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Host Cell Redox-Regulated Pathways as Targets for Novel Anti-influenza Strategy

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Every year, influenza occurs globally with an attack rate estimated at 5-10% in adults and 20-30% in children, causing thousands of hospitalizations, especially among the elderly, young children, immuno-compromised individuals or subjects affected by chronic diseases at increased risk of developing complications. Worldwide, annual epidemics are estimated to result in about 3 to 5 million cases of severe illness and about 250,000 to 500,000 deaths [1]. Influenza virus is an enveloped virus belonging to the *Orthomyxoviridae* family, characterized by a negative-sense, single-stranded and segmented RNA genome, that possesses eight segments encoding 10 well-known proteins, and other novel proteins identified in the last years [2,3]. The envelope contains the hemagglutinin (HA), the neuraminidase (NA), and the matrix 2 (M2) proteins, that project from the surface of the virus. The matrix protein 1 (M1) lies under the envelope, and the core of the virus comprises

The ribonucleoprotein (RNP) complex, consisting of the viral RNA segments, the polymerase proteins (PB1, PB2 and PA) and the nucleoprotein. Based on the HA and the NA glycoproteins, influenza A viruses are divided into different subtypes, that are 18 HA(H1-H18) and 11 NA(N1-N11) subtypes [4]. The high frequency of genetic recombination and antigenic variations on viral HA and NAcause recurrent outbreaks at intervals of 1-3 years. In contrast, pandemics are occasional and occur with a frequency ranging from 10 to 50 years. In the spring of 2009, a new influenza A (H1N1) strain was identified in Mexico and caused the first pandemic of the twenty-first century, characterized by moderate infections and mortality comparable to that of seasonal influenza, even if acute respiratory crisis and pneumonia, especially in children and young adults,have been reported [5,6].

Presently, the most effective preventive measure against influenza is represented by vaccination, but because of the great antigenic variability of the virus strains, every year a new vaccine must be formulated and effective vaccines cannot be produced quickly enough to deal with emergency threats. The antiviral therapy has two classes of drugs available for use in humans: the adamantanes, which target the M2 ion channel and inhibit viral uncoating and NA inhibitors, oseltamivir and zanamivir, which impair release of virus from the infected cells. However, the toxicity of these drugs and the rapid emergence of new drug-resistant viral strains, highlight the urgent need for molecules that act on novel molecular targets, providing safe and effective protection against the influenza virus [7].

In this context, targeting of interactions between virus and host cell has been proposed as a novel antiviral strategy, both reducing viral replication and lung inflammation, being this latter the cause of severity of disease. Influenza virus is able to induce an imbalance of the oxido-reductive (redox) state in the host cell, characterized by a depletion of glutathione (GSH, the main intracellular antioxidant) and an increase of reactive oxygen species [8]. Virus-induced oxidative stress activates specific redox-mediated signaling pathways, including the Mitogen Activated Protein Kinases (MAPK), the Protein Kinase C (PKC) or transcription factors such as the Nuclear Factor-kB, that are hijacked by virus to ensure its own replication. Interestingly, the same pathways are also involved in multiple physiological functions of the cell, including immune and inflammatory responses, as well as cell death/survival of host cell [8]. For this reason, many efforts have been made to study the effectiveness of different antioxidants in the inhibition of influenza virus infection. Several compounds, natural o synthesized, have been proposed to be effective. Among them, our research group has reported the antiviral efficacy of two different antioxidants, a n-butanoyl derivative of GSH (GSH-C4) and the natural compound Resveratrol (RV). Each compoundis able to potently inhibit influenza virus replication in both *in vitro* and *in vivo* models, even if their mechanism of action is different [9,10]. The effect of GSH-C4 is strictly related to its antioxidant properties, in fact, by restoring intracellular GSH levels; GSH-C4interfereswith maturation of the viral glycoprotein HA. This process is largely mediated by the redox-sensitive activities of host-cell oxidoreductase-protein disulfide isomerase (PDI). Indeed, the oxidative environment caused by influenza virusis needed to increase the expression and oxidation of PDI in the endoplasmic reticulum, accelerating protein folding and enhancing viral glycoprotein maturation. The polyphenol RV reduces viral replicationthrough inhibition of MAPK and PKCactivities, both pathwaysinvolved in the regulation of vRNP nuclear-cytoplasmic translocation. However, no correlation between RV's antioxidant and antiviral activityis found. In particular, RV treatment is not able to restore influenza virus-induced GSH depletion and rather in uninfected cells it diminishes the intracellular GSH content. This event can be explained since some antioxidants can produce *in vivo* antioxidant or pro-oxidant effects, depending on their own oxidative status, which in turn reflects the specific redox potential in the microenvironment [11].

Based on these assumptions, we suggest that inactivation of redox-sensitive host cell pathways may be considered as novel target for new strategies against influenza, since it offers two important advantages: it is more difficult for the virus to adapt to, and it can also be expected to affect viral replication independently of the invader's type, strain and antigenic properties. However, it must be noted that not all antioxidants act in the same way and their efficacy may depend on the dose, the ability to affect redox-regulated pathways and on the redox state of the microenvironment. Thus, these concepts should be taken into account

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before recommending the use of antioxidants in the treatment of viral infections.

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