biomarkers in immunized mice useful for predicting the severity and outcome of acute respiratory virus infection [136]. Other studies have identified an important synergistic role for immune responses in inducible bronchus-associated lymphoid tissue (iBALT) and draining lymph nodes for optimal IAV-specific CD4+ T cell responses [137]. In contrast, nasal-associated lymphoid tissues (NALTs) have been shown to support the recall but not priming of IAV-specific cytotoxic T cells [138•].

Co-evolution of respiratory viruses and the host

Genomics, next-generation sequencing [139] and single cell imaging and analysis [140] facilitated in-depth investigation of the evolution, recombination and spread of infectious pathogens and extend the scope of virology research. In addition to these molecular biology tools, methods such as analyses of DC responses [141] and digital cell quantification (DCQ), which combine genome-wide gene expression data with immune cell functional studies, will help identify immune cell subpopulations [142]. Especially critical for understanding the ecology of RNA viruses, such as IAV and CoV, will be obtaining respiratory samples from camels (MERS-CoV) and patients in both cross-sectional and longitudinal studies. These samples will be useful for identifying carriers and understanding virus evolution and transmission dynamics [143,144]. Recent analyses of MERS-CoV-infected camels [145] have also increased our knowledge of virus demography and evolution across diverse populations.

Although gene sequencing and crystallographic analyses have provided insight into the molecular evolution of IAV, the inability to predict future virus evolution remains an obstacle in managing epidemic and pandemic spread. Models using canalized evolutionary trajectory induced by selective dynamics [146], intra-host IAV dynamics [147], sequence based epidemiology [148], genomic diversification and adaptation during experimental serial passages [149] will help in the development of accurate prediction models. However, successful modeling to prospectively predict the emergence of new virus strains relies on solid experimental data obtained from field investigations. The standardization of protocols and normalization of data are key challenges in developing useful models of virus evolution.

Summary

This brief review outlines how the host immune response plays both protective and pathogenic roles in respiratory virus infections. To decrease the burden that respiratory viruses place on society, increased understanding of all aspects of the host immune response remains a critical research goal.

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