Intensive Care Med (2019) 45:1012–1014
https://doi.org/10.1007/s00134-019-05582-5

UNDERSTANDING THE DISEASE

Understanding the role of host response in influenza pneumonitis

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Introduction

Most influenza-related deaths are caused by influenza pneumonitis, a serious complication of influenza virus infection characterised by uncontrolled lung inflammation, acute lung injury and respiratory failure. This serious complication has a high mortality risk (18–32%) [1]. The currently available antiviral therapy (e.g. neuraminidase inhibitor) has limited efficacy in reducing fatality caused by influenza pneumonitis.

Host factors, in additional to viral factors, are important in determining patient outcomes in influenza pneumonitis [2, 3]. A better understanding of the host factors associated with severe disease is therefore needed; it may help discover pathogenic pathways that determine disease progression and enable researchers identify new therapeutic targets. Here, we examine the immune cells underpinning the host response to influenza infection.

Innate immune cells

Alveolar macrophages in lungs are involved in the first line of defence. Following phagocytosis of virons and recognition by pathogen pattern molecules, alveolar macrophages produce an array of pro-inflammatory cytokines, including TNF-α, IL-1, IL-6 and IFN-α/β, to limit viral replication and promote recruitment of immune cells, such as activated T lymphocytes and inflammatory monocytes. Recent animal study also revealed that these cells are involved in the antibody-induced inflammation and antibody-dependent cellular phagocytosis, both of which are critical in establishing a broad-spectrum antiviral state. Similarly, monocytes elicit potent inflammatory cascade designed to contain the virus spread. Upon infection, neutrophils constitute the biggest influx of recruited immune cells to the infected lung. In addition, neutrophils activate CD8 T cells, which are pivotal for subsequent viral clearance. Other important innate cells include natural killer cells, which kill influenza-infected host cells and therefore limit the virus spread to other cells. Dendritic cells provide a critical link between innate and adaptive immunity. By direct or cross-presentation of viral peptides, these cells prime T lymphocytes to eliminate influenza virus. In addition, plasmacytoid dendritic cells (a subset of dendritic cells) are the most potent producers of antiviral molecules (e.g. type I interferon).

Adaptive immune cells

Cytotoxic CD8 T cells are the major effectors of the antiviral cellular response; they enable killing of influenza virus and elimination of virally infected host cells. B cells mediate humoral response, which can be induced, maintained and reactivated in the lungs after primary and secondary infection. These cells produce influenza virus-specific antibodies in a CD4 T cells-dependent manner and have multiple strategies for adjusting antibody repertoires, including the formation of B cell repertoires for antigenically conserved epitopes. CD4 T cells augment CD8 cell response to influenza infection, but they have their own antiviral effects that are independent of CD8 cell activity. Finally, regulatory T cells limit the extent of the inflammatory response by suppressing activated effector T cells. Therefore, they assist the resolution of the host response.

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Host immune mechanisms mediating influenza pneumonitis

Early, excessive, innate, pro-inflammatory responses (day 1–7 post-infection)

Monocytes and neutrophils orchestrate an early, pro-inflammatory response in influenza pneumonitis. The inflammatory cascade is triggered by an intracellular recognition of viral RNA through a variety of pattern recognition receptors (PRRs), including TLR3, TLR7, TLR8 and RIG-I. This signalling cascade releases pro-inflammatory cytokines (TNF-α, IL-1, IL-6, and type I and II interferons), which lead to further recruitment of immune cells, thereby perpetuating lung inflammation. A substantial amount of evidence has recently emerged implicating neutrophils in maintaining this vicious cycle [4–7]. Activated neutrophils release vasoactive substances, including cathepsin G, elastase and proteinase 3. The excessive innate response to influenza virus promotes vascular leakage and causes flooding of inflammatory fluid into the alveoli, all of which are hallmarks of influenza pneumonitis (Fig. 1).

Impaired adaptive immune responses (> day 7 post-infection)

In late influenza infection, an impaired adaptive response resulting from either reduced T lymphocyte function or numbers (i.e. lymphopenia) is strongly linked to the development of immune suppression [8]. Immune suppression has contributed, at least in part, to the increased susceptibility to secondary infection including bacterial superinfection (e.g. Staphylococcus aureus, Streptococcus pneumoniae) and invasive aspergillosis [9, 10]. Collectively, these host-mediated mechanisms continue to impede host recovery despite initial viral clearance or antiviral therapy.

Other host and viral factors

Other host factors (age, immune-compromised state, cancer) contribute to the impaired host response by possessing additional mechanisms that may also compromise immunity. For example, cancer patients commonly have some degree of immune suppression, and their impaired immune response can be further compromised by an over-exuberant neutrophil response triggered by

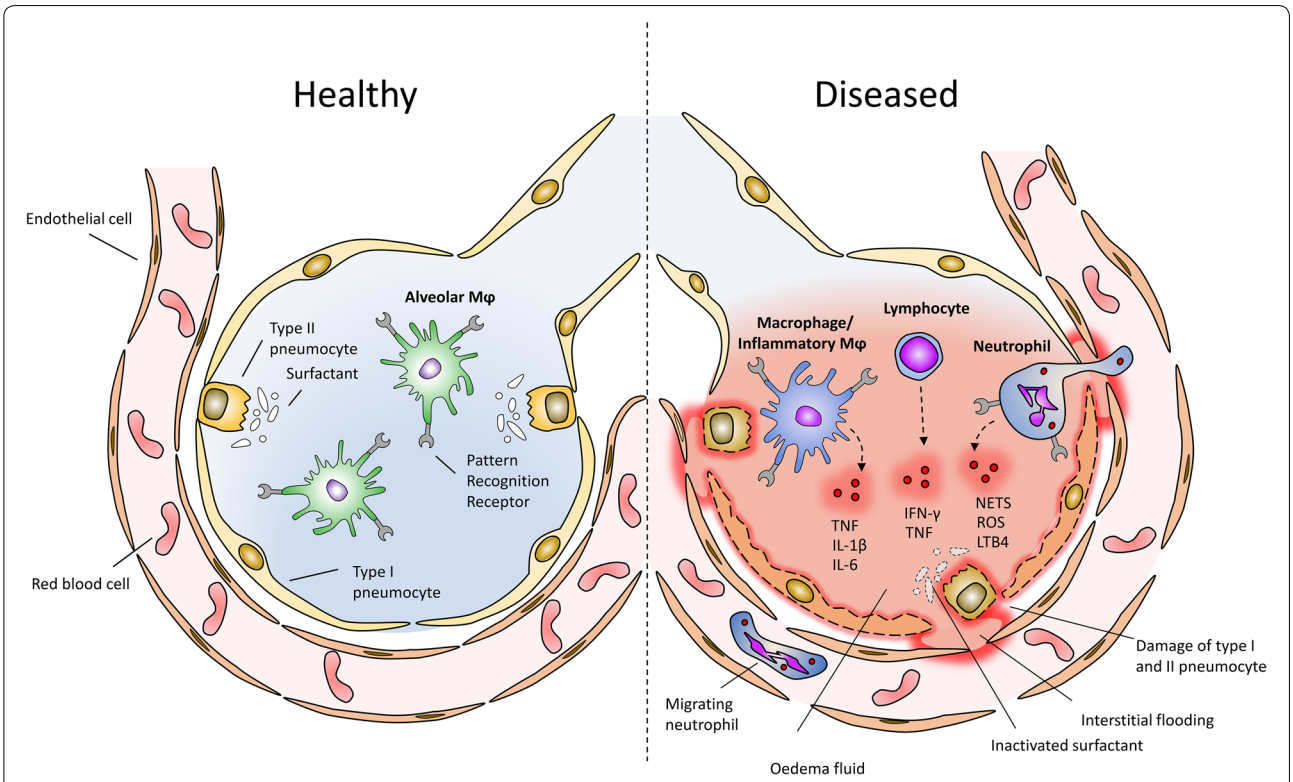

Fig. 1 Immune state in both health and influenza. The alveolus in health (left side) and influenza infection (right side). The major type of immune cells in the alveolar space of a healthy individual is alveolar macrophages. Following influenza virus infection, neutrophils migrate from circulation into the lungs, as guided by release of chemo-attractants from infected tissue. Some of these mediators recruit more neutrophils as well as inflammatory monocytes and activated T cells to the site of infection, further accelerating the inflammatory process. The inflammation can promote vascular leakage and cause flooding of inflammatory fluid into the alveoli, further impairing oxygenation in the lung

influenza infection. Conversely, neutropenia is frequently present in patients in post-chemotherapy phase. Since some degree of a neutrophil response is usually needed to combat infection, neutropenia can thus lead to suboptimal inflammation, reduced viral clearance and increased susceptibility to secondary infection. Other immune deficits (e.g. myelosuppression) are also frequently present in patients receiving chemotherapy; these deficits may also further impair the host's ability to clear the virus.

Influenza virus genotypes also influence host response. In the pro-inflammatory phase of the viral infection (outlined above), influenza A virus protein PB1-F2 affects the extent of lung inflammation. In the late immune suppressive phase, H3N2 viruses are found to be more potent inducers of secondary pneumococcal infection than H1N1 viruses, possibly due to increased H3 tropism to human epithelial cells.

Future therapeutic options

A better understanding of immune response biology provides a road map to aid the design of host-directed therapy. For example, T-cell-based universal vaccine exploits the fact that T-cell response is highly conserved across different influenza subtypes [11]. It is possible that T-cell-targeted vaccine may help circumvent the decade-long problem of reduced vaccine effectiveness due to emergence of new influenza strains. Other novel therapies target a myriad of host factors implicated in both the early and late phase of influenza pneumonitis. For example, animal studies have shown that, in the early phase of infection, modulation of the exuberant neutrophil-mediated response could improve outcome. Neutrophil-targeted agents include those directed against the formation of histone proteins (released during neutrophil extracellular trap formation), such as anti-histone antibodies [12]. Alternatively, in the late phase of infection, therapies directed to treat the immune suppressive state may be of benefit, as shown in recent sepsis studies [13]. These novel therapies include interleukin-7, GM-CSF and immune check-point inhibitor (e.g. anti-PD1 antibodies). In the future, it is likely that a combinational approach will be used to target both the virus (by antiviral) and the host response (by immune therapy).

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Acknowledgements
We thank Andrew Sawyer for his graphic design of Fig. 1.

Compliance with ethical standards

Conflicts of interest
On behalf of all the authors the corresponding author states that there are no conflicts of interest.

Publisher's Note

Received: 4 November 2018 Accepted: 25 February 2019
Published online: 24 April 2019

References

1. Álvarez-Lerma F, Marín-Corral J, Vilà C et al (2017) Characteristics of patients with hospital-acquired influenza A (H1N1)pdm09 virus admitted to the intensive care unit. J Hosp Infect 95:200–206. https://doi.org/10.1016/j.jhin.2016.12.017
2. Herold S, Becker C, Ridge KM, Budinger GRS (2015) Influenza virus-induced lung injury: pathogenesis and implications for treatment. Eur Respir J 45:1463–1478. https://doi.org/10.1183/09031936.00186214
3. Short KR, Kroeze EJBV, Fouchier RAM, Kuiken T (2014) Pathogenesis of influenza-induced acute respiratory distress syndrome. Lancet Infect Dis 14:57–69. https://doi.org/10.1016/S1473-3099(13)70286-X
4. Brandes M, Klauschen F, Kuchen S, Germain RN (2013) A systems analysis identifies a feedforward inflammatory circuit leading to lethal influenza infection. Cell 154:197–212. https://doi.org/10.1016/j.cell.2013.06.013
5. Dunning J, Blankley S, Hoang LT et al (2018) Progression of whole-blood transcriptional signatures from interferon-induced to neutrophil- associated patterns in severe influenza. Nat Immunol 19:625–635. https://doi.org/10.1038/s41590-018-0111-5
6. Narasaraju T, Yang E, Samy RP et al (2011) Excessive neutrophils and neutrophil extracellular traps contribute to acute lung injury of influenza pneumonitis. Am J Pathol 179:199–210
7. Guan W, Yang Z, Wu NC et al (2018) Clinical correlations of transcriptional profile in patients infected with avian influenza H7N9 virus. J Infect Dis 218:1238. https://doi.org/10.1093/infdis/jiy317
8. Venet F, Monneret G (2018) Advances in the understanding and treatment of sepsis-induced immunosuppression. Nat Rev Nephrol 14:121–137. https://doi.org/10.1038/nrneph.2017.165
9. Mina MJ, Klugman KP (2014) The role of influenza in the severity and transmission of respiratory bacterial disease. The Lancet Respir Med 2:750–763. https://doi.org/10.1016/S2213-2600(14)70131-6
10. Schauwvlieghe AFAD, Rijnders BJA, Philips N et al (2018) Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. The Lancet Respir Med 6:782–792. https://doi.org/10.1016/S2213-2600(18)30274-1
11. Sridhar S (2016) Heterosubtypic T-cell immunity to influenza in humans: challenges for universal T-cell influenza vaccines. Front Immunol 7:5086. https://doi.org/10.3389/fimmu.2016.00195
12. Teluguakula N, Harshini A (2016) Neutrophils as possible therapeutic targets in severe influenza pneumonia. J Infect Pulm Dis 2:1
13. Venet F, Monneret G (2018) Advances in the understanding and treatment of sepsis-induced immunosuppression. Nat Rev Nephrol 14:121–137. https://doi.org/10.1038/nrneph.2017.165