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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.

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-1B), 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...
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 be 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

| 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] |
| | MERS-CoV | 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] |
| | | 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] |
| | 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] |
| | | 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. | [17] |
| | | Cross-talk among antibodies of varying specificities determines the magnitude of Fc receptor-mediated effector functions. | [27] |
| | MERS-CoV | Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. | [32] |
| Crosstalk between immune components | 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] |
| | MERS-CoV | 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] |
| Maintenance of immune memory | IAV | IAV-specific CD8+ T cells exacerbate infection following high dose challenge of aged mice. | [25] |
| Immunopathology | IAV | Different subsets of CD8+ T cells interact with subsets of innate cells through costimulatory molecules to balance protection and immunopathology. | [15] |
| Immunotherapy | IAV, CoV | Identification of protective and pathogenic T cell epitopes in IAV H7N9-infected patients. | [18] |
| | | High titer anti-IAV or CoV sera may be useful prophylactically and therapeutically in exposed and infected patients. | [24,33] |
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

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

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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 posttranslational 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 (STAT3)-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 (PGD2) 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 (PLA2G2D) in impaired DC migration to DLN and age-related susceptibility to SARS-CoV infection [107]. PLA2G2D is upstream of PGD2 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 deubiquitinate also inhibited the host immune response [108]. Recently, Feht 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 glyco-biology 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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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Zhao J, Zhao J, Van Rooijen N, Perlman S: Evasion by stealth: inefficient immune activation underlies poor T cell response and severe disease in SARS-CoV-infected mice. PLoS Pathog 2009, 5:e1000636.

2. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S: Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016, 19:181-193.
3. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guaderrama JM, Fernandez-Delgado R, Fett C, Castaneda-Rodriguez C, Perilman S, Enjunes L: Inhibition of NF-κappaB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. J Virol 2014, 88:319-324.

4. Berri F, Le VB, Jandrot-Perrus M, Lina B, Riteau B: Switch from protective to adverse inflammation during influenza: viral determinants and hemostasis are caught as culprits. Cell Mol Life Sci 2013, 71:885-898.

5. Ong JD, Mansell A, Tate MD: Hero turned villain: NLRP3 inflammasome-induced inflammation during influenza A virus infection. J Leukoc Biol 2017, 101:863-874.

6. Shirey KA, Lai W, Patel MC, Pletneva LM, Pang C, Kurt-Jones E, Lipsky M, Roger T, Calandra T, Tracey KJ et al.: Novel strategies for targeting innate immune responses to influenza. Mucosal Immunol 2016, 9:1173-1182.

7. Kurikoski T, Kanneganti TD: Regulation and functions of NLRP3 inflammasomes in influenza virus infection. Mol Immunol 2017, 86:56-64.

8. Kuiken T, Riteau B, Feuchrier R, Rimmelzwaan G: Pathogenesis of influenza virus infections: the good, the bad and the ugly. Curr Opin Virol 2012, 2:276-286.

9. Kanegai CM, Xi Y, Donne ML, Gotts JE, Driver IH, Amidzic G, Lechaj AJ, Jones KD, Vaughan AE, Chapman HA et al.: Persistent pathology in influenza-infected mouse lungs. Am J Respir Cell Mol Biol 2016, 55:613-615.

10. Jin S, Li Y, Pan R, Zou X: Characterizing and controlling the inflammatory network during influenza A virus infection. Sci Rep 2014, 4:3799.

11. Duan M, Hibbs ML, Chen W: The contributions of lung macrophage and monocyte heterogeneity to influenza pathogenesis. Immunol Cell Biol 2016, 95:225-235.

12. Braciale TJ, Sun J, Kim TS: Regulating the adaptive immune response to respiratory virus infection. Nat Rev Immunol 2012, 12:295-305.

13. Baumgarth N: How specific is too specific? B-cell responses to viral infections reveal the importance of breadth over depth. Immunol Rev 2013, 255:82-94.

14. Chu H, Zhou J, Wong BH, Li C, Chan JF, Cheng ZS, Yang D, Wang D, Lee AC, Li G et al.: Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. J Infect Dis 2016, 213:904-914.

15. Duan S, Thomas PG: Balancing immune protection and immune pathology by CD8+ T-cell responses to influenza infection. Front Immunol 2016, 7:25.

16. Gonzalez Y, Juarez E, Carranza C, Sada E, Pedraza-Sanchez S, Torres M: Diminished effector and memory CD8+ circulating T lymphocytes in patients with severe influenza caused by the AH1N1 pdm09 virus. Virology 2016, 500:139-148.

17. He W, Tan GS, Mullarkey CE, Lee AJ, Lam MM, Krammer F, Harry C, Wilson PC, Askar AA, Palese P et al.: Epitope specificity plays a critical role in regulating antibody-dependent cell-mediated cytotoxicity against influenza A virus. Proc Natl Acad Sci U S A 2016, 113:11931-11936.

18. Cross talk among antibodies of varying specificities determined the magnitude of Fc receptor-mediated effector functions.

19. Hou D, Ying T, Wang L, Chen C, Lu S, Wang Q, Seeley E, Xu J, Xi X, Li T et al.: Immune repertoire diversity correlated with mortality in avian influenza A (H7N9) virus infected patients. Sci Rep 2016, 6:33843.

20. Kai McKinstry K, Dutton RW, Swain SL, Strutt TM: Memory CD4+ T-cell-mediated immunity against influenza A virus: more than a little helpful. Arch Immunol Ther Exp 2013, 61:341-353.

21. Laidlaw BJ, Decman V, Ali MA, Abt MC, Wolf AJ, Monticelli LA, Mozdzanowska K, Angelosanto JM, Artis D, Erikson J et al.: Cooperativity between CD8+ T cells, non-neutralizing antibodies, and alveolar macrophages is important for heterosubtypic influenza virus immunity. PLoS Pathog 2013, 9:e1003207.

22. Miller MS, Gardner TJ, Krammer F, Aguado LC, Tortorella D, Basler CF, Palese P: Neutralizing antibodies against previously encountered influenza virus strains increase over time: a longitudinal analysis. Sci Transl Med 2013, 5:198ra107.

23. Ng OW, Chia A, Tan AT, Jadi RS, Leong HN, Bertolotti A, Tan YJ: Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. Vaccine 2016, 34:2008-2014.

24. Nicholls JM: The battle between influenza and the innate immune response in the human respiratory tract. Infect Chemother 2013, 48:11-21.

25. Parzych EM, Dimeenna LJ, Latimer BP, Small JC, Kannan S, Manson B, Lasaro MO, Wherry EJ, Ertl HC: Influenza virus specific CD8+ T cells exacerbate infection following high dose influenza challenge of aged mice. Biomed Res Int 2013, 2013:876314.

26. Quinones-Parra SM, Clemens EB, Wang Z, Crew HA, Kedzierski L, McMvern J, Vijaykrishna D, Kedzierska K: A role of influenza exposure history in determining pandemic susceptibility and CD8+ T cell responses. J Virol 2016, 90:6936-6947.

27. Rowe RK, Pyle DM, Tomlinson AR, Lu T, Hu Z, Gill MA: IgE cross-linking impairs monocyte antiviral responses and inhibits influenza-driven Th1 differentiation. J Allergy Clin Immunol 2017, 140:294-298.e8.

28. Tai W, Wang Y, Fett CA, Zhao G, Li F, Perilman S, Jiang S, Zhou Y, Du L: Recombinant receptor-binding domains of multiple Middle East respiratory syndrome coronaviruses (MERS-CoVs) induce cross-neutralizing antibodies against divergent human and camel MERS-CoVs and antibody escape mutants. J Virol 2017, 91:e01651-16.

29. Trieu MC, Zhou F, Larley S, Jul-Larsen A, Mialaland S, Siriward S, Cox RJ: Long-term maintenance of the influenza-specific cross-reactive memory CD4+ T-cell responses following repeated annual influenza vaccination. J Infect Dis 2016, 215:740-749.

30. Zamitsyna VJ, Lavine J, Ellebedy A, Ahmed R, Antia R: Multi-epitope models explain how pre-existing antibodies affect the generation of broadly protective responses to influenza. PLoS Pathog 2016, 12:e1005592.

31. Zens KD, Chen JK, Farber DL: Vaccine-generated lung tissue-resident memory T cells provide heterosubtypic protection to influenza infection. JCI Insight 2016, 1:e85832.

32. Zhao J, Alshukairi AA, Baharoon SA, Ahmed WA, Bokhari AA, Nehdi AM, Layqah AL, Alghamdi MQ, Al Gethamy MM, Dada AM et al.: Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. Sci Immunol 2017, 2:eaa5939.

First paper illustrating the correlation between recovery of MERS-CoV infected patients with their cellular and humoral immune responses.

33. Mair-Jenkins J, Saavedra-Campos M, Baille J, Cleary P, Kham FW, Lim WS, Makki S, Rooney KD, Nguyen-Van-Tam JS, Beck CR et al.: The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015, 211:80-90.

34. Oslund KL, Baumgarth N: Influenza-induced innate immunity: regulators of viral replication, respiratory tract pathology and adaptive immunity. Future Virol 2011, 6:951-962.

35. Stifter SA, Bhattacharyya N, Pillay R, Florido M, Triccas JA, Britton WJ, Feng CG: Functional interplay between type I and II interferons is essential to limit influenza A virus-induced tissue inflammation. PLoS Pathog 2016, 12:e1005378.
36. Priest SO, Baumgart N: The role of innate signals in B cell immunity to influenza virus. Front Biosci 2013, 3:105-117.

37. Kandasamy M, Suryawanshi A, Kundup S, Perez JT, Schmalke M, Manickavasagam S, Manickavasagam B: RIG-I signaling is critical for efficient polyfunctional T cell responses during influenza virus infection. PLoS Pathog 2012, 8:e1002574.

38. Pillai PS, Molony RD, Martinod K, Dong H, Pang IK, Tai MC, Solis AG, Bielecki P, Mohanty S, Treltangale M et al.: Mx1 reveals innate pathways to antiviral resistance and lethal influenza disease. Science 2016, 352:463-466.

In the absence of Mavs-mediated and TRLR7-mediated antiviral resistance, vulnerability to IAV disease, depending on caspase signals rather than viral load.

39. Monticelli LA, Sonnenberg GF, Abt MC, Alenghat T, Ziegler CG, Doering TA, Angelosanto JM, Laidlaw BJ, Yang CY, Sathalayavalap T et al.: Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. Nat Immunol 2011, 12:1045-1054.

40. Sun X, Zeng H, Kumar A, Belser JA, Maines TR, Tumpey TM: Constitutively expressed IFITM3 protein in human pulmonary endothelial cells poses an early infection block to human influenza viruses. J Virol 2016, 90:11157-11167.

41. Armstrong SM, Mubareka S, Lee WL: The lung microvascular endothelium as a therapeutic target in severe influenza. Antiviral Res 2013, 99:113-118.

42. Reilly EC, Lambert-Emo K, Topham DJ: The effects of acute neutrophil depletion on resolution of acute influenza infection, establishment of tissue resident memory (TRM), and heterosubtypic immunity. PLOS ONE 2016, 11:e0164247.

43. Samarasinghe AE, Melo RC, Duan S, LeMessurier KS, Liedmann S, Surman SL, Lee JI, Hurwitz JL, Thomas PG, McCullers JA: Eosinophilic promotes antiviral immunity in mice infected with influenza A virus. J Immunol 2017, 198:3214-3226.

44. Zarnegar B, Mendez-Enriquez E, Westin A, Soderberg C, Dahlin JS, Gronvik KO, Hallgren J: Influenza infection in mice induces accumulation of lung mast cells through the recruitment and maturation of mast cell progenitors. Front Immunol 2017, 8:310.

45. Cole SL, Ho LP: Contribution of innate immune cells to pathogenesis of severe influenza virus infection. Clin Sci (Lond) 2017, 131:269-283.

46. Zens KD, Chen JK, Guyer RS, Wu FL, Cvetkovic F, Mirom M, Farber DL: Reduced generation of lung tissue-resident memory T cells during infancy. J Exp Med 2017; pii:jem.20170521.

Mouse and human infant T cells exhibited increased T-bet expression after activation, which impaired the establishment of tissue-resident memory T cells in infant mice.

47. Coates BM, Staricha KL, Wiese KM, Ridge KM: Influenza A virus infection, innate immunity, and childhood. JAMA Pediatr 2015, 169:956-963.

48. Bahadoran A, Lee SH, Wang SM, Manikam R, Rajarajeswaran J, Raju CS, Sekaran SD: Immune responses to influenza virus and its correlation to age and inherited factors. Front Microbiol 2016, 7:1841.

49. Hsu AC, See HV, Wark PA: Innate immunity to influenza in chronic airways diseases. Respilology 2012, 17:1166-1175.

50. Cobey S, Hensley SE: Immune history and influenza virus susceptibility. An excellent review of the correlation between immune history and IAV susceptibility.

51. Arora S, Lim W, Bist P, Perumalsamy R, Lukman HM, Li F, Welker LB, Yan B, Sethi G, Tambhy PA et al.: Influenza A virus enhances its propagation through the modulation of Annexin-A1 dependent endosomal trafficking and apoptosis. Cell Death Differ 2016, 23:1243-1256.

52. Batra J, Tripathi S, Kumar A, Katz JM, Cox NJ, Lal RB: Sambhara S, Lal SK: Human heat shock protein 40 (Hsp40/DnaJ-B1) promotes influenza A virus replication by assisting nuclear import of viral ribonucleoproteins. Sci Rep 2016, 6:19063.

53. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S: Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol 2016, 198:4046-4053.

54. Cohen JR, Lin LD, Machamer CE: Identification of a Golgi complex-targeting signal in the cytoplasmic tail of the severe acute respiratory syndrome coronavirus envelope protein. J Virol 2011, 85:5794-5803.

55. cottam EM, Whelband MC, Wileman T: Coronavirus NSp6 restricts autophagosomal expansion. Autophagy 2014, 10:1426-1441.

56. Earnest JT, Hantak MP, Li K, McCray PB Jr, Perlman S, Gallagher T: The tetraspanin CD9 facilitates MERS-coronavirus entry by scaffolding host cell receptors and proteases. PLoS Pathog 2017, 13:e1006546.

57. Fan Y, Mok CK, Chan MC, Zhang Y, Nal-Rogier B, Kien F, Bruzzone R, Sanyal S: Cell cycle independent role of cyclin D3 in host restriction of influenza virus infection. J Biol Chem 2017, 292:5070-5088.

58. Feizi N, Mehrbod P, Romani B, Soleimani-Harr, Bamdad T, Feizi A, Jazaeri EO, Targhi HS, Saleh M, Jamali A et al.: Autophagy induction regulates influenza virus replication in a time-dependent manner. J Med Microbiol 2017, 66:536-541.

59. Hall OJ, Nachbagauer R, Vermillion MS, Fink AL, Phuong V, Krammer F, Klein SL: Progesterone-based contraceptives reduce adaptive immune responses and protection against sequential influenza A virus infections. J Virol 2017; pii:e02160-16.

60. Herold S, Ludwig S, Pleschka S, Wolff T: Apoptosis signaling in influenza virus propagation, innate host defense, and lung injury. J Leukoc Biol 2012, 92:75-82.

61. Kilipp MJ, Smith M, Jackson D, Randall RE: Activation of the interferon induction cascade by influenza A viruses requires viral RNA synthesis and nuclear export. J Virol 2014, 88:3942-3952.

62. Kim JA, Seong RK, Shin OS: Enhanced viral replication by a cell-specific replicative senescence. Immune Netw 2016, 16:286-295.

63. Marcos-Villar L, Pazo A, Nieto A: Influenza virus and the chromatin: Role of CHD1 chromatin remodeler on virus life cycle. J Virol 2016, 90:3694-3707.

64. Nippan K, Suptawiwat O, Boonkart C, Phuangphung P, Sathirarueangchai S, Uprasertkul M, Auswarakul P: Expression of importin-alpha isoforms in human nasal mucosa: implication for adaptation of avian influenza A viruses to human host. Viral J 2016, 13:90.

65. Resa-Infante P, Gabriel G: The nuclear import machinery is a determinant of influenza virus host adaptation. BioEssays 2013, 35:23-27.

66. Rialdi A, Hulquist J, Jimenez-Morales D, Perafa Z, Campisi L, Ramalho JR, Alouati R, Moshkina N, Wang ZZ, Laflleur B, Kaake RM et al.: The RNA exosome syncs IAV-RNAIP transcription to promote viral ribogenesis and infectivity. Cell 2017, 169:679-692 e614.

Exosome deficiency uncoupled chromatin targeting of the IAV polymerase complex and the formation of cellular-viral RNA hybrids, which licensed transcription of antisense genomic viral RNAs.

67. Vale-Costa S, Almeu M, Sousa AL, Kellen B, Ramalho J, Tranfield EM, Amorim MJ: Influenza A virus ribonucleoproteins modulate host recycling by competing with Rab11 effectors. J Cell Sci 2016, 129:1697-1710.

68. Yadav V, Panganiban AT, Honer Zu Bentrup K, Voss TG: Influenza infection modulates vesicular trafficking and induces Golgi complex disruption. Virus Dis 2016, 27:357-368.

69. Zelaya H, Alvarez S, Kitazawa H, Villena J: Respiratory antiviral immunity and immunobiotics: beneficial effects on inflammation-coagulation interaction during influenza virus infection. Front Immunol 2016, 7:633.
Viral immunology

70. Lin TY, Brass AL: Host genetic determinants of influenza pathogenicity. Curr Opin Virol 2013, 3:531-536.

71. Ciancanelli MJ, Abel L, Zhang SY, Casanova JL: Host genetics of severe influenza: from mouse Mx1 to human IRF7. Curr Opin Immunol 2016, 38:109-120.

72. Brooke CB: Population diversity and collective interactions during influenza virus replication and evolution. J Virol 2017, pii:JVI.01164-17.

73. Dimitrakopoulos K, Dimitrakopoulos GN, Wilk E, Tsiampouris C, Sgarbas KN, Schughart K, Bezerianos A: Influenza A Immunomics and Public Health Omics: the dynamic pathway interplay in host response to H1N1 infection. Omics 2014, 18:167-183.

74. Tisoncik-Jo G, Jasper DJ, Kyle JE, Eifeld AJ, Selinger C, Hatta M, Morrison J, Korth MJ, Zink EM, Kim YM et al.: Integrated Omics analysis of the dynamic host responses during pandemic H1N1 influenza virus infection: the crucial role of lipid metabolism. Cell Host Microbe 2016, 19:254-266.

Key role of lipid metabolism in IAV infection was illustrated USING integrated omics analysis.

75. Schafer A, Baric RS: Epigenetic landscape during coronavirus infection. Pathogens 2017, 6 E8.

76. Peteranderl C, Morales-Nebeda L, Selvakumar B, Lecuona E, Vadassery J, Morty RE, Schmidt C, Bespalowa J, Wolff T, Pleschka S et al.: Macrophage-epithelial paracrine crosstalk inhibits lung edema clearance during influenza infection. J Clin Invest 2016, 126:1566-1580.

Interaction between macrophage and epithelial cells exacerbated disease severity by inhibiting lung edema clearance.

77. Cardani A, Boulton A, Kim TS, Braciale TJ: Alveolar macrophages prevent lethal influenza pneumonia by inhibiting infection of type-1 alveolar epithelial cells. PLoS Pathog 2017, 13:e1006140.

Alveolar macrophage prevents lethal pneumonia by inhibiting IAV infection on epithelial cells.

78. Cao P, Yan AW, Heffernan JM, Petrie S, Moss RG, Carolan LA, Guaracci TA, Kelso A, Barr IG, McVernon J et al.: Innate immunity and the immune–infector interface determine the dynamics of secondary influenza virus infection and explain observed viral hierarchies. PLoS Comput Biol 2015, 11: e1004334.

79. Phua KKL, Liu Y, Sim SH: Non-linear enhancement of mRNA delivery efficiencies by influenza A derived NS1 protein engendering host gene inhibition property. Biomaterials 2017, 133:29-36.

80. Moriyama M, Chen YJ, Kawaguchi A, Koshita T, Nagata K, Takeyama H, Hasegawa H, Ichinohe T: The RNA- and TRIM25-binding domains of influenza virus NS1 protein are essential for suppression of NLPR3 inflammasome-mediated IL-1beta secretion. J Virol 2016, 90:4105-4114.

81. Garcia-Sastre A: Induction and evasion of type I interferon responses by influenza viruses. Virus Res 2011, 162:12-18.

82. Anastasina M, Le May N, Bugai A, Fu Y, Soderholm S, Gaeilings L, Ohman T, Tyneel J, Kyttanen S, Barboric M et al.: Influenza virus NS1 protein binds cellular DNA to block transcription of antiviral genes. Biochim Biophys Acta 2016, 1868:1440-1448.

83. Qian W, Wei X, Guo K, Li Y, Lin X, Zou Z, Zhou H, Jin M: The C-terminal effector domain of non-structural protein 1 of influenza A virus blocks IFN-beta production by targeting TNF receptor-associated factor 3. Front Immunol 2017, 8:779.

84. Kuo RL, Li LH, Lin SJ, Li ZH, Chen GW, Chang CK, Wang YR, Tam EH, Gong YN, Krug RM et al.: The role of N-terminus-truncated NS1 proteins of influenza A virus in inhibiting IRF3 activation. J Virol 2016, 90:4696-4705.

85. Schierhorn KL, Jolmes F, Bespalova J, Saenger S, Peteranderl C, Dzieciolowski J, Budd M, Pleschka S, Herrmann A, Harald S et al.: Influenza A virus virulence depends on two amino acids in the N-terminal domain of its NS1 protein facilitating inhibition of PKR. J Virol 2017, 91:pic00198-17.

86. Bar-On Y, Glasner A, Meningher T, Achdout H, Gur C, Lankry D, Vitsentzou A, Meyers AF, Mandelboim M, Mandelboim O: Neuraminidase-mediated, NKP44-dependent immune-evasion mechanism of influenza viruses. Cell Rep 2013, 3:1044-1050.

87. Hu S, Yin L, Mei S, Li J, Xu F, Sun H, Liu X, Cen S, Liang C, Li A et al.: BST-2 restricts IAV release and is countered by the viral M2 protein. Biochim J 2017, 474:715-730.

88. Kuss SK, Mata MA, Zhang L, Fontoura BM: Nuclear imprisonment: viral strategies to arrest host mRNA nuclear export. Viruses 2013, 5:1842-1849.

89. Gotz V, Magar L, Dornfeld D, Giese S, Pohlmann A, Hoper D, Kong SW, Jans DA, Beer M, Haller O et al.: Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. Sci Rep 2016, 6:23138.

90. Marvin SA, Russier M, Huerta CT, Russell CJ, Schultz-Cherry S: Influenza overcomes cellular blocks to productively replicate impacting macrophage function. J Virol 2017, 91:pi01417-1416.

91. de-Weber-Gerlach M, Weber F: To conquer the host, Influenza virus is packing it in: interferon-antagonistic strategies beyond NS1. J Virol 2016, 90:8389-8394.

92. Shin D, Lee J, Park JH, Min JY: Double PHD Fingers 2 (DPF2) promotes the immune escape of influenza virus by suppressing interferon-beta production. J Virol 2017, 91: pii: e02260-16.

93. Kindler E, Gil-Cruz C, Spanier J, Li Y, Wilhelm J, Rabouw HH, Zust R, Hwang M, V’Kovski P, Stalder H et al.: Early endonuclease-mediated evasion of RNA sensing ensures efficient coronavirus replication. PLoS Pathog 2017, 13: e1006195.

94. Deng X, Hackbart M, Mettelman RC, O’Brien A, Mielech AM, Yi G, Kao CC, Baker SC: Coronavirus nonstructural protein 15 mediates evasion of dsRNA sensors and limits apoptosis in macrophages. Proc Natl Acad Sci U S A 2017, 114:E2451-E2460.

95. Two independent studies illustrating nsp15-mediated immune evasion by CoV.

96. Lei J, Hilgenfeld R: RNA-virus proteases counteracting host innate immunity. FEBS Lett 2017.

97. Hu Y, Li W, Gao T, Cui Y, Jin Y, Li P, Ma Q, Liu X, Cao C: SARS coronavirus nucleocapsid inhibits type I interferon production by interacting with TRIM25-Mediated RIG-I ubiquitination. J Virol 2017, 91:pi02143-16.

98. Dumitri V, Dengel J: Autophagosomal protein dynamics and influenza virus infection. Front Immunol 2012, 3:43.

99. Miyake Y, Ishii K, Honda A: Influenza virus infection induces host pyruvate kinase M which interacts with viral RNA-dependent RNA polymerase. Front Microbiol 2017, 8:162.

100. Abbas YM, Lundenbach BT, Martinez-Montero S, Cencic R, Habijan M, Pichtlmaier A, Damha MJ, Pelletier J, Nagar B: Structure of human IFIT1 with capped RNA reveals adaptable mRNA binding and mechanisms for sensing N1 and N2 ribose 2'-O methylation. Proc Natl Acad Sci U S A 2017, 114:E2106-E2115.

101. Kesavardhana S, Kuriakose T, Guy CS, Samir P, Malireddi RKS, Mishra A, Kanneganti TD: ZBP1/DAI ubiquitination and sensing of influenza vRNPs activate programmed cell death. J Exp Med 2017, 214:2217-2229.

102. Gao S, Dhungel P, Yang Z: Going against the tide: selective cellular protein synthesis during virally induced host shut off. J Virol 2017, 91:pi00071-17.

103. Wang C, Liu H, Luo J, Chen L, Li M, Su W, Zhao N, Liu S, Xie L, Jia Y et al.: HA triggers the switch from MEK1 SUMOylation to phosphorylation of the ERK pathway in influenza A virus infected cells and facilitates its infection. Front Cell Infect Microbiol 2017, 7:27.

104. Hui KP, Li HS, Cheung MC, Chan RW, Yuen KM, Mok CK, Nicholls JM, Peiris JS, Chan MC: Highly pathogenic avian influenza H5N1 virus delays apoptotic responses via activation of STAT3. Sci Rep 2016, 6:28593.
Immune responses in respiratory virus infections

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To EE, Vilahos R, Luong R, Halls ML, Reading PC, King PT, Chan C.
- Drummond GR, Sobey CG, Broughton BRS et al.: Endosomal NOX2 oxidase exacerbates virus pathogenicity and is a target for antiviral therapy. Nat Commun 2017, 8:69.
- Activated NOX2 exacerbated virus-mediated pathogenicity via production of reactive oxygen species (ROS).

Yu G, Liang W, Liu J, Meng D, Wei L, Chai T, Cai Y: Proteomic analysis of differential expression of cellular proteins in response to avian H9N2 virus infection of A549 cells. Front Microbiol 2016, 7:1962.

Zhao J, Zhao J, Legge K, Perlman S: Age-related increases in PGD2 expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice. J Clin Invest 2011, 121:4921-4930.

Vijay R, Hua X, Meyerhozl DK, Miki Y, Yamamoto K, Gelb M, Murakami M, Perlman S: Critical role of phospholipase A2 group IID in age-related susceptibility to severe acute respiratory syndrome-CoV infection. J Exp Med 2015, 212:1851-1868.

Alfuwaires M, Altaher A, Kandeel M: Molecular dynamic studies of interferon and innate immunity resistance in MERS CoV Non-Structural protein 3. Biol Pharm Bull 2017, 40:345-351.

Fehr AR, Channappanavar R, Jankevics G, Fett C, Zhao J, Athmer J, Meyerhozl DK, Ahel I, Perlman S: The conserved coronavirus macronetwork promotes virulence and suppresses the innate immune response during severe acute respiratory syndrome coronavirus infection. Mbio 2016, 7:pil-e01721-16.

Aoudi W, Blanjoie A, Vasseur JJ, Debart F, Canard B, Decoly E: Binding of the methyl donor SAM to MERS-CoV 2'-O- methylenetransferase nsP16 promotes the recruitment of the allosteric activator nsP10. J Virol 2016, 91:pico0217-16.

Nagesh PT, Husain M: Influenza A virus dysregulates host histone deacetylation 1 that inhibits viral infection in lung epithelial cells. J Virol 2016, 90:4614-4625.

Zhang T, Ye Z, Yang X, Qin Y, Hu Y, Tong X, Lai W, Ye X: NEDDylation of PB2 reduces its stability and blocks the replication of influenza A virus. Sci Rep 2017, 7:43691.

Soderholm S, Kainov DE, Ohman T, Denisesova OV, Schepens B, Kuleskisky E, Imanishi SY, Corthals G, Hintansen P, Attokkollo T et al.: Phosphoproteomics to characterize host response during influenza A virus infection of human macrophages. Mol Cell Proteomics 2016, 15:3203-3213.

Khatti K, Klein JA, White MR, Grant OC, Leymanie N, Woods RJ, Hartshorn KL, Zaia J: Integrated omics and computational glycomics reveal structural basis for Influenza A virus glycan microheterogeneity and host interactions. Mol Cell Proteomics 2016, 15:1895-1912.

Alymova IV, York IA, Air GM, Cipollo JF, Gatusi S, Baranovitch T, Kumar A, Zheng G, Gansebom S, McCullers JA: Glycosylation changes in the globular head of H3N2 influenza hemagglutinin modulate receptor binding without affecting virus virulence. Sci Rep 2016, 6:36216.

Peck KM, Scoeby T, Swanstrom J, Jensen KL, Burch CL, Baric RS, Heise MT: Permissivity of DP44 orthologs to MERS-CoV is governed by glycosylation and other complex determinants. J Virol 2017, 91:pico0534-17.

Air GM: Influenza virus-glycan interactions. Curr Opin Virol 2014, 7C:128-133.

Abdelwab EM, Veits J, Tauscher K, Ziller M, Grund C, Haasen MK, Staheen M, Harder TC, Telfke JP, Stech J et al.: Progressive glycosylation of the hemagglutinin of avian influenza H5N1 modulates virus replication, virulence and chicken-to-chicken transmission without significant impact on antigenic drift. J Gen Virol 2016, 97:3193-3204.

Tate MD, Job ER, Deng YM, Gunalan V, Maurer-Stroh S, Reading PC: Playing hide and seek: how glycosylation of the influenza virus hemagglutinin can modulate the immune response to infection. Viruses 2014, 6:1294-1316.

Parsons LM, An Y, de Vries RP, de Haan CA, Cipollo JF: Glycosylation characterization of an influenza H5N7 hemagglutinin series with engineered glycosylation patterns: implications for structure-function relationships. J Proteome Res 2016, 16:398-412.

Zhao D, Liang L, Wang S, Nakao T, Li Y, Liu L, Guan Y, Fukuyama S, Bu Z, Kawaoka Y et al.: Glycosylation of the HA protein of H5N1 virus increases its virulence in mice by exacerbating the host immune response. J Virol 2017, 91:pii:e02215-16.

Liu WC, Jan JT, Huang YJ, Chen TH, Wu SC: Unmasking stem-specific neutralizing epitopes by abolishing N-linked glycosylation sites of influenza hemagglutinin proteins for vaccine design. J Virol 2016, 90:8496-8508.

Wu CY, Lin CW, Tsai TL, Lee CD, Chuang HY, Chen JB, Tsai MH, Chen BR, Lo PW, Liu CP et al.: Influenza A surface glycosylation and vaccine design. Proc Natl Acad Sci U S A 2016, 114:280-285.

IAV surface glycosylation and implications for vaccine design.

Gudjonsson A, Lysen A, Balan S, Sundvold-Gjerstad V, Arnold-Schrauf C, Richter L, Baekkevold ES, Dalad M, Bogen B, Fossum E: Targeting influenza virus hemagglutinin to Xcr1+ dendritic cells in the absence of rReceptor: regulated endocytosis enhances protective antibody responses. J Immunol 2017, 198:2785-2795.

Lynn DJ, Pulendran B: The potential of the microbiota to influence vaccine responses. J Leukoc Biol 2017, pii:jlb.5MR0617-216F.

Furman D, Jojic V, Kidd B, Shen-Orr S, Price J, Jarrel J, Tse T, Huang H, Lund P, Maecker HT et al.: Apoptosis and other immune biomarkers predict influenza vaccine responsiveness. Mol Syst Biol 2013, 9:659.

McMichael AJ, Haynes BF: Influenza vaccines: mTOR inhibition surprisingly leads to protection. Nat Immunol 2013, 14:1205-1207.

Lees WD, Moss DS, Shepherd AJ: Evolution in the influenza A H3 stalk — a challenge for broad-spectrum vaccines? J Gen Virol 2013, 95:317-324.

Cruz JL, Perez-Giron JV, Ludtke A, Gomez-Medina S, Ruibal P, Idoyaga J, Munoz-Fontela C: Monocyte-derived dendritic cells enhance protection against secondary influenza challenge by controlling the switch in CD82 T-cell immunomodulation. Eur J Immunol 2016, 46:340-352.

Hwang HS, Lee YT, Kim KH, Ko EJ, Lee Y, Kwon YM, Kang SM: Virus-like particle vaccine primes immune responses preventing inactivated-virus vaccine-enhanced disease against respiratory syncytial virus. Virology 2017, 511:142-151.

Zhao J, Zhao J, Mangalam AK, Channappanavar R, Fett C, Meyerhozl DK, Agnihotham S, Baric RS, David CS, Perlman S: Airway memory CD4(+) T cells mediate protective immunity against emerging respiratory coronaviruses. Immunity 2016, 44:1379-1391.

Conserved epitopes-specific airway memory CD4(+) T cells induced by vaccine protected animals from SARS-CoVs and MERS-CoV infection.

Pizzolla A, Nguyen THO, Smith JM, Brooks AG, Kedzieska K, Heath WR, Reading PC, Wakim LM: Resident memory CD8(+) T cells in the upper respiratory tract prevent pulmonary influenza virus infection. Sci Immunol 2017, 2 pii:eaaam6970.

Slutter B, Van Braeckel-Budimir N, Abboud G, Varga SM, Salek-Ardakani S, Harty JT: Dengue-induced lung-resident memory T cells underlie waning heterosubtypic immunity. Sci Immunol 2017, 2 pii:eaaag2031.

Neu KE, Henry Dunand CJ, Wilson PC: Heads, stalks and everything else; how can antibodies eradicate influenza as a human disease? Curr Opin Immunol 2016, 42:48-55.

Vanderven HA, Jegaskanda S, Wheatley AK, Kent SJ: Antibody-dependent cellular cytotoxicity and influenza virus. Curr Opin Virol 2017, 22:89-96.

Burke TW, Henao R, Soderblom E, Taalik EL, Thompson JW, McClain MT, Nichols M, Nicholson BP, Veldman T, Lucas JE et al.: Nasophasyngeal protein biomarkers of acute respiratory virus infection. EBioMedicine 2017, 17:172-181.
cell dynamics during influenza infection. Mol Syst Biol 2014, 10:720.

137. Richert LE, Harmsen AL, Rynda-Apple A, Wiley JA, Servid AE, Douglas T, Harmsen AG: Inducible bronchus-associated lymphoid tissue (iBALT) synergizes with local lymph nodes during antiviral CD4(+) T cell responses. Lymphat Res Biol 2013, 11:196-202.

138. Pizzolla A, Wang Z, Groom JR, Kedzierska K, Brooks AG, Reading PC, Wakim LM: Nasal-associated lymphoid tissues (NALTs) support the recall but not priming of influenza virus-specific cytotoxic T cells. Proc Natl Acad Sci U S A 2017, 114:5225-5230.

NALTs support the recall but not priming of IAV-specific cytotoxic T cells.

139. Beyleveld G, White KM, Ayllon J, Shaw ML: New-generation screening assays for the detection of anti-influenza compounds targeting viral and host functions. Antiviral Res 2013, 100:120-132.

140. Wang D, Ma W: Visualization of IAV genomes at the single-cell level. Trends Microbiol 2017, 25:781-782.

141. Hartmann BM, Thakar J, Albrecht RA, Avey S, Zaslavsky E, Marjanovic N, Chikina M, Fribourg M, Hayot F, Schmolke M et al.: Human dendritic cell response signatures distinguish 1918, pandemic and seasonal H1N1 influenza viruses. J Virol 2015, 89:10190-10206.

142. Altboum Z, Steuerman Y, David E, Barnett-Itzhaki Z, Valadarsky L, Keren-Shaul H, Meningher T, Mendelson E, Mandelboim M, Gat-Viks I et al.: Digital cell quantification identifies global immune responses. J Virol 2013, 88:1039-1050.

143. Sonnberg S, Webby RJ, Webster RG: Natural history of highly pathogenic avian influenza H5N1. Virus Res 2013, 178:63-77.

144. Zumla A, Hui DS, Perlman S: Middle East respiratory syndrome. Lancet 2015, 386:995-1007.

145. Hemida MG, Alnaeem A, Chu DK, Perera RA, Chan SM, Almathen F, Yau E, Ng BC, Webby RJ, Poon LL et al.: Longitudinal study of Middle East respiratory syndrome coronavirus infection in dromedary camel herds in Saudi Arabia, 2014-2015. Emerg Microbes Infect 2017, 6:e56.

146. Bedford T, Rambaut A, Pascual M: Canalization of the evolutionary trajectory of the human influenza virus. BMC Biol 2012, 10:38.

147. Manchanda H, Seidel N, Krumbholz A, Sauerbrei A, Schmidtke M, Guthke R: Within-host influenza dynamics: a small-scale mathematical modeling approach. BioSystems 2014, 118:51-59.

148. Tria F, Pompei S, Loreto V: Dynamically correlated mutations drive human Influenza A evolution. Sci Rep 2013, 3:2705.

149. Woo HJ, Reifman J: Quantitative modeling of virus evolutionary dynamics and adaptation in serial passages using empirically inferred fitness landscapes. J Virol 2013, 88:1039-1050.