Cytokine Storm in Viral Respiratory Pandemic

Subjects: Allergy

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H1N1 MERS SARS COVID-19 Cytokine Storm

1. Cytokine Storm

The term “cytokine storm” (CS) refers to a spectrum of different immune dysregulation disorders characterized by constitutional symptoms, systemic inflammation and multiorgan dysfunction [1]. The trigger for the CS is an uncontrolled immune response with the continuous activation and expansion of immune cells, lymphocytes and macrophages, which produce immense amounts of proinflammatory cytokines [2]. In viral infections, the release of proinflammatory factors leads to apoptosis of lung epithelial cells, and pulmonary alveolar and microvascular endothelial cells, leading to complications such as alveolar edema and hypoxia. The uncontrolled production of proinflammatory factors, containing IL-6, IL-8, IL-1β and GM-CSF, and chemokines such as CCL2, CCL-5, IP-10 and CCL3, along with reactive oxygen species, results in pulmonary fibrosis [3]. CXCL8 chemokine is also involved in the inflammation and trafficking of immune cells in the context of viral infections, as it has a chemotactic action for neutrophils and monocytes in the respiratory tract [4]. The clinical picture of the cytokine storm, although variable, generally manifests itself as laboratory “overlap syndrome” with a decreased cell count, a decreased ESR, an increased ferritin level, NK dysfunction and hemophagocytosis [5]. This clinically results in the increased perivascular infiltration of activated macrophages, neutrophils and fibroblasts, accompanied by extensive fibrin deposition and alveolar collapse, leading to acute respiratory distress syndrome (ARDS) [6][7].

2. COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously 2019-nCoV) was registered in the Wuhan city of China for the first time, and since then 445,188 deaths related to the disease have been reported. It is an enveloped, positive-sense single-stranded genomic RNA virus (+ssRNA) [8][9], and entry of viral RNA into host cells occurs due to the affinity of the SARS-CoV protein S for the ACE-2 receptor [10]. The common symptoms observed in patients with COVID-19 are fever, cough, severe headache, myalgia and fatigue [11]. In most cases, SARS-CoV-2 infections occur asymptomatically or cause only mild and less fatal symptoms than MERS-CoV and SARS-CoV infections. However, in 10–20% of cases they can progress to interstitial pneumonia and acute respiratory distress syndrome (ARDS), especially in those with advanced age and associated comorbidities [12].

Since the COVID-19 pandemic first began in December 2019, SARS-CoV-2 has continuously evolved, with many variants emerging around the world [13]. These mutations, especially when they occur on the S gene encoding the spike protein (S), can affect both the viral entry into the target cells and the effectiveness of the antibodies [14]. The result is a greater visual transmissibility and a greater ability to escape the previous immunity [15]. The variants that attract the most attention as potentially dangerous to public health include B.1.1.7 (UK), P.1 (Brazilian) and B.1.351 (South African). Added to these are also variants of interest that are emerging and expanding in some countries, but are found sporadically in others, such as B.1.427 and B.1.429 (Californians) or B.1.617 (Indian) [16].

The cytokine storm caused by COVID-19 has been suggested to be associated with COVID-19 severity [17][18]. The cytokine storm is considered to be the main cause of the disease severity and death in COVID-19 patients, and is related to the high levels of circulating cytokines, severe lymphopenia, thrombosis and massive mononuclear cell infiltration in multiple organs [19]. The excessive local release of cytokines is considered to be the determinant of pathological alterations and the clinical manifestation of acute respiratory distress syndrome (ARDS).

SARS-CoV-2 infection triggers an immune response producing inflammatory cytokines along with a weak response to interferon (IFN). Thereafter, membrane-bound immune receptors and downstream signaling pathways mediate the proinflammatory immune responses of pathogenic Th1 cells and intermediate CD14 + CD16 + monocytes. This process therefore favors the infiltration of macrophages and neutrophils into the lung tissue, which leads to the cytokine storm [20].

In particular, SARS-CoV-2 can rapidly activate pathogenic Th1 cells resulting in the secretion of proinflammatory cytokines, including granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-6 (IL-6). GM-CSF then activates inflammatory CD14 + CD16 + monocytes to produce IL-6, tumor necrosis factor-α (TNF-α) and other cytokines. Membrane-bound immune receptors, including Fc and Toll-like receptors, might contribute to an imbalanced inflammatory response, whereas weak IFN-γ induction might amplify cytokine production [21]. Neutrophil extracellular traps (NETs) might also contribute to cytokine release. Overall, the cytokine storm in COVID-19 is characterized by the high expression of IL-6 and TNF-α [22].

3. SARS

In 2002/2003, there was an epidemic of severe respiratory disease known as severe acute respiratory syndrome (SARS) which infected 8096 people worldwide and killed 774 (9.5%) of them. This pandemic was first reported in Guangdong Province, China, in November 2002, and spread to 29 countries around the world [23][24]. SARS-CoV is a positive, single-stranded, enveloped RNA virus. Its RNA encodes a nonstructural polyprotein replicase and structural proteins, including spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins, which causes infection first from the upper respiratory tract to affect the lower one, characterized by functionally critical lung damage through the binding of the spike protein with ACE2 and the subsequent downregulation of this receptor [25] [26]. Lymphopenia and thrombocytopenia are commonly present. The decrease of both CD4+ and CD8+ T-lymphocytes occurs early and adversely affects the prognosis [27]. The animal reservoir of SARS-CoV in nature remains to be identified.

During SARS-CoV infection, the levels of IL-1β, IL-6, IL-8, IL-12, inducible protein 10 (IP-10), MCP-1 and IFN-γ increase significantly [28]. This is countered by low levels of the cytokine Th2 IL-4 [29].

SARS and COVID-19 infections can cause MAS and cytokine storms. Massive release of proinflammatory mediators, including IL-6 and IL-1, contributes to vascular permeability, plasma loss and DIC processes, thus causing lung damage and ARDS, as well as multi-organ failure [30][31]. In SARS-Cov and MERS-Cov, increased IFN-γ levels have been associated with inflammation and extensive lung damage [32][33]. The elevated levels of IL-6 in the pathogenesis of SARS-Cov-1 lays the foundation for the hypothesis that the two members of the Coronaviridae family may indeed share common pathophysiological mechanisms [34]. High viral concentrations and dysregulated cytokine / chemokine responses cause a "cytokine storm" with lung immunopathological changes following SARS-CoV infection [35].

An interferon-related cytokine storm was induced by post-SARS coronavirus infection, thus contributing to the genesis of immunopathological damage in SARS patients [36].

4. MERS

Coronavirus Middle East respiratory syndrome (MERS-CoV), a positive-sense single-stranded RNA (ssRNA) genome about 30 kb in size [37], develops in Saudi Arabia in June 2012, and as of 16 October 2018, over 2260 cases of confirmed MERS-CoV infection and 803 related deaths have been reported [38]. MERS-CoV uses the N-terminal part of its peak, the so-called S1 protein, to bind to two host cell surface molecules, dipeptidyl peptidase-4 (DPP4) and α2,3-sialic acids [39]. The major clinical manifestations are fever, chills, cough, shortness of breath, generalized myalgia, malaise, drowsiness, diarrhea, confusion, dyspnea and pneumonia [40]. Although in most subjects the disease progresses asymptomatically or paucisymptomatically, in patients with comorbidities such as diabetes, renal insufficiency and underlying immunosuppression, the clinical manifestations are markedly more serious and potentially fatal [41].

Middle East respiratory syndrome coronavirus (MERS-CoV) became one of the most serious pandemics of last 30 years. As with the other pandemic, it was also clinically characterized by ARDS, and in turn associated to a significant cytokine storm occurrence [42].

More specifically, MERS-CoV infection was reported to induce increased concentrations of IL-15, IL-17, IFN-γ and TNF-α [23][32].

In the past, significantly higher serum levels of proinflammatory cytokines (IL-6, IFN-α), and chemokines (IL-8, CCL5, CXCL8 and CXCL-10) were also detected in patients with severe SARS-CoV or MERS-CoV infections compared to those with milder infections [43][44]. Upregulation of proinflammatory cytokines, notably the IL-6, together with downregulation of antiviral cytokine, was observed in MERS-CoV infections [31][45].

5. H1N1 Influenza A

On 21 April 2009, the Centers for Disease Control and Prevention (CDC) have confirmed two cases of febrile respiratory disease caused by an infection with a new influenza A (H1N1) virus in pediatric age in Southern California [46]. The pandemic (H1N1) influenza A virus is a novel reassortant virus comprising two swine strains, one human strain and one avian strain of influenza [47]. Clinically, the infection occurs frequently with the onset of symptoms such as fever, cough, sore throat, runny nose, body ache, headache, chills and fatigue. A significant number also have gastrointestinal symptoms, such as diarrhea and vomiting. In the most severe forms, the chest X-ray shows an image of pneumonia and mild interstitial fibrosis [48].

Influenza A viruses proliferate in human epithelial cells, which produce inflammatory cytokines/chemokines as a “cytokine storm”, eventually attenuated with the viral nonstructural protein 1 (NS1) [49]. Notably, the uncontrolled viral replication and the associated “cytokine storm” of IL-6, IL-8, IP-10, MIG and MCP-1 are responsible for this infection’s serious clinical manifestations and poor outcomes [50][51][52].

In the presence of the H_2O_2-MPO system, viral NS1 protein produced in the cells is associated with the enhanced production of large amounts of the chemokines IL-8 by neutrophils and MCP-1 by macrophages, suggesting that NS1 of the H1N1 (PR-8) influenza virus may play a key role in the “cytokine storm” when the H_2O_2-MPO system is active [53].

In animal models, the studies exclude a role for lymphocytes as key regulators of the influenza virus-induced cytokine storm [54]. $S1P_1$ receptor signaling in lung endothelial cells suppresses the cytokine storm. The infiltration of macrophages and NK cells alone does not appear to be associated with cytokine storms.

Chemokines such as CCL2, CCL3, CXCL2 and CXCL10 induce the recruitment of innate immune cells into the lungs, exacerbating the cytokine storm and further damaging the lungs. Overall, patients suffering from H1N1-induced pneumonia and consequent ARDS have excessively elevated levels of serum interferons, cytokines and chemokines, which is characteristic of a cytokine storm [55][56][57]. Although the immune dysregulation observed in these individuals varies with the severity of the disease; it has been observed that some mediators, more than others, are more commonly reported, as in the case of IFN-γ, IL-6, IL-1α, IL-1β, TNF-α, IL-15, IL-12p70, IL -17, IL-10, MCP-1, MIP-1β, IL-8, MIG, IP-10, MIP-1α, GM-CSF and RANTES [58][59][60][61][62].

In addition, a positive association was found between IL-6 levels and disease severity [63][64][65][66].

References

1. Fajgenbaum, D.C.; June, C.H. Cytokine Storm. N. Engl. J. Med. 2020, 383, 2255–2273.
2. Ragab, D.; Eldin, H.S.; Taeimah, M.; Khattab, R.; Salem, R. The COVID-19 Cytokine Storm; What We Know So Far. Front. Immunol. 2020, 11, 1446.
3. Khadke, S.; Ahmed, N.; Ahmed, N.; Ratts, R.; Raju, S.; Gallogly, M.; de Lima, M.; Sohail, M.R. Harnessing the immune system to overcome cytokine storm and reduce viral load in COVID-19: A

review of the phases of illness and therapeutic agents. Virol. J. 2020, 17, 154.

4. Coperchini, F.; Chiovato, L.; Croce, L.; Magri, F.; Rotondi, M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020, 53, 25–32.
5. Lukan, N. “Cytokine storm”, not only in COVID-19 patients. Mini-review. Immunol. Lett. 2020, 228, 38–44.
6. De La Rica, R.; Borges, M.; Gonzalez-Freire, M. COVID-19: In the Eye of the Cytokine Storm. Front. Immunol. 2020, 11, 2313.
7. Fara, A.; Mitrev, Z.; Rosalia, R.A.; Assas, B.M. Cytokine storm and COVID-19: A chronicle of pro-inflammatory cytokines. Open Biol. 2020, 10, 200160.
8. Morens, D.M.; Taubenberger, J.K.; Harvey, H.A.; Memoli, M.J. The 1918 influenza pandemic: Lessons for 2009 and the future. Crit. Care Med. 2010, 38 (Suppl. 4), e10.
9. Yüce, M.; Filiztekin, E.; Özkaya, K.G. COVID-19 diagnosis—A review of current methods. Biosens. Bioelectron. 2020, 172, 112752.
10. Salian, V.S.; Wright, J.A.; Vedell, P.T.; Nair, S.; Li, C.; Kandimalla, M.; Tang, X.; Porquera, E.M.C.; Kalari, K.R.; Kandimalla, K.K. COVID-19 Transmission, Current Treatment, and Future Therapeutic Strategies. Mol. Pharm. 2021, 18, 754–771.
11. Alsharif, W.; Qurashi, A. Effectiveness of COVID-19 diagnosis and management tools: A review. Radiography 2020, 27, 682–687.
12. Lee, C.; Choi, W.J. Overview of COVID-19 inflammatory pathogenesis from the therapeutic perspective. Arch. Pharm. Res. 2021, 44, 99–116.
13. Choi, J.Y.; Smith, D.M. SARS-CoV-2 Variants of Concern. Yonsei Med. J. 2021, 62, 961–968.
14. Singh, J.; Pandit, P.; McArthur, A.G.; Banerjee, A.; Mossman, K. Evolutionary trajectory of SARS-CoV-2 and emerging variants. Virol. J. 2021, 18, 166.
15. Boehm, E.; Kronig, I.; Neher, R.A.; Eckerle, I.; Vetter, P.; Kaiser, L. Novel SARS-CoV-2 variants: The pandemics within the pandemic. Clin. Microbiol. Infect. 2021, 27, 1109–1117.
16. Cantón, R.; De Lucas Ramos, P.; García-Botella, A.; García-Lledó, A.; Gómez-Pavón, J.; González Del Castillo, J.; Hernández-Sampelayo, T.; Martín-Delgado, M.C.; Martín Sánchez, F.J.; Martínez-Sellés, M.; et al. New variants of SARS-CoV-2. Rev. Esp. Quimioter. 2021, 34, 419–428.
17. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395, 497–506.

18. Mehta, P.; McAuley, D.F.; Brown, M.; Sanchez, E.; Tattersall, R.S.; Manson, J.J. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020, 395, 1033–1034.
19. Merad, M.; Martin, J.C. Pathological inflammation in patients with COVID-19: A key role for monocytes and macrophages. Nat. Rev. Immunol. 2020, 20, 355–362.
20. Hussman, J.P. Cellular and Molecular Pathways of COVID-19 and Potential Points of Therapeutic Intervention. Front. Pharmacol. 2020, 11, 1169.
21. Zuo, Y.; Yalavarthi, S.; Shi, H.; Gockman, K.; Zuo, M.; Madison, J.A.; Blair, C.; Weber, A.; Barnes, B.J.; Egeblad, M.; et al. Neutrophil extracellular traps in COVID-19. JCI Insight 2020, 5, e138999.
22. Drexler, J.F.; Corman, V.M.; Drosten, C. Ecology, evolution and classification of bat coronaviruses in the aftermath of SARS. Antivir. Res. 2013, 101, 45–56.
23. Taylor, D.R. Obstacles and advances in SARS vaccine development. Vaccine 2006, 24, 863–871.
24. Du, L.; He, Y.; Zhou, Y.; Liu, S.; Zheng, B.-J.; Jiang, S. The spike protein of SARS-CoV—A target for vaccine and therapeutic development. Nat. Rev. Microbiol. 2009, 7, 226–236.
25. de Wit, E.; Van Doremalen, N.; Falzarano, D.; Munster, V.J. SARS and MERS: Recent insights into emerging coronaviruses. Nat. Rev. Microbiol. 2016, 14, 523–534.
26. Tong, T.R. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Perspect. Med. Virol. 2006, 16, 43–95.
27. Ziebuhr, J. Molecular biology of severe acute respiratory syndrome coronavirus. Curr. Opin. Microbiol. 2004, 7, 412–419.
28. Openshaw, P.J. What does the peripheral blood tell you in SARS? Clin. Exp. Immunol. 2004, 136, 11–12.
29. Al-Samkari, H.; Berliner, N. Hemophagocytic Lymphohistiocytosis. Annu. Rev. Pathol. Mech. Dis. 2018, 13, 27–49.
30. Soy, M.; Keser, G.; Atagündüz, P.; Tabak, F.; Atagündüz, I.; Kayhan, S. Cytokine storm in COVID-19: Pathogenesis and overview of anti-inflammatory agents used in treatment. Clin. Rheumatol. 2020, 39, 2085–2094.
31. Mahallawi, W.H.; Khabour, O.F.; Zhang, Q.; Makhdoum, H.M.; Suliman, B.A. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine 2018, 104, 8–13.
32. Wong, C.K.; Lam, C.W.K.; Wu, A.K.L.; Ip, W.K.; Lee, N.L.S.; Chan, I.H.S.; Lit, L.C.W.; Hui, D.S.C.; Chan, M.H.M.; Chung, S.S.C.; et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin. Exp. Immunol. 2004, 136, 95–103.

33. Zhang, X.; Wu, K.; Wang, D.; Yue, X.; Song, D.; Zhu, Y.; Wu, J. Nucleocapsid protein of SARS-CoV activates interleukin-6 expression through cellular transcription factor NF-κB. Virology 2007, 365, 324–335.
34. Channappanavar, R.; Perlman, S. Pathogenic human coronavirus infections: Causes and consequences of cytokine storm and immunopathology. Semin. Immunopathol. 2017, 39, 529–539.
35. Huang, K.-J.; Su, I.-J.; Theron, M.; Wu, Y.-C.; Lai, S.-K.; Liu, C.-C.; Lei, H.-Y. An interferon-gamma?-related cytokine storm in SARS patients. J. Med Virol. 2004, 75, 185–194.
36. Shah, V.K.; Firmal, P.; Alam, A.; Ganguly, D.; Chattopadhyay, S. Overview of Immune Response During SARS-CoV-2 Infection: Lessons from the Past. Front Immunol. 2020, 11, 1949.
37. Bleibtreu, A.; Bertine, M.; Bertin, C.; Houhou-Fidouh, N.; Visseaux, B. Focus on Middle East respiratory syndrome coronavirus (MERS-CoV). Med. Mal. Infect. 2019, 50, 243–251.
38. Chafekar, A.; Fielding, B. MERS-CoV: Understanding the Latest Human Coronavirus Threat. Viruses 2018, 10, 93.
39. Widagdo, W.; Na Ayudhya, S.S.; Hundie, G.B.; Haagmans, B.L. Host Determinants of MERS-CoV Transmission and Pathogenesis. Viruses 2019, 11, 280.
40. Nassar, M.; Bakhrebah, M.A.; Meo, S.A.; Alsuabeyl, M.S.; Zaher, W.A. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: Epidemiology, pathogenesis and clinical characteristics. Eur. Rev. Med. Pharm. Sci. 2018, 22, 4956–4961.
41. Zumla, A.; Hui, D.S.; Perlman, S. Middle East respiratory syndrome. Lancet 2015, 386, 995–1007.
42. Min, C.-K.; Cheon, S.; Ha, N.-Y.; Sohn, K.M.; Kim, Y.; Aigerim, A.; Shin, H.M.; Choi, J.-Y.; Inn, K.-S.; Kim, J.H.; et al. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. Sci. Rep. 2016, 6, 25359.
43. Sun, X.; Wang, T.; Cai, D.; Hu, Z.; Chen, J.; Liao, H.; Zhi, L.; Wei, H.; Zhang, Z.; Qiu, Y.; et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev. 2020, 53, 38–42.
44. Chan, J.F.-W.; Lau, S.K.P.; To, K.K.W.; Cheng, V.C.C.; Woo, P.C.Y.; Yuen, K.-Y. Middle East Respiratory Syndrome Coronavirus: Another Zoonotic Betacoronavirus Causing SARS-Like Disease. Clin. Microbiol. Rev. 2015, 28, 465–522.
45. Phung, T.T.B.; Sugamata, R.; Uno, K.; Aratani, Y.; Ozato, K.; Kawachi, S.; Nguyen, L.T.; Nakayama, T.; Suzuki, K. Key role of regulated upon activation normal T-cell expressed and secreted, nonstructural protein1 and myeloperoxidase in cytokine storm induced by influenza

virus PR-8 (A/H1N1) infection in A549 bronchial epithelial cells. Microbiol. Immunol. 2011, 55, 874–884.

46. Sullivan, S.J.; Jacobson, R.M.; Dowdle, W.R.; Poland, G.A. 2009 H1N1 Influenza. Mayo Clin. Proc. 2010, 85, 64–76.
47. Patel, M.; Dennis, A.; Flutter, C.; Khan, Z. Pandemic (H1N1) 2009 influenza. Br. J. Anaesth. 2010, 104, 128–142.
48. Khanna, M.; Gupta, N.; Gupta, A.; Vijayan, V.K. Influenza A (H1N1) 2009: A pandemic alarm. J. Biosci. 2009, 34, 481–489.
49. Zeng, H.; Belser, J.A.; Goldsmith, C.S.; Gustin, K.M.; Veguilla, V.; Katz, J.M.; Tumpey, T.M. A(H7N9) virus results in early induction of proinflammatory cytokine responses in both human lung epithelial and endothelial cells and shows increased human adaptation compared with avian H5N1 virus. J. Virol. 2015, 89, 4655–4667.
50. Beigel, J.H.; Farrar, J.; Han, A.M.; Hayden, F.G.; Hyer, R.; de Jong, M.D.; Lochindarat, S.; Nguyen, T.K.; Nguyen, T.H.; Tran, T.H.; et al. Avian influenza A (H5N1) infection in humans. N. Engl. J. Med. 2005, 353, 1374–1385.
51. Peiris, J.; Yu, W.; Leung, C.; Cheung, C.; Ng, W.; Nicholls, J.M.; Ng, T.; Chan, K.; Lai, S.; Lim, W.; et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet 2004, 363, 617–619.
52. Monteagudo, P.L.; Muñoz-Moreno, R.; Fribourg, M.; Potla, U.; Mena, I.; Marjanovic, N.; Hartmann, B.; Sealfon, S.C.; García-Sastre, A.; Ramos, I.; et al. Differential Modulation of Innate Immune Responses in Human Primary Cells by Influenza A Viruses Carrying Human or Avian Nonstructural Protein 1. J. Virol. 2019, 94, e00999-19.
53. Teijaro, J.R.; Walsh, K.B.; Cahalan, S.; Fremgen, D.M.; Roberts, E.; Scott, F.; Martinborough, E.; Peach, R.; Oldstone, M.B.; Rosen, H. Endothelial Cells Are Central Orchestrators of Cytokine Amplification during Influenza Virus Infection. Cell 2011, 146, 980–991.
54. D'Elia, R.V.; Harrison, K.; Oyston, P.C.; Lukaszewski, R.A.; Clark, G.C. Targeting the "Cytokine Storm" for Therapeutic Benefit. Clin. Vaccine Immunol. 2013, 20, 319–327.
55. Jose, R.J.P.; Manuel, A. COVID-19 cytokine storm: The interplay between inflammation and coagulation. Lancet Respir. Med. 2020, 8, e46–e47.
56. Liu, Q.; Zhou, Y.-H.; Yang, Z.-Q. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell. Mol. Immunol. 2015, 13, 3–10.
57. Oldstone, M.B.; Teijaro, J.R.; Walsh, K.B.; Rosen, H. Dissecting influenza virus pathogenesis uncovers a novel chemical approach to combat the infection. Virology 2012, 435, 92–101.

58. Bermejo-Martin, J.F.; De Lejarazu, R.O.; Pumarola, T.; Rello, J.; Almansa, R.; Ramírez, P.; Martin-Loeches, I.; Varillas, D.; Gallegos, M.C.; Serón, C.; et al. Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. Crit. Care 2009, 13, R201.
59. Betakova, T.; Kostrabova, A.; Lachova, V.; Turianova, L. Cytokines Induced During Influenza Virus Infection. Curr. Pharm. Des. 2017, 23, 2616–2622.
60. Jin, S.; Li, Y.; Pan, R.; Zou, X. Characterizing and controlling the inflammatory network during influenza A virus infection. Sci. Rep. 2014, 4, 3799.
61. La Gruta, N.L.; Kedzierska, K.; Stambas, J.; Doherty, P.C. A question of self-preservation: Immunopathology in influenza virus infection. Immunol. Cell Biol. 2007, 85, 85–92.
62. Coon, B.G.; Baeyens, N.; Han, J.; Budatha, M.; Ross, T.D.; Fang, J.S. Intramembrane binding of VE-cadherin to VEGFR2 and VEGFR3 assembles the endothelial mechanosensory complex. J. Cell Biol. 2015, 208, 975–986.
63. Hagau, N.; Slavcovici, A.; Gonganau, D.N.; Oltean, S.; Dirzu, D.S.; Brezoszki, E.S.; Maxim, M.; Ciuce, C.; Mlesnite, M.; Gavrus, R.L.; et al. Clinical aspects and cytokine response in severe H1N1 influenza A virus infection. Crit. Care 2010, 14, R203.
64. Oshansky, C.M.; Gartland, A.J.; Wong, S.-S.; Jeevan, T.; Wang, D.; Roddam, P.L. Mucosal immune responses predict clinical outcomes during influenza infection independently of age and viral load. Am. J. Respir. Crit. Care Med. 2014, 189, 449–462.
65. To, K.K.; Hung, I.F.; Li, I.W.; Lee, K.L.; Koo, C.K.; Yan, W.W. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2010, 50, 850–859.
66. Woo, P.C.Y.; Tung, E.T.K.; Chan, K.; Lau, C.C.Y.; Lau, S.K.P.; Yuen, K.-Y. Cytokine Profiles Induced by the Novel Swine-Origin Influenza A/H1N1 Virus: Implications for Treatment Strategies. J. Infect. Dis. 2010, 201, 346–353.