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Oxidative Stress Following Influenza Virus; An Overview

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Abstract

Oxidative stress causes from an imbalance between the cells' capacity to remove them through detoxification processes and generation of reactive oxygen species (ROS). Apart from triggering the host's immune response, the influenza virus has the ability to cause oxidative stress by directly targeting the cellular antioxidant systems. In this article, we will discuss the multifaceted role of oxidative stress in the pathogenesis of the influenza virus. On the one hand, oxidative stress can contribute to the clearance of the virus by stimulating the host's immune response. On the other hand, excessive oxidative stress can also contribute to the severity of the disease by causing tissue damage and inflammation.

Introduction

The influenza virus belongs to the Orthomyxoviridae family, characterized by an enveloped structure and a negative-sense single-stranded RNA genome. In humans, Type A and Type B influenza viruses cause significant morbidity and mortality. Despite annual vaccination campaigns, the virus is capable of evading host immune responses by continually generating new strains via antigenic shift, drift, and mutation. These mechanisms enable the virus to establish infection and cause disease in susceptible populations [1].

Reactive oxygen species (ROS) are generated as a regular byproduct of cellular metabolism and participate in numerous biological pathways. However, an imbalance in the cellular redox state can result in oxidative stress, leading to deleterious effects such as DNA damage, inflammation, and dysregulation of cell proliferation. These consequences reflect the multifaceted nature of ROS and highlight the importance of maintaining redox homeostasis for proper cellular function [2].

Multiple studies have suggested that influenza viruses induce excessive ROS production, leading to oxidative stress and respiratory cell pathophysiology. Despite the virus's ability to generate ROS, various cellular processes are activated to maintain a normal redox state during infection. Among these processes, the superoxide dismutase (SOD) family plays a crucial role as the most significant cellular antioxidant factor.

Notably, research indicates that influenza virus infection downregulates SOD1 levels, resulting in increased ROS production. Prolonged exposure to excessive ROS exacerbates the virus's pathogenesis and contributes to tissue damage. These findings highlight the delicate balance between ROS and cellular redox state during influenza virus infection and underscore the significance of SOD as a key regulator of ROS production [3,4].

Findings

Several studies have shown that influenza viruses cause oxidative stress state within the cell [5]. In the following article, the possible mechanisms of the virus in inducing oxidative stress will be discussed. One mechanism for the Influenza A virus (IAV) to increase reactive oxygen species (ROS) is by downregulating superoxide anion dismutase 1 (SOD1). Influenza virus PB1-F2 induces cell death by inactivating matrix metalloproteinases and releasing proapoptotic proteins [6]. Through inhibiting SOD1, PB1-F2 contributes to alveolar epithelial cells production of mitochondrial ROS. Moreover, PB1-F2-induced ROS cause the inflammasome to activate and secrete IL-1β which is one of the inflammatory cytokines [3]. Furthermore, PB1-F2 represses the mitochondrial internal-membrane potential. PB1-F2 can trigger the permeabilization and instability of mitochondrial membranes by forming a variety of sized pores in planar lipid membranes [7].

The NOX family, which includes the members NOX1 to NOX5, DUOX1, and DUOX2, are present in cells and phagosome mem-

branes [8]. It is seen that following A549 cell lines infection with H5N1 IV, NOX was upregulated whereas SOD1, SOD3, CAT, and Nrf2 were downregulated [9]. In IV infection, NOX2 and NOX4 appear to be implicated in the formation of ROS [10,11]. Activation of DUOX2-induced ROS production in airway cells was observed via IFN induction and stimulated the expression of the melanoma-associated differentiation gene 5 (MDA5) and the double-stranded RNA helicase enzyme RIG-1-like receptor (RIG-1) [12].

Another mechanism involved in the OS establishment of the virus is through an surge in ROS and a decrease in intracellular glutathione (GSH). Glucose- 6-phosphate dehydrogenase (G6PD) regenerates the reduced form of GSH, which also maintains redox equilibrium. However, Infection with the influenza virus leads to a decrease in both the expression and activity of G6PD [13]. Moreover, sirtuin 2 (SIRT2) and nuclear factor erythroid 2-related factor 2 (NRF2) expression were both downregulated together with G6PD following infection [14].

The third mechanism involved in OS induction is through NS1 protein. In chicken oviduct epithelial cells (COECs) treated with NS1 expression plasmids, the quantity of avian influenza virus NS1 protein was associated with elevated levels of ROS. It's interesting to note that NS1-transfected COECs showed lower superoxide dismutase and catalase activity [2].

However, through the OS state within the cell, MicroRNAs (miRNAs) expression is changed. MiRs are one of the important noncoding RNAs that regulate a variety of cellular pathways by regulating gene expression. Interactions and regulation between Ros and miRNA can occur during influenza virus infection [4]. Different experimental models demonstrate differential expression of miRNAs under oxidative stress (mainly miR-9, -21, -220a, and -141) [15]. MiR-9 expression is stimulated by IAV through OS generation, which augments viral replication and mitochondrial dysfunction [4].

As a result of IAV induced ROS, miR-141 expression is enhanced to diminish cellular inflammation through the Nrf2 pathway [16]. In ROS conditions, miR-21 and miR-200a also seem to be upregulated which are involved in IAV infected cells-inhibited apoptosis [17].

IV infection can decrease downstream molecules of the Nrf2 pathway, such as SOD1, HO-1, NQO1, and CAT; thus, regulation of these molecules has a significant role in elevated ROS following IV infection [18,19].

IVs have the ability to control various oxidative-stress signaling pathways, such as PI3K/AKT, NF-κB, and MAPK, which ultimately enhance viral replication and contribute to the development of disease. Therefore, manipulating these signaling pathways may exacerbate the lung damage caused by IV infection [20] (Figure 1).

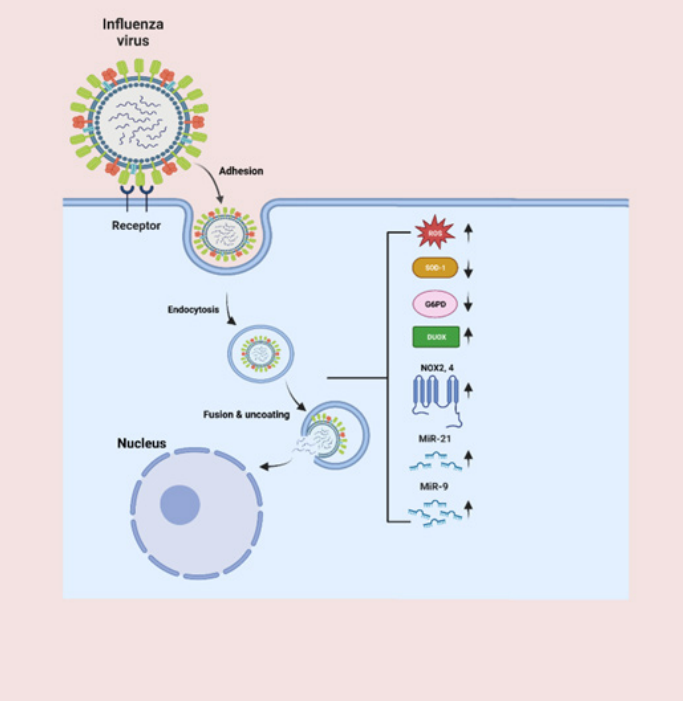

Figure 1: Oxidative stress following influenza infection. Upon infection, the virus triggers an elevation in free radicals and a reduction in antioxidant levels. Virus also leads to a subsequent rise in the quantity of MiR-21, which in turn contributes to the further accumulation of free radicals. On the other hand, the upsurge in MiR-9 is a direct consequence of the heightened levels of free radicals.

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Discussion

Influenza virus infection is a major cause of respiratory illness worldwide. The virus infects the respiratory epithelial cells, leading to an inflammatory response and tissue damage. One of the mechanisms underlying this damage is oxidative stress induction, which occurs due to the excessive production of ROS by infected cells.

ROS and RNS are known to damage cellular macromolecules and disrupt cellular signaling pathways, leading to cellular dysfunction and death. Moreover, these species are also known to activate pro-inflammatory pathways, leading to an exacerbation of the inflammatory response. Several studies have demonstrated the induction of oxidative stress during influenza virus infection [11,21].

The induction of oxidative stress during influenza virus infection has important implications for disease pathogenesis and treatment. For example, antioxidants have been shown to reduce oxidative stress, influenza associated complications such as pneumonia and improve lung function [22]. Moreover, a recent study showed that treatment with the antioxidant N-acetylcysteine (NAC) reduced viral replication and inflammation in mice infected with the H5N1 highly pathogenic influenza virus [21,23]. Oxidative stress induction is a key mechanism underlying the pathogenesis of influenza virus infection. Targeting oxidative stress pathways may represent a promising approach for the treatment of this disease.

Conclusion

It is evident that augmenting comprehension of the oxidative stress mechanism of the influenza virus can yield novel insights into the pathogenesis of the virus. Additionally, it can offer a therapeutic avenue for curtailing and managing influenza virus infection, particularly in cases of highly virulent human avian influenza.

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