Reactive Oxygen Species (ROS) Homeostasis in Influenza Virus Infection

Ker-Kong Chen[1], Moeko Minakuchi[2], Kenly Wuputra[3, 4], Chia-Chen Ku[3, 4], Jia-Bin Pan[3,4], Kung-Kai Kuo[5], Ying-Chu Lin[1], Shigeo Saito[2,6], Chang-Shen Lin[3, 7]*, and Kazunari K. Yokoyama[3, 4]*

[1]School od Dentistry, [3]Graduate Institute of Medicine, [4]Center for Stem Cell Research, Kaohsiung Medical University, Kaohsiung 807, Taiwan; [2]Waseda Research Institute for Science and Engineering, Shinjuku, Tokyo 162-8480, Japan, [5]Department Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan: [6]Saito Laboratory of Cell Technology Institute, Yaita 329-1471, Tochigi, Japan; [7]Department of Biological Sciences, National Sun Yat-sen University, Kaohsiung 80424, Taiwan

*Drs. Kazunari K. Yokoyama and Chang-Shen Lin are the corresponding authors, Graduate Institute of Medicine, Kaohsiung Medical University, 100 Shih-Chuan 1st Rd., San-Ming District, Kaohsiung 80807, Taiwan; Phone, +886-712-1101, ext 2729; Fax, +886-7313-3849: e-mail, kazu@kmu.edu.tw and changshenlin@gmail.com

Abstract: Cellular oxidation is responsive to external and internal stimulation and is generated via signal molecules in defense mechanisms through networks of cell proliferation, differentiation, intracellular detoxification, bacterial infection, and immune reactions. Oxidative stress is not necessarily harmful per se; it depends on the balance between oxidation and antioxidation cascades, which are induced according to stimuli and can maintain oxygen homeostasis. The reactive oxygen species (ROS) that are generated during influenza virus (IV) infection have critical effects on both the virus and host cells. In this review, we outline the link between viral infection and ROS production, using IV as an example. We introduce the current state of knowledge on the molecular relationship between cellular oxidation mediated by ROS production and various effects of IV infection. We also summarize the potential anti-IV agents that act by targeting oxidative stress.

Keywords: antioxidation; aryl hydrocarbon receptor; cellular oxidation; nuclear factor E2-related factor 2; reactive oxygen species

1. Introduction

Influenza viruses (IVs) have been found in pandemics and seasonal epidemics and are serious threats to humans [1–4]. Currently, vaccination is a key strategy against IV infection; however, effective vaccines may not be produced that precisely target new and emerging IV strains. Several anti-influenza drugs, including adamantanes, target the IV M2 protein and inhibit virus uncoating, whereas neuraminidase (NA) inhibitors block virus release from host cells [5,6]. However, because of resistance to antiviral agents, additional anti-influenza drugs should be developed to control IV outbreaks.

Reactive oxygen species (ROS) are often generated during IV infection [7], thus promoting apoptosis, lung injury (LI), and inflammation/allergy [7–10]. Inhibitors of NADPH oxidase 2 (NOX2), an enzyme that is responsible for ROS production, are useful to protect mammals against severe IV infection [10]. These studies indicate the crucial roles of ROS in IV infection, which may have implications for therapy. In this review, we summarize ROS generation and redox control of the host cells upon IV infection and discuss how ROS can influence IV replication. We also describe the potential therapeutics against IV infection through modulating ROS and antioxidation of host cells and list their merits for clinical use.

1.1. ROS generation and antioxidation system in cells

Mitochondria are the target organelle of oxidation–reduction reactions [11]. Mitochondria play major roles not only in the production of adenosine triphosphate but also in the generation of ROS during oxidative phosphorylation [12]. The hydrogen peroxide (H_2O_2), hydroxyl radicals ($HO^{\bullet}$), and superoxide anions ($O_2^{\bullet-}$) produced during oxidation are identified as ROS [13]. Intracellular ROS are produced mainly by enzymes, such as mitochondrial nicotine adenine dinucleotide phosphate (NADPH) oxidase (NOX) [14], xanthine oxidase (XO) [15,16], cytochrome p450 (CYP) [17,18], and other mitochondrial respiratory complexes, polyamines, lipid-catabolizing enzymes, and dual oxidase (DUOX) family members.

The mechanisms underlying superoxide anion production and the single-electron reduction of 8-nitroguanosine into the respective anion radical via NADPH-cytochrome P450 reductase (POR) have been reported [7]. Any of the isoforms of nitrogen oxide synthase (iNOS), or even XO, subsequently transfers electrons to molecular oxygen [19].

The balance of redox reactions is maintained in normal cells by the antioxidant system, which includes enzymatic antioxidant systems, such as superoxide dismutases (SODs) and catalases (CATs), glutathione peroxidase (GPx), and glutaredoxins (GR), and a nonenzymatic system, which consists of anserine, carnosine, carotenoids, flavonoids, GSH, homocarnosine, melatonin, vitamin C, and vitamin E [20,21]. The decrease in GSH/GSSG, which is a cellular antioxidant index, is caused by the decrease in the level of GSH, which acts as a redox buffer within cells [22]. GSH is a scavenger of singlet oxygen and hydroxyl radicals, a detoxification molecule of hydrogen and lipid peroxide, and a cofactor of enzymes of detoxification. It also plays a key role in suppressing oxidative stress in several RNA viruses, including IVs [23].

Nuclear factor E2-related factor 2 (Nrf2) regulates the expression of enzymes that participate in the defense against oxidation [63]. In the presence of normal levels of ROS, the expression of Nrf2 is regulated by the Kelch-like ECH-associated protein 1 (Keap 1), which targets Nrf2 to ubiquitin-mediated degradation in the cytoplasm. In the presence of increased ROS production, the Nrf2 molecule dissociates from Keap 1 and translocates into the nucleus, where it binds to the antioxidant-response element (ARE) together with the small Maf transcription factors in the promoters of target genes that encode antioxidant enzymes. Notably, the promoter of the *Nrf2* gene itself contains AREs [24] and amplifies the redox cascades via positive-feedback regulation.

The cytoplasmic aryl hydrocarbon receptor (AhR) protein binds to the ligands that have translocated into the nucleus and activates the expression of a large family of antioxidant molecules, i.e., the cytochrome p450 proteins (CYP1A1, CYP1A2, and CYP1B) [25], as well as several other antioxidation proteins, such as NAD(P)H quinone oxidoreductase 1 (NQO1), after the formation of heterodimers with Arnt. These enzymes catalyze primarily oxidative-detoxification reactions.

1.2. IV

The genomes of IVs consist of negative single-stranded RNAs that are associated with the viral

nucleoprotein (NP) and interact with heterotrimeric viral RNA-dependent RNA polymerases, i.e., polymerase basic protein 1 (PB1), PB2, and polymerase acidic protein (PA), to build the viral ribonucleoprotein (vRNP) complexes.

Various antioxidation molecules are activated by IV infection, to ameliorate ROS damage in host cells. To examine the role of oxygen free radicals in hosts, SOD conjugated with a copolymer of pyran was administered to decay free radicals; this approach prevented infection with IV in mice [26]. GSH inhibits the expression of viral matrix proteins, IV replication, and the production of virion particles. Furthermore, GSH suppresses the upregulation of Fas, caspase activation, and apoptosis in infected cells [27]. However, IV infection disrupts redox balance by decreasing GSH production and promoting the propagation of their progeny, thus resulting in cell death [28]. The mechanism underlying the IV-induced downregulating of GSH remains unknown.

The replication of IVs is also affected by the Nrf2-regulated redox state [29]. The activation of the Nrf2/heme oxygenase 1 (HO-1) and toll-like receptor (TLR)/mitogen activated protein kinase (MAPK)/nuclear factor kappa B (NF-κB) signaling pathways is involved in IV replication and IV-related pneumonia [30,31]. In some cases, the aryl hydrocarbon receptor (AhR) also regulates redox genes, such as the *NQO1* gene, to maintain the ROS balance in host cells [32].

At the molecular level, IVs induce oxidative stress via AhR in the cytoplasm, especially in the endoplasmic reticulum (ER) and mitochondria, which is followed by the production of ROS. Simultaneously, the AhR transcription factor is translocated into the nucleus to activate the phase I target genes, which encode detoxification enzymes, several antioxidation enzymes, and genes for the immunoregulatory and allergy related genes of anti-viral immunity [7,33,34]. If the extent of ROS production surpasses the level of antioxidation, the ROS balance was abrogated, and the IV-infected cells commit to apoptosis and necrosis for cell death. If the ROS generation is cancelled by the antioxidation, the redox balance is remained to commit the resistance of host cells to the IV infection and the anti-viral immunity.

Cellular proliferation and cellular apoptosis/necrosis, in addition to the immunity and allergy, are mostly dependent on the ROS balance [35]. Thus, ROS act as bifunctional reactors and exhibit both "good and bad" aspects in living cells, which might be similar in IV-infected host cells and the propagation of IV progeny [35].

2. ROS production in IV-infected cells

Increased ROS, activation of iNOS 2 for reactive nitrogen species (RNS) production, and higher level of nitrotyrosine have been detected in IV patients [9]. Some source of IV-infected ROS in host cells are summarized below.

2.1. PB1-F2 induces ROS production in host cells

PB1-F2 in influenza type A interacts with the adenine nucleotide translocator and the voltage-dependent anion channel 1 and inactivates matrix metalloproteinases, releases proapoptotic proteins, and induces cell death [36,37]. PB1-F2 is involved in the generation of mitochondrial ROS in alveolar epithelial cells by downregulating SOD1 [38]. In addition, H7N9 PB1-F2-induced ROS trigger inflammasome activation and IL-1β secretion, which is inhibited by Mitotempo, an inhibitor of mitochondrial ROS [39]. After viral infections, NOD-like receptor pyrin domain-containing-3 (NLRP3)/ /inflammasomes are activated to induce pyroptosis, a death pathway that is inherently associated with inflammation by activating caspase-1 and the secretion of cytokines from infected cells [38,39].

2.2. NOX and DUOX protein families

IV infection can induce cell death through viral PB1-F2, which targets mitochondria. Moreover, this cell death is conserved in influenza type A viruses, but not in influenza type B viruses [36,37]. In addition to the mitochondrial respiratory complex, ROS generated from NOX are involved in the pathogenesis of IV infection. The NOX family is found in cell and phagosome membranes and comprises several members: NOX1 to NOX5 and DUOX1 and DUOX2 [40]. An increase of NOX expression and downregulation of SOD1, SOD3, the

nuclear factor E2-related factor 2 (Nrf2), and catalase were also downregulated in H5N1-infected A549 cells [28]. Infection with H5N1 decreased *SOD1* promoter activity, whereas the forced expression of SOD1 disrupted H5N1 virus replication in A547 cells.

NOX2 seems to be involved in the production of ROS during IV infection [8,10,11]. In a mouse model, Nox2-derived superoxide is critical for IV-induced pulmonary damage. $Nox2^{-/-}$ knockout (KO) mice exhibit a milder airway inflammation and less apoptotic alveolar epithelium after IV infection than do wild-type mice [41]. The IV-mediated production of ROS and reactive nitrogen species (RNS) was decreased in $Nox2^{-/-}$ KO mice [41]. Furthermore, the titer of active competent viruses and their associated inflammatory activities were decreased in these KO mice [42]. Therefore, NOX2 is a candidate anti-ROS therapy to manage IV infection [41].

NOX4 plays a role in ROS production in lung cancers and in IV-infected primary epithelium cells [42]. The production of superoxide anion in bronchoalveolar lavage fluid-derived fibroblasts from H3N2-infected $Nox1^{-/-}$ KO mice was inhibited at day 7 postinfection; however, on day 3 (in the early stages of infection), it was unchanged compared with the level detected in the wild-type littermates [43]. Mice expressing an inactive Nox1 ($Nox1^{*/y}$) exhibited a greater survival rate after an influenza type A virus challenge than control mice [44]. The adaptive immune response was altered after the IV challenge in these mice, such as a decrease in virus-specific CD8+ T cells in the lung, an increase in the number of virus-specific CD8+ T cells expressing CD127 (IL7 receptor) in the lung, and draining of lymph nodes. Thus, Nox1 may affect negatively the early adaptive immune response to IAV infection.

DUOX2 is another source of ROS production during IV infection [45,46]. IV enhances the induction of DUPX2/DUOXA2 and a moderate reduction of DUOX1 [45]. This DUOX2/DUOXA2 induction is mediated by H1N1, but not by H3N2 [43]. DUOX2-induced ROS formation was triggered in the airway cells via type 1 and type 3 interferon (IFN) pathways, inducing the RIG-1-like receptor dsRNA helicase enzyme (RIG-1) and the melanoma-associated differentiation gene 5 (MDA5) in human nasal epithelium and mouse nasal mucosa [47]. The enhancement of ROS in mitochondria mediated by DUPOX2 or NOX2 is indicative of mitochondrial dysfunction [48].

The generation of iNOS, nitric oxide, and 8-nitroguanosine represents IV-induced production of superoxide anion [9,49,50].

3. ROS in IV-induced tissue injury and cell death

Viral infection may alter oxidative stress and the antioxidation machineries. For example, Lin et al. reported that infection with H5N1 results in a higher level of ROS in A549 cells compared with infection with H1N1, accompanied by a significant reduction in the ration of reduced glutathione (GSH)/oxidized glutathione (GSSG) [28].

3.1. IV-induced cell injury in the lung

In humans, IV infection causes a contagious respiratory disease in which many alterations of biological functions are induced, such as apoptosis and necrosis [51], autophagy [52], inflammation [53], LI [54,55], DNA damage and oxidation in host cells [56], lipid peroxidation [57,58], and antioxidation reactions mediated by enzymes [59,60].

Oxygen radicals are produced in the lungs of mice infected with IV [61] and ROS play a critical role in the acute lung injury (ALI) that occurs in mice infected with the highly pathogenic avian IV type A (H5N1) [62]. Moreover, in some cases, infection with H5N1 induced a high viral load and a strong proinflammatory reaction [63]. This action of H5N1 increases mortality and generates a more pronounced oxidative stress than other IVs, such as the human influenza A virus (H1N1).

Recent studies have reported that ROS production exhibits a positive or negative function during IV infection [64]. In the former case, viral infection can generate moderate ROS levels, which play a critical role in biological reactions with few cellular damage events. In contrast, excessive ROS are the major cause of LI. Downstream ROS targets, such as NOX1, NOX2, NOX4, and DUOX2, are involved in apoptotic cell death in the epithelium and ALI [43,65]. After infection, IVs hijack the biological functions of host cells to enhance viral

replication [21]. Accordingly, the imbalance between the redox control against IV and the production of excess ROS results in tissue damage [65].

3.2. *Effect on the nervous systems*

IVs damage the central nervous system (CNS), leading to IV-associated encephalitis and encephalopathy [66–68]. Previous studies have suggested that IVs can infect astrocytes, which are the most abundant cells in the CNS and an integral part of the blood–brain barrier and induce a proinflammatory cytokine response and apoptosis [69,70]. Lin et al. reported that human astrocytes exhibit induction of the expression of several cytokines/chemokines, such as CXCL9-11, NF-κB, and p38MAPK phosphorylation, and receptors of neurotransmitters, such as the melanocortin 2 receptor, cholinergic receptor nicotinic gamma subunit, purinergic receptor, gamma-aminobutyric acid (GABA) A receptor α1, and epidermal growth factor receptor 2, which are involved in synaptic transmission and CNS disorders [71]. More recently, it was reported that H5N1 bound and cleaved HA with a specificity for alpha-2,3-linked sialic acids, allowing efficient binding of IVs and their efficient replication in CNS cells [72].

4. IV-mediated ROS on cellular components

These IV-mediated functions such as TLR family, inflammation, MMP, and ERs stress in host cells are tiriggered, at least in part, by regulation of Nrf2/ROS signaling and signaling pathways of PI3K/AKT, p38/JNK MAPK and NFkB.

4.1. *TLR family and membrane receptors*

Human IV infections, such as H1N1 and H3N2, increase the expression of TLR family members, including TLR 3, 7, 8, and 9; however, TLR2 and 4 are suppressed in this setting [73]. Another report showed that the expression of TKR2, 3, and 9 was correlated with H1N1 [74]. The upregulation of signaling molecules of IkB, P-MAPKs, and inflammatory cytokines (such as IL6, sTNFR-1, MCP-1, CXCL10, and IFN gamma) is closely related with the upregulation of TLRs, MyD88, IRAK4, and TRAF6 and with human, avian, and swine IVs [73–77].

TLR3$^{-/-}$ KO mice exhibit higher survival rates with lower viral titers, lower production of mediators of inflammation, and fewer pathological alterations in their lungs after IV infection than their wild-type counterparts [78,79]. TLR7 is also required for the efficient replication of IVs [80]. The inhibitors of the TLR7/8–MyD88 axis possibly also inhibit IV replication and control proinflammatory cytokines and matrix metalloproteases (MMPs) [75]. In contrast, the expression levels of TLR4 determined H1N1 entry and infection tropism via MyD88–p38 MAPK signaling [81]. Inactivated avian H5N1 can rapidly lead to the activation of the TLR4/TRIF/TRAF6/NF-κB axis [8]. TLR4$^{-/-}$ KO mice are refractory to H1N1-induced ALI, and a TLR4 antagonist decreases H1N1 viral titer and its lethality [80].

The generation of NADPH and ROS requires the activation of TLRs, RIG-like receptors (RLRs), and NOD-like receptors (NLRs); moreover, these pattern-recognition receptors can promote innate immunity to protect host cells [73,82]. In addition, the mucosal defenses of the lungs against influenza type A can be followed by a single inhaled treatment comprising a synergistic combination of a TLR agonist (such as the diacylated lipopeptide ligand of TLR2/6, Pam2CSK4) and a CpG ligand for TLR9 (ODN362). These antiviral responses to viral burden attenuated the infectivity and enhanced survival potency via the protective responses afforded by ROS generation [83].

4.2. *MMP*

H3N2 infection induces the expression of MMP-9, but not of MMP-2, in Vero cells. MMP-2 production was increased in Madin–Darby canine kidney (MDCK) cells. Thus, the induction of MMPs is dependent on the epithelial cell type [84]. The expression of MMP-9 is increased in the lungs of a mouse model of IAV infection [85]. The immunopathological response to IV strains via the production of MMP-9 was compared between the human IV viruses H1N1 and H3N2 in mice and revealed that H1N1 induces high mortality and severe lung changes with G-1+ and CD11b+ cell infiltration and upregulation of CxCL6/GCP-2, CCL2/MCP-1, and the tissue inhibitor of metalloproteinase 1 (TIMP1) [86]. Infection with H1N1 upregulated the active and latent forms of MMP-9 in the lung and inhibitor of MMP-2 or MMP-9 reduced partially in lung pathology.

Both Gr-1+ and CD11b+ cells in H1N1-infected lungs produced ROS and RNS, indicating MMP expression is controlled by oxidative stress and antioxidation. The human influenza type A virus induced infiltration of neutrophils, which produced MMP-9 [87]. In contrast, MMP-9 production was not increased in human neutrophils by IV type A [88]. Thus, MMP-9 production in neutrophils is not controlled by IV *per se*. Other cell types, such as macrophages, might regulate IV-mediated MMP-9 production. H1N1 induced the expression of the *MMP-9* gene and the cleavage of pro-MMP-2 into an active intermediate protein in human fetal membrane cells, resulting in the weakening of the membrane integrity and the degradation of the extracellular matrix [89].

4.3. Inflammation and ER stress

IV infection induces a robust production of cytokines, such as IFNs; interleukins (ILs); chemokines, such as CXCL10 and CCL5; tumor necrosis factors (TNFs); and ROS, which can promote the expression of inflammatory cytokines [90,91]. The generation of ROS is required in host cells after the activation of TLRs, which may be used by IVs to promote innate immunity functions in their hosts [8,63]. IVs trigger the production of proinflammatory cytokines/chemokines, such as CCL5/RANTES, CXCL10 (C-X-C motif chemokines), IL1β, IL6, IL8, and TNFα [92,93]. Some of these factors belong to the NF-κB signaling pathway, including IL2, IL6, IL8, MIP1a, MCP-1, and RANTES [94]. These issues were reviewed by other authors [95,96].

After IVs infect the host cells and the production of ROS/NOS surpasses the normal levels, events such as the production of oxidizing nitrogen oxides and peroxynitrite occur concomitantly. In turn, these events induce the oxidation or nitration of amino acid residues, lipid peroxidation, and DNA strand breaks, finally producing apoptotic signals in states of ER stress or of oxidative stress in mitochondria [97]. Thus, the generation of ROS is related to the cascades that commit the ER and mitochondria to apoptosis.

IV infection also induced ER stress and generated ROS in inflamed tissues [96,98–100]. IVs induce proteasome-dependent ER-associated degradation through the inositol-requiring enzyme 1/x-box binding protein 1 (IRE1/XBP1) signaling pathway and commitment to SOD1 downregulation, thus allowing ROS accumulation. ROS-mediated JNK or the IRE1-mediated JNK1 contributes to the control of IV infection and propagation [101].

4.4. Lipid oxidation

Malondialdehyde, F2-isoprostane, 7-ketocholesterol, and 7β-hydroxycholesterol were identified as lipid alterations induced by IV-mediated ROS [21,102]. IV infection induces oxidative stress, which is accompanied by an increase in the levels of lipid peroxidation [103] in the presence of vitamin E, conjugated dienes, and total malondialdehyde.

4.5. DNA oxidation on host cells

DNA is the most common target of ROS, which they modify to give, for example, 8′-hydroxy-2′-deoxyguanosine (8-OHdG) on the 8-position of dG in host DNA. 8-OHdG is produced via a transversion mutation of G to A in the host DNA and increases the risk of neoplasia [7,104].

5. Cellular signaling mediated by IV-induced ROS

The triggering of IV mediated these functions is related with the ROS generation and its redox regulation.

5.1. Nrf2 signaling pathway

Redox homeostasis is maintained by cellular enzymes such as SODs, CAT, and GPx, which participate in antioxidant defense systems. IV infection can decrease the production of antioxidation targets, such as HO-1 and NQO1. SOD, GR, CAT, and GPx are all downstream effectors of the Nrf2 pathway after IV infection. Thus, Nrf2 plays an important role in the redox regulation upon IV infection [24,105–108]. IVs activate the Nrf2/ARE antioxidation pathway via the nuclear translocation of Nrf2, followed by the transcriptional activation of Nrf2 target genes, such as *HO-1* [108,109].

The highly pathogenic avian H5N1 IV reduces the levels of phosphorylated Nrf2 in the nucleus and downregulates the expression of fibronectin to a greater extent than does the human H1N1 IV [110]. Several studies found no changes in the levels of SOD in IV-infected cells [111]; however, other studies found a contradictory lower level of SOD1 caused by protease degradation [27,112]. Increased expression of SOD1 was

reported in patients with asymptomatic IV infection [113]. Decreased levels of SOD1 have been found in children infected with H1N1 [114]. Therefore, whether SOD1 is a marker of IV infection remains uncertain.

Similar controversial findings have been reported for other antioxidant enzymes, such as CAT and indolamine-2,3-dioxygenase (IDO). IDO scavenges superoxide anion for oxidation or for converting tryptophan into kynurenine [115]. The IDO level is unaltered and the CAT levels are reduced in IV-infected cells in vitro [111]. In contrast, in infected mice, both IDO and HO-1 are induced and CAT is unchanged [116]. CAT- and peroxiredoxin-6 (PRDX-6)-deficient mice infected with H1N1 exhibit depletion of IV-permissive bronchial Clara cells and/or alveolar type 2 (AT-2) cells [109]. Similar studies reported the induction of other enzymes, such as GPX3 and HO-1. Other Nrf family members, such as Nrf1, bind to the ARE in the promoter regions of redox-related genes, although to a lesser extent than that observed for Nrf2. In contrast, Nrf3 does not behave similarly [117].

5.1. The p38 MAPK signaling pathway

p38 MAPK plays a vital role in cell proliferation, differentiation, development, and death. For example, phosphorylated p38 translocated into the cell nucleus and upregulated cytokines/chemokines under oxidative stress. p38 MAPK signaling is sensitive to oxidants and is involved in IV replication [107,108]. Thus, it is a critical mediator of oxidation-induced apoptosis, to increase ROS and COX-2 production [118,119].

5.2. The NF-κB signaling pathway

NF-κB plays a key role in the activation of the immune system. The NF-κB complex comprises five proteins, namely Rel A (p65), c-Rel, Rel B, p50, and p52. The NF-κB p50/p65 heterodimer associated with IκBα is related to the outcome of oxidative stress [120,121]. After phosphorylation of p65 at Ser 276, NF-κB antagonizes Nrf2 and suppresses the transcription of ARE-dependent genes by recruiting histone deacetylase 3 to the ARE [121]. Thus, inhibition of NF-κB activity may benefit Nrf2-mediated antioxidation and the suppression of IV-induced inflammation.

5.3. The PI3K/AKT signaling pathways

IVs can modulate several oxidative-stress- and redox-activated signaling pathways, such as those involving NF-κB, MAPK, and PI3K/AKT [122–125], to promote viral replication and pathogenesis [125–128]. Therefore, the modulation of these signaling pathways may attenuate IV-induced pulmonary damage [127,128].

6. Activation of AhR augments IV virulence

TCDD-treated and IV-infected mice exhibit activation of AhR in the lungs and a decrease in survival, which suggests a relationship between the susceptibility to viral respiratory infections and exposure to environmental toxin ligands [129]. In this model, increased iNOS levels in endothelial cells of virus-infected mice and an increased number of neutrophils around pneumocytes were observed after AhR activation, which requires a nuclear transport signal and intact DNA-binding domains within AhR [130]. The activation of the AhR, which occurs via kynurenine mediation, regulates the production of IFNβ negatively after IV infection, which allows virus propagation [131]. IV infection can increase kynurenine production by upregulating the expression of indoleamine-2,3-dioxygenase (IDO1), which is a key enzyme in the kynurenine biosynthesis pathway [132].

In addition to the increased pulmonary neutrophilia and iNOS levels resulting from IV infection, mice treated with TCDD, which activates AhR only transiently, exhibited a diminished IV-specific $CD8^+$ T-cell response [133]. This suggests that the prolonged AhR activation induced by the environmental pollutant

TCDD correlates with increased respiratory IAX infection. Furthermore, Boule et al. [134] compared the effects of four AhR agonists, TCDD, 3,3′,4,4′,5-pentachlorobiphenyl-126 (PCB126) 2-(1*H*-indol-3-ylcarbonyl)-4-thiazolecarboxylic acid methyl ester (ITE), and FICZ, on the immune response in mice infected by IVs. Treatment with TCDD, PCB, and ITE decreased the virus-specific IgM/IgG levels and the number of helper T cells and $CD8^+$ cytotoxic T cells but increased the number of regulatory T cells. However, FICZ alone decreased the levels of virus-specific IgG and the $CD8^+$ T-cell response and increased the number of helper T cells. These studies suggest that harnessing AhR activity is critical for modulating the host cell immunity to IV infection.

Regarding ROS production and AhR activity *in vivo*, singlet molecular oxygen ($^1O_2$) is not fully characterized in mammals, but its role is well established in plants, bacteria, and fungi. Although the mammalian enzyme myeloperoxidase mediates the production of $^1O_2$, the physiological role of $^1O_2$ in mammals (other than photosensitization of the skin by the UVA component of solar radiation) has not been established [135]. A recent report by Stanley et al. [136] showed that $^1O_2$ plays a critical role in redox regulation in atrial relaxation and in controlling blood pressure in mammals during inflammation accompanied by endothelial IDO1 expression. Thus, $^1O_2$ is an important ROS in the fields of biology and medicine.

7. Possible anti-influenza therapies

Antioxidant genes, which can be upregulated by Nrf2, play a critical role in the elimination of ROS/RNS; therefore, enhancement of Nrf2 activity and inhibition of AhR activity have been proposed as approaches to ameliorate the IV-associated pathology. For example, the downstream target of Nrf2, SOD conjugated with a copolymer of pyran was administered to decay free radicals; this approach prevented infection with IV in mice [26].

7.1. Inhibition of AhR activity

AhR activation during IV infection disrupts host immunity and causes increased lung inflammation and mortality in mice [102,134,138,139]. The suppression of AhR activity is assumed to attenuate IV-induced lung damage. The level of IV-induced IFNβ is increased in AhR-deficient cells and mice, thus leading to the suppression of viral replication [138]. Several AhR antagonists, such as CH-223191 and Stem Regenin 1, have been identified; however, their therapeutic value against IV-infection-induced LI is unclear. Because AhR responds differentially to diverse intrinsic and extrinsic ligands and affects multiple types of immune cells [139], a careful examination of the advantages and disadvantages of these AhR antagonists is required to assess their value in the treatment of IV infection.

7.2. N-acetyl L-cysteine (NAC)

NAC is a precursor of intracellular cysteine and GSH in mammals. NAC resists IV infection through mechanisms including the inhibition of IV replication, the production of proinflammatory cytokines, and the prevention of IV-induced apoptosis [140–143]. NAC suppresses viral replication and the expression of IV-mediated inflammatory factors, such as TNFα, IL-6, and IL-1β [141]. In addition, cellular damage in the lungs suppresses TLR4 [141]. However, Garigliany et al. insisted that NAC was strain dependent and lacked inhibitory activity against some IVs. NAC was effective for A/PR/8 and H5N1, but not for murinized swine H1N1 IV [144]. The synergistic use of NAC and antiviral drugs as a combination therapy provided effective protection against IV infection in mice [140,142].

7.3. Glutathione

The antiviral activity of GSH may be involved in inhibiting the synthesis of viral proteins [145]. A higher level of GSH might interfere with the formation of disulfide bonds, thus preventing the correct folding of viral

hemagglutinin (HA), followed by the alteration of its transport and its insertion into host cell membranes [146]. Furthermore, a derivative of GSH, *N*-butanoyl glutathione (GSH-C4), which is a cell-permeable chemical compound [147], diminishes IV replication by maintaining the immature monomeric HA in the ER and inhibiting the targeting of mature membrane glycoproteins, which is achieved by an increase in GSH levels [20, 148].

GSH inhibits the viral apoptosis induced by IVs and the production of IV particles. It also depresses the expression of viral matrix proteins, caspase cascades, and Fas induction [27]. Moreover, nutritional supplements that induce GSH may afford resistance to the major pathogenic processes of H5N1 [149]. Bakuchiol, a phenolic isoprenoid, activates the Nrf2 pathway and blocks IV infection, which suggests that bakuchiol has antiviral activity [96]. Overexpression of Nrf2 or addition of sulforaphane and EGCG decreases the replication and protein synthesis in IVs [145,150] (**Figure 1**). Moreover, Nrf2 knockdown increases the entry and replication of IVs and enhances IV-induced pulmonary cell injury. Nrf2 is also a factor in the outcome of IV-infected mice after exposure to cigarette smoke [151]. Nrf2-deficient mice exhibit more severe bronchial inflammation, permeability damage in the lungs, mucus hypersecretion, and higher mortality rates after IV infection and cigarette smoke exposure than did wild-type mice. Taken together, these results suggest that the Nrf2-mediated antioxidant pathway plays a critical role in suppressing IV-induced LI under oxidative conditions, such as cigarette smoke exposure [149,151–153].

7.4. Other small molecules

Isoprenoid phenols (baicalein and biochanin) prevent the replication of the highly pathogenic avian H5N1 virus by repressing ROS production [154]. EGCG and catechin exhibited an antiviral activity that involved antioxidant activity [155,156]. Quercetin decreases the production of superoxide in alveolar macrophages during IV infection [58]. Quercetin also has antiviral activity by inhibiting HA2 during IV infection [157]. A biflavonoid isolated from *Garcinia kola* seeds (kolaviron) exhibited a strong anti-IV activity that occurred via antioxidative activity [158].

7.5. Nontargeted inhibition (NF-κB, p38 MAPK, and PI3K/AKT inhibitors)

The effects of the dietary flavonoid kaempferol on H9N2-mediated acute LI included the repression of oxidative stress and inflammatory responses via the downregulation of NF-κB [77]. Kaempferol inhibits the NF-κB and MAPK pathways, leading to an increase in SOD activity, the attenuation of ROS levels, and H9N2-induced acute LI [77]. Some ROS scavengers, such as polyphenols, may modulate the NF-κB and MAPK pathways and upregulate GSH biosynthesis through Nrf2 activation [139,159–163]. The immune-regulatory properties of NAC and IV-induced pneumonia are related to the inhibition of the p38 MAPK pathway [164]. Thus, NF-κB activation and the p38 MAPK and pI3K/AKT pathways may serve as biomarkers of oxidative stress [165]. These cascades are also involved in the nontargeted signaling induced by IV.

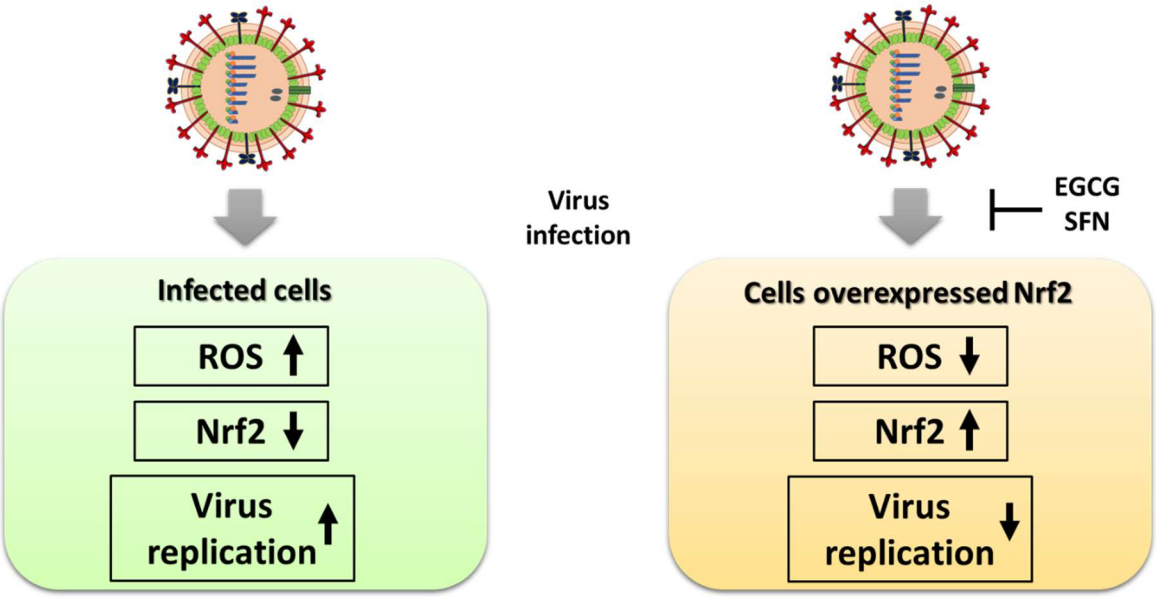

Figure 1. Model of infection of influenza viruses in normal host cells and cells overexpressing Nrf2. Infection by influenza viruses led to the production of reactive oxygen species (ROS). Antioxidation through the Nrf2 transcription factor and viral replication are illustrated. The addition of sulforaphane (SFN) or epigallocatechin gallate (EGCG) inhibits the viral infection of IV via activation of the antioxidation pathway.

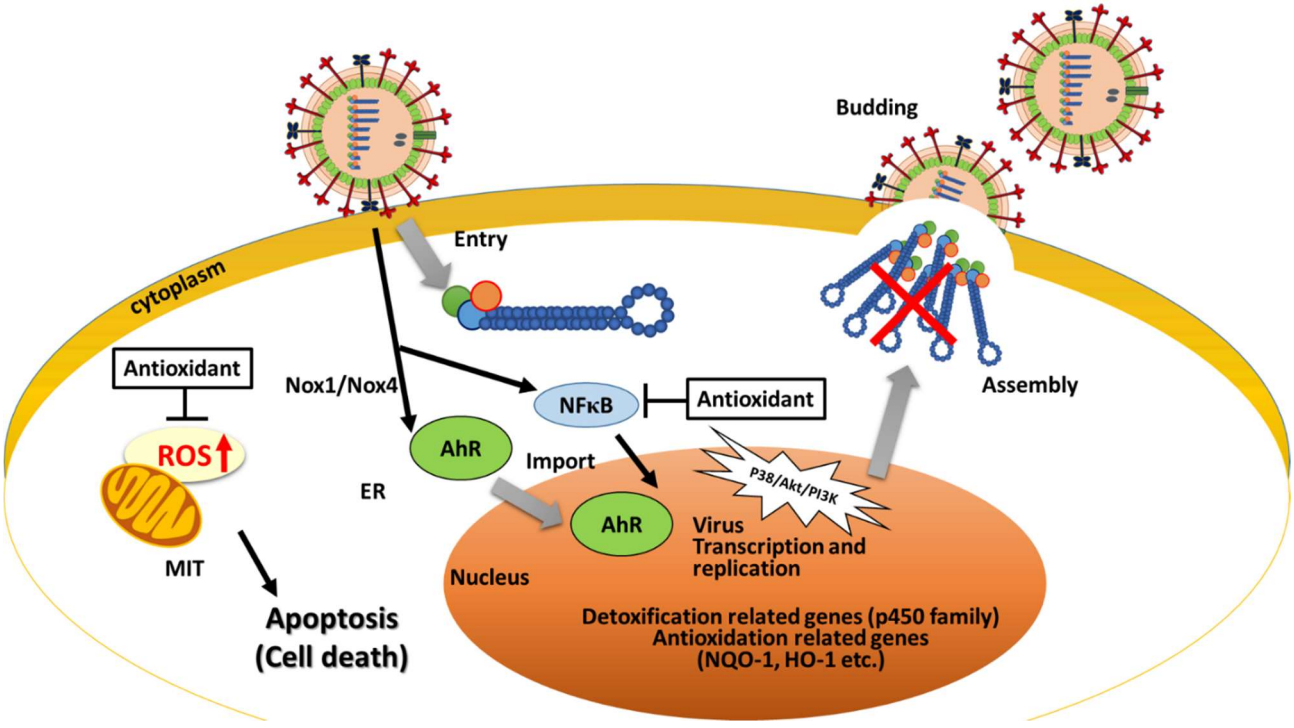

Figure 2. Schematic model of the mechanism of ROS production and antioxidation during infection with influenza viruses. During the life cycle of IVs, infection with these viruses causes oxidative-stress reactions in host cells, thus inducing Nox1/Nox4 and AhR and the production of ROS, followed by the replication of the viruses. Nrf2 and other signaling molecules, such as p38, AKT, and PI3K, are also involved in this ROS stress

and redox control. Oxidative stress also induces the translocation of the AhR transcription factor to the ER and mitochondria (MIT), to enhance ROS production. The antioxidation against ROS via the Nrf2 transcription factor leads to the prevention of cell damage at the initial phase; however, the excess of ROS causes apoptosis and other types of cellular death in infected host cells. The life cycle of IVs is summarized and the possible targets of drugs to treat IV infection are also indicated.

Table 1. Drugs and small molecules that prevent infection with influenza viruses.

[Against ROS]

Thiol compounds and prodrugs	**Effect on influenza virus infection**	**References**
N-acetyl-L-cysteine (NAC)	Reduction of the cell population at the G0/G1 phase Reduction of pro-inflammatory molecule production (CXCL8, CXCL10, CCL5, and IL-6)	Geiler et al. [141] Wu et al. [169]
Glutathione (GSH)	Affects viral mRNA export and decreases the expression of late viral proteins Inhibition of caspase activation and Fas upregulation	Nencioni et al.[59] Cai et al. [27]
GSH-C4	Inhibition of influenza virus HA maturation	Sgarbanti et al. [170]
PDTC (pyrrolidine dithiocarbamate)	Decrease in viral RNA synthesis Inhibition of apoptosis	Uchide et al. [171]
Hydroxyl antioxidants	**Effect on influenza virus infection**	**References**
NDGA (Nordihydroguaiaretic acid)	Inhibition of apoptotic DNA fragmentation and virus proliferation	Uchide et al. [172]
Thujaplicin	Inhibition of apoptosis, virus replication and release from the infected cells	Miyamoto et al. [173]
Resveratrol/ Vitisin A (tetramer of resveratrol)	Inhibition of the nuclear–cytoplasmic translocation of vRNP Downregulation of viral proteins Inhibition of protein kinase C activity Inhibition of virus-induced RANTES production, to decrease of the virus-stimulated phosphorylation of Akt and STAT1	Palamara et al. [174] Huang et al. [175]
Ambroxol	Stimulation of the release of pulmonary surfactants, mucus protease inhibitor, IgA, and IgG Suppression of the release of cytokines, TNF-α IFN-γ, and interleukin-12	Yang et al. [176]
Ascorbic acid	Inhibition of the entry of viruses Increase in the production of IFN-α/β at the initial stage of infection Inhibition of excessive CORT synthesis	Wang et al. [177] Kim et al. [178] Cai et al. [179]
Tert-buthylhydroquinone (tBHQ)	Inhibiting of ROS production and increase antioxidation	Antanasijevic et al. [186, 187]
Curcumin + Resveratrol	Scavenging of H2O2, HON, and ROON Inhibition of TLR 2/4, p38MAPK, and NFkB	Sharma et al. [180]; Barzeger et al. [181]; Dai et al. [182]

Emodin (1,3,8-trihydroxy-6-methyl anthraquinone)	Inhibition of IA replication, IV pneumonia Inhibition of TLR 4, p38/JNK, and NFkB	Dai et al. [183]
Oxymatrine (OMT); C15H24N2O20, imunosuppressive reagent	Antioxidant Suppression of inflammation and viral infections Hepatoprotective and immunosuppressive Inducer of TLR4, p38 MAPK, NFkB, and PI3K/AkT	Dai et al. [184]
Aurantiamide acetate (E17)	Strong anti-inflammatory and antiviral effects	Zhou et al. [185]
4-PBA (4-phenyl butyrate)	Inhibitor of ER stress	Jung et al. [148]
Kaempferol	Inhibition of TLR4/MyD88-mediated signaling of NFkB and MAPK	Zhang et al. [77]
Apocynin	Inhibitor of NOX2 Inhibition of ROS and IV-induced cytokine production	Ye et al. [206]
Flavonoids	**Effect on influenza virus infection**	**References**
Dianthus (quercetin 3; isorhamnetin 3)	Binding to IV polymerase membrane glycoproteins ROS inhibitor	Kim et al. [197]
Quercetin	Protecting low-density lipoprotein against oxidation Antithrombic, antivirus, and anti-inflammatory effcets	Formica et al. [198]
Polyphenol	**Effect on influenza virus infection**	**References**
Chlorogenic acid	Antivirus and antihypertension effects Protection of dopaminergic neurons against neuroinflammation	Zhao et al. [199]; Shen et al. [200]
Chemicals	**Effect on influenza virus infection**	**References**
Poly (aniline-co-pyrrole) polymerized nanoregulators (PASomes) with mPEG-b-pPhe (methoxy polyethylene glycol-block-polyphenylalanine copolymer)	Inhibition of ROS production Inhibition of viral replication and cell death	Kim et al. [210]
Cholesterol conjugated gp91 of NOX2 oxidase gp91phox sequence linked to the human immunodeficiency virus-tat peptide (Cgp91de-TAT)	Inhibitor of NOX2 oxidase Inhibitor of ROS and inflammation	To et al. [209]

[Against Influenza viruses]

Hydroxyl antioxidants	**Effect on influenza virus infection**	**References**
Atorvastatin (Lipitor)	Inhibition of HMG-CoA reductase	Episcopio et al. [208]
Clarithromycin (Biaxin)	Inhibition of MCP-1 and MMP-9, Increases of IL6 and IFNgamma	Takahashi et al. [211]
Flavonoids	**Effect on influenza virus infection**	**References**
5,7,4′-Trihydroxy-8-methoxyflavone	Inhibition of virus fusion with endosome/lysosome membranes	Nagai et al. [188–192]
Catechins	Inhibition of HA and NA activity	Song et al. [156]

	Inhibition of viral endonuclease activity	Kazuhara et al. [193]
Quercetin 3-rhamnoside	Reduction of the cytopathic effect (CPE)	Choi et al. [194]
Isoquercetin	Decrease in viral titers	Kim et al. [195]
Oligonol (+NAC)	Inhibition of nuclear export of vRNP	Gangehei et al. [196]
Viral enzymes and membrane proteins as targets	**Effect on influenza virus infection**	**References**
Amantadine	Inhibitor of the matrix protein M2	Pica and Palese [201]
	Selenium nanoparticles with amantadine ROS-mediated AKT phosphorylation signal against H1N1	Nabar et al. [202]
	Selenium nanoparticles with ribavirin RNA polymerase inhibitor	Lin et al. [203]
	Activation of the caspase-3 apoptotic pathway against H1N1	Li et al. [220]
Oseltamivir and zanamivir	Inhibitor of neuraminidase (NA)	Kode et al. [204]
Laninamivir	Inhibitor of HA	Tomozawa et al. [212]
Peramivir	Inhibitor of HA	Scott et al. [216]
Rimantadine	Inhibitor of M2 ion channel	Alves Galvão et al. [215]
NMS-873	Inhibitor of p97 (AAA+ ATPase, VCP) Oseltamivir resistant strain specific	Zhang et al. [213]
Baloxavir marboxil	Cap-dependent endonuclease inhibitor	O'Hanlon et al. [214]
1,3-dihydorxy-6-benzo[C] chromone D715-2441 + zanamivir	PB2 Inhibitor Binding to PBcap	Liu et al. [217]
Salinomycin + oseltamivir (OSV-P)	M2 channel blocker Inhibition of HA	Jang et al., [218]
10e (Am2-S31N blocker)	Proton channel blocker and M2 blocker	Hu et al. [219]
Favipiravir	PB1 inhibitor	Goldhill et al. [221]
Triple combination of Zanamivir + Clarithromycin + Flufenamic acid (FFA)	Inhibitor of HA	Lee et al. [222]

8. Conclusions

The pathophysiology of IV infection is concerned, at least in part, with the imbalance between oxidation and antioxidation systems, as well as with the state of AhR activation (**Figure 2**). In this review, we presented several examples of the effect of the IV–host interaction on the intracellular redox and ROS states. Based on this knowledge, several potential therapeutics for the treatment or prevention of IV infection are presented (**Table 1**). Heaton et al. [166] reported a CRISPR activation screening that aimed to identify a pan-avian IV inhibitor host factor; those authors isolated the glycosyltransferase B4GALNT2, which can modify glycans containing α-2,3-linked sialic acids. However, most of these proposed therapeutic strategies require validation using animal models of IV infection and human clinical trials. Although many studies have uncovered the multifaceted roles of the cellular redox system and of ROS activity in IV-infection-induced lung inflammation and injury, several questions remain unanswered that are important for illustrating the precise IV–host

interaction and that await further investigation. For example, both oxidative stress and virus replication result in chromatin remodeling, which largely affects gene expression, including that of Nrf2- and AhR-regulated genes, and determines the outcome of the virus–host interaction. Understanding the precise cross-talk between multiple chromatin modifiers, such as histone acetyltransferases/deacetylases and methyltransferases/demethylases, and the transcription factors Nrf2 and AhR upon IV infection is required to predict the consequences of virus infection accurately. Accordingly, a more specific and effective intervention for IV infection may be developed by targeting either ROS homeostasis or chromatin modifiers [167,168]. In conclusion, this review presents the notion that, in addition to virus components, the therapeutic treatment of IV infection may be achieved by targeting virus-induced ROS and redox-associated cellular responses, which may suppress IV propagation and reduce adverse inflammation in the host.

Abbreviations

ARE, antioxidant-response element; AP1, activated protein 1; AhR, aryl hydrocarbon receptor; CYP, cytochrome p450; DUOX, dual oxidase; EGCG, epigallocatechin gallate; FICZ, 6-formylindolo[3,2-b]carbazole; HIF, hypoxia response factor; IV, influenza type A virus; IDO, indoleamine-2, 3-dioxygenase; iNOS, inducible nitric oxide; ITE, 2-(1*H*-indole-3-ylcarbonyl)-4-thiozolecarboxylic acid methyl ester; Keap 1, Kelch-like ECH-associated protein 1; NA, neuraminidase; NADPH, nicotine adenine dinucleotide phosphate; NOX, NADPH oxidase; NO, nitric oxide; Nrf2, nuclear factor E2 related factor 2; NP, nucleoprotein; PA, polymerase acidic protein; PB, polymerase basic protein; ROS, reactive oxygen species; SFN, sulforaphane; SOD, superoxide dismutase; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; vRNP, ribonucleoprotein

Acknowledgments

We thank researchers in Yokoyama's and Lin's laboratories for useful discussions when editing this manuscript. This work was supported partially by grants from the Ministry of Science and Technology (MOST 106-2320-B-037-001-MY3, MOST 107-2314-B-037-085, MOST 107-2320-B-037-026, and MOST 108-2320-B-037-005), by the National Health Research Institutes (NHRI-EX108-10720SI); and Kaohsiung Medical University grants (KMU-TC108A02).

Author contributions: KKC, MK, KW, KKK, YCL, SS, KKY, and CSL participated in the study design and wrote the draft. KKC, KW, MK, KKK, JBP, and CCK collected documentation materials. KKC, MK, KW, JBP, CCK, SS, CSL, and KKY participated in the study design and helped revise the draft. All authors read and approved the manuscript.

Ethics approval and consent to participate: Not relevant.

Conflicts of interests: The authors declare that they have no competing interests.

References

1. Kuiken, T.; Taubenberger, J.K. Pathology of human influenza revisited. *Vaccine* **2008**, *26 Suppl 4*, D59-66, doi:10.1016/j.vaccine.2008.07.025.
2. Furuta, Y.; Gowen, B.B.; Takahashi, K.; Shiraki, K.; Smee, D.F.; Barnard, D.L. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral research* **2013**, *100*, 446-454, doi:10.1016/j.antiviral.2013.09.015.
3. Obayashi, E.; Yoshida, H.; Kawai, F.; Shibayama, N.; Kawaguchi, A.; Nagata, K.; Tame, J.R.; Park, S.Y. The structural basis for an essential subunit interaction in influenza virus RNA polymerase. *Nature* **2008**, *454*, 1127-1131, doi:10.1038/nature07225.
4. Yuan, P.; Bartlam, M.; Lou, Z.; Chen, S.; Zhou, J.; He, X.; Lv, Z.; Ge, R.; Li, X.; Deng, T., et al. Crystal structure of an avian influenza polymerase PA(N) reveals an endonuclease active site. *Nature* **2009**, *458*, 909-913, doi:10.1038/nature07720.
5. Massari, S.; Goracci, L.; Desantis, J.; Tabarrini, O. Polymerase Acidic Protein-Basic Protein 1 (PA-PB1) Protein-Protein Interaction as a Target for Next-Generation Anti-influenza Therapeutics. *Journal of medicinal chemistry* **2016**, *59*, 7699-7718, doi:10.1021/acs.jmedchem.5b01474.
6. Stevaert, A.; Naesens, L. The Influenza Virus Polymerase Complex: An Update on Its Structure, Functions, and Significance for Antiviral Drug Design. *Medicinal research reviews* **2016**, *36*, 1127-1173, doi:10.1002/med.21401.
7. Peterhans , E,; Grob, M.; Bürge, T.; Z anoni, R. Virus-induced formation of reactive oxygen intermediates in phagocytic cells. *Free Radic Res Commun.***1987**, 3, 39-46.
8. Imai, Y.; Kuba, K.; Neely, G.G.; Yaghubian-Malhami, R.; Perkmann, T.; van Loo, G.; Ermolaeva, M.; Veldhuizen, R.; Leung, Y.H.; Wang, H., et al. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell* **2008**, *133*, 235-249, doi:10.1016/j.cell.2008.02.043.
9. Akaike, T.; Okamoto, S.; Sawa, T.; Yoshitake, J.; Tamura, F.; Ichimori, K.; Miyazaki, K.; Sasamoto, K.; Maeda, H. 8-nitroguanosine formation in viral pneumonia and its implication for pathogenesis. *Proceedings of National Academy of Sciences of the United States of America* **2003**, *100*, 685-690, doi:10.1073/pnas.0235623100.
10. Vlahos, R.; Stambas, J.; Bozinovski, S.; Broughton, B.R.; Drummond, G.R.; Selemidis, S. Inhibition of Nox2 oxidase activity ameliorates influenza A virus-induced lung inflammation. *PLoS Pathol.* **2011**, 7, e1001271.doi: 10.1371/journal.ppat.1001271.
11. Michaelis L. Die vitale Färbung, eine Darstellungsmethode der Zellgranula. *Archiv für mikroskopische Anatomie*. **1900,** 55, 558–575, 10.1007/BF02977747.
12. Murphy, M.P. How mitochondria produce reactive oxygen species. *The Biochemical journal* **2009**, *417*, 1-13, doi:10.1042/bj20081386.
13. Cadenas, E. Mitochondrial free radical production and cell signaling. *Molecular aspects of medicine* **2004**, *25*, 17-26, doi:10.1016/j.mam.2004.02.005.
14. Griendling, K.K.; Sorescu, D.; Ushio-Fukai, M. NAD(P)H oxidase: role in cardiovascular biology and disease. *Circulation research* **2000**, *86*, 494-501, doi:10.1161/01.res.86.5.494.
15. Spiekermann, S.; Landmesser, U.; Dikalov, S.; Bredt, M.; Gamez, G.; Tatge, H.; Reepschlager, N.; Hornig, B.; Drexler, H.; Harrison, D.G. Electron spin resonance characterization of vascular xanthine and NAD(P)H oxidase activity in patients with coronary artery disease: relation to endothelium-dependent vasodilation. *Circulation* **2003**, *107*, 1383-1389, doi:10.1161/01.cir.0000056762.69302.46.
16. Akaike, T.; Ando, M.; Oda, T.; Doi, T.; Ijiri, S.; Araki, S.; Maeda, H. Dependence on O2- generation by xanthine oxidase of pathogenesis of influenza virus infection in mice. *The Journal of clinical investigation* **1990**, *85*, 739-745, doi:10.1172/jci114499.
17. Porter, T.D.; Coon, M.J. Cytochrome P-450. Multiplicity of isoforms, substrates, and catalytic and regulatory mechanisms. *The Journal of biological chemistry* **1991**, *266*, 13469-13472.
18. Zangar, R.C.; Davydov, D.R.; Verma, S. Mechanisms that regulate production of reactive oxygen species by cytochrome P450. *Toxicology and applied pharmacology* **2004**, *199*, 316-331, doi:10.1016/j.taap.2004.01.018.
19. Sawa, T.; Akaike, T.; Ichimori, K.; Akuta, T.; Kaneko, K.; Nakayama, H.; Stuehr, D.J.; Maeda, H. Superoxide generation mediated by 8-nitroguanosine, a highly redox-active nucleic acid derivative. *Biochemical and biophysical research communications* **2003**, *311*, 300-306, doi:10.1016/j.bbrc.2003.10.003.

20. Sgarbanti, R.; Nencioni, L.; Amatore, D.; Coluccio, P.; Fraternale, A.; Sale, P.; Mammola, C.L.; Carpino, G.; Gaudio, E.; Magnani, M.; Ciriolo, M.R.; Garaci, E.; Palamara, A.T. Redox regulation of the influenza hemagglutinin maturation process: a new cell-mediated strategy for anti-influenza therapy. *Antioxid Redox Signal.* **2011**, 15, 593-606. doi: 10.1089/ars.2010.3512. Epub 2011 May 19.
21. Ng, M.P.; Lee, J.C.; Loke, W.M.; Yeo, L.L.; Quek, A.M.; Lim, E.C.; Halliwell, B.; Seet, R.C. Does influenza A infection increase oxidative damage? *Antioxidants & redox signaling* **2014**, *21*, 1025-1031, doi:10.1089/ars.2014.5907.
22. Masella, R.; Di Benedetto, R.; Varì, R.; Filesi, C.; Giovannini, C. Novel mechanisms of natural antioxidant compounds in biological systems: involvement of glutathione and glutathione-related enzymes. *J Nutr Biochem.* **2005**, 16, 577-586.
23. Reshi, M.L.; Su, Y.C.; Hong, J.R. RNA Viruses: ROS-Mediated Cell Death. *Int J Cell Biol.* **2014,** 2014, 467452. doi: 10.1155/2014/467452.
24. Krajka-Kuzniak, V.; Paluszczak, J.; Baer-Dubowska, W. The Nrf2-ARE signaling pathway: An update on its regulation and possible role in cancer prevention and treatment. *Pharmacological reports : PR* **2017**, *69*, 393-402, doi:10.1016/j.pharep.2016.12.011.
25. Murray, I.A.; Patterson, A.D.; Perdew, G.H. Aryl hydrocarbon receptor ligands in cancer: friend and foe. Nat Rev. *Cancer* **2014**, 14, 801-814. doi: 10.1038/nrc3846.
26. Oda, T.; Akaike, T.; Hamamoto, T.; Suzuki, F.; Hirano, T.; Maeda, H. Oxygen radicals in influenza-induced pathogenesis and treatment with pyran polymer-conjugated SOD. *Science (New York, N.Y.)* **1989**, *244*, 974-976, doi:10.1126/science.2543070.
27. Cai, J.; Chen, Y.; Seth, S.; Furukawa, S.; Compans, R.W.; Jones, D.P. Inhibition of influenza infection by glutathione. *Free radical biology & medicine* **2003**, *34*, 928-936, doi:10.1016/s0891-5849(03)00023-6.
28. Lin, X.C.; Wang, R.; Zou, W.; Sun, X.; Liu, X.; Zhao L., Wang, S.; Jin, M. The influenza virus H5N1 infection can induce ROS production for viral replication and host cell death in A549 cells modulated by human Cu/Zn superoxide dismutase (SOD1) overexpression. *Viruses*, **2016**, 8, 13, doi:10.3390/y8010013.
29. To, E.E.; Erlich, J.R.; Liong, F.; Luong, R.; Liong, S.; Esaq, F.; Oseghale, O.; Anthony, D.; McQualter, J.; Bozinovski, S.; Vlahos, R.; O'Leary, J.J.; Brooks, D.A.; Selemidis, S. Mitochondrial Reactive Oxygen Species Contribute to Pathological Inflammation During Influenza A Virus Infection in Mice. *Antioxid Redox Signal.* **2019**, doi: 10.1089/ars.2019.7727.
30. Checconi, P.; Salzano, S.; Bowler, L.; Mullen, L.; Mengozzi, M.; Hanschmann, E.M.; Lillig, C.H.; Sgarbanti, R.; Panella, S.; Nencioni, L.; Palamara, A.T.; Ghezzi, P. Redox proteomics of the inflammatory secretome identifies a common set of redoxins and other glutathionylated proteins released in inflammation, influenza virus infection and oxidative stress. *PLoS One* **2015**, 10, e0127086. doi: 10.1371/journal.pone. 0127086. eCollection 2015.
31. Dai, J.P.; Wang, Q.W.; Su, Y.; Gu, L.M.; Deng, H.X.; Chen, X.X.; Li, W.Z.; Li, K.S. Oxymatrine Inhibits Influenza A Virus Replication and Inflammation via TLR4, p38 MAPK and NF-κB Pathways. *Int J Mol Sci.* **2018**, 19. pii: E965. doi: 10.3390/ijms19040965.
32. Ma, Q.; Kinneer, K.; Bi, Y.; Chan, J.Y.; Kan, Y.W. Induction of murine NAD(P)H:quinone oxidoreductase by 2,3,7,8-tetrachlorodibenzo-p-dioxin requires the CNC (cap 'n' collar) basic leucine zipper transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2): cross-interaction between AhR (aryl hydrocarbon receptor) and Nrf2 signal transduction. *The Biochemical journal* **2004**, *377*, 205-213, doi:10.1042/bj20031123.
33. Jin, G.B.; Moore, A.J.; Head, J.L.; Neumiller, J.J.; Lawrence, B.P. Aryl hydrocarbon receptor activation reduces dendritic cell function during influenza virus infection. *Toxicol Sci* **2010**, *116*, 514-522. doi: 10.1093/toxsci/kfq153.
34. Head, J.L.; Lawrence, B.P. The aryl hydrocarbon receptor is a modulator of anti-viral immunity. *Biochem Pharmacol* **2009**, 77, 642-653. doi: 10.1016/j.bcp.2008.10.031.
35. Patel, R.; Rinker, L.; Peng, J.; Chilian, W.M. Reactive Oxygen Species: The Good and the Bad, Reactive Oxygen Species (ROS) in Living Cells, Filip, C.; Albu, E. *IntechOpen*, doi: 10.5772/intechopen.71547.

36. Bruns, K.; Studtrucker, N.; Sharma, A.; Fossen, T.; Mitzner, D.; Eissmann, A.; Tessmer, U.; Roder, R.; Henklein, P.; Wray, V., et al. Structural characterization and oligomerization of PB1-F2, a proapoptotic influenza A virus protein. *The Journal of biological chemistry* **2007**, *282*, 353-363, doi:10.1074/jbc.M606494200.
37. Kamal. R.K.; Alymova, I.V.; York, I.A. Evoliution anmd virulnce of influenza A virus protein PB1-F2. *International J. of Molecular Sciences*, **2018**, 19, 96,doi:10.3390/ijms/9010096.
38. Shin, N.; Pyo, C.W.; Jung, K.I.; Choi, S.Y. Influenza A virus PB1-F2 is involved in regulation of cellular redox state in alveolar epithelial cells. *Biochemical and biophysical research communications* **2015**, *459*, 699-705, doi:10.1016/j.bbrc.2015.03.010.
39. Pinar, A.; Dowling, J.K.; Bitto, N.J.; Robertson, A.A.; Latz, E.; Stewart, C.R.; Drummond, G.R.; Cooper, M.A.; McAuley, J.L.; Tate, M.D., et al. PB1-F2 Peptide Derived from Avian Influenza A Virus H7N9 Induces Inflammation via Activation of the NLRP3 Inflammasome. *The Journal of biological chemistry* **2017**, *292*, 826-836, doi:10.1074/jbc.M116.756379.
40. Bedard, K.; Krause, K.H. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. *Physiological reviews* **2007**, *87*, 245-313, doi:10.1152/physrev.00044.2005.
41. To, E.E.; Vlahos, R.; Luong, R.; Halls, M.L.; Reading, P.C.; King, P.T.; Chan, C.; Drummond, G.R.; Sobey, C.G.; Broughton, B.R.S., et al. Endosomal NOX2 oxidase exacerbates virus pathogenicity and is a target for antiviral therapy. *Nature communications* **2017**, *8*, 69, doi:10.1038/s41467-017-00057-x.
42. Amatore, D.; Sgarbanti, R.; Aquilano, K.; Baldelli, S.; Limongi, D.; Civitelli, L.; Nencioni, L.; Garaci, E.; Ciriolo, M.R.; Palamara, A.T. Influenza virus replication in lung epithelial cells depends on redox-sensitive pathways activated by NOX4-derived ROS. *Cellular microbiology* **2015**, *17*, 131-145, doi:10.1111/cmi.12343.
43. Selemidis, S.; Seow, H.J.; Broughton, B.R.; Vinh, A.; Bozinovski, S.; Sobey, C.G.; Drummond, G.R.; Vlahos, R. Nox1 oxidase suppresses influenza a virus-induced lung inflammation and oxidative stress. *PloS one* **2013**, *8*, e60792, doi:10.1371/journal.pone.0060792.
44. Hofstetter, A.R.; De La Cruz, J.A.; Cao, W.; Patel, J.; Belser, J.A.; McCoy, J.; Liepkalns, J.S.; Amoah, S.; Cheng, G.; Ranjan, P., et al. NADPH Oxidase 1 Is Associated with Altered Host Survival and T Cell Phenotypes after Influenza A Virus Infection in Mice. *PloS one* **2016**, *11*, e0149864, doi:10.1371/journal.pone.0149864.
45. Strengert, M.; Jennings, R.; Davanture, S.; Hayes, P.; Gabriel, G.; Knaus, U.G. Mucosal reactive oxygen species are required for antiviral response: role of Duox in influenza a virus infection. *Antioxidants & redox signaling* **2014**, *20*, 2695-2709, doi:10.1089/ars.2013.5353.
46. Hong, S.N.; Kim, J.Y.; Kim, H.; Kim, D.Y.; Won, T.B.; Han, D.H.; Rhee, C.S.; Kim, H.J. Duox2 is required for the transcription of pattern recognition receptors in acute viral lung infection: An interferon-independent regulatory mechanism. *Antiviral research* **2016**, *134*, 1-5, doi:10.1016/j.antiviral.2016.08.017.
47. Kim, H.J.; Kim, C.H.; Kim, M.J.; Ryu, J.H.; Seong, S.Y.; Kim, S.; Lim, S.J.; Holtzman, M.J.; Yoon, J.H. The Induction of Pattern-Recognition Receptor Expression against Influenza A Virus through Duox2-Derived Reactive Oxygen Species in Nasal Mucosa. *American journal of respiratory cell and molecular biology* **2015**, *53*, 525-535, doi:10.1165/rcmb.2014-0334OC.
48. Daiber, A.; Di Lisa, F.; Oelze, M.; Kroller-Schon, S.; Steven, S.; Schulz, E.; Munzel, T. Crosstalk of mitochondria with NADPH oxidase via reactive oxygen and nitrogen species signalling and its role for vascular function. *British journal of pharmacology* **2017**, *174*, 1670-1689, doi:10.1111/bph.13403.
49. Burggraaf, S.; Bingham, J.; Payne, J.; Kimpton, W.G.; Lowenthal, J.W.; Bean, A.G. Increased inducible nitric oxide synthase expression in organs is associated with a higher severity of H5N1 influenza virus infection. *PLoS One* **2011**, 6, e14561. doi: 10.1371/journal.pone.0014561.
50. Zablockienė, B.; Kačergius, T.; Ambrozaitis, A.; Žurauskas, E.; Bratchikov, M.; Jurgauskienė, L.; Zablockis, R.; Gravenstein, S. Zanamivir Diminishes Lung Damage in Influenza A Virus-infected Mice by Inhibiting Nitric Oxide Production. *In Vivo* **2018**, 32, :473-478.
51. Atkin-Smith, G.K.; Duan, M.; Chen, W.; Poon, I.K.H. The induction and consequences of Influenza A virus-induced cell death. *Cell Death Dis*. **2018**, 9, 1002. doi: 10.1038/s41419-018-1035-6.
52. Zhang, R., Chi, X., Wang, S., Qi, B., Yu, X., Chen, J.L. The regulation of autophagy by influenza A virus. *Biomed Res Int*. **2014**, 2014, 498083. doi: 10.1155/2014/498083.

53. Biondo, C.; Lentini, G.; Beninati, C.; Teti, G. The dual role of innate immunity during influenza. *Biomedical J.* **2019,** 42, 8-18. doi: 10.1016/j.bj.2018.12.009.
54. Gregory, D.J.; Kobzik. L Influenza lung injury: mechanisms and therapeutic opportunities. *Am J Physiol Lung Cell Mol Physi.* **2015**, 309, L1041-6. doi: 10.1152/ajplung.00283.2015.
55. Budinger, G.R. . Herold, S., Becker, C., Ridge, K.M. Influenza virus-induced lung injury: pathogenesis and implications for treatment. *Eur Respir J.* **2015**, 45, 1463-78. doi: 10.1183/09031936.00186214.
56. Li, N. Kiraly, O.; Chow, V.T.; Engelward, B.P.; Parrish, M.; Chan, T.K.; Yin, L.; Rai, P.; Yoshiyuki, Y.; Abolhassani, N.; Tan, K.B. Influenza infection induces host DNA damage and dynamic DNA damage responses during tissue regeneration. *Cell Mol Life Sci*. **2015**, 72, 2973-2988. doi: 10.1007/s00018-015-1879-1.
57. Mileva, M.; Marazov, K.; Galabov, A.S. Gastric mucosal lesions in influenza virus infected mice: role of gastric lipid peroxidation. *Methods Find Exp Clin Pharmacol.* **2003**, 25, 521-524.
58. Kumar, P., Sharma, S., Khanna, M., Raj, H.G. Effect of Quercetin on lipid peroxidation and changes in lung morphology in experimental influenza virus infection. *Int J Exp Pathol.* **2003**, 84,127-133.
59. Nencioni, L.; Palamara, A.T. Nencioni, L.; Sgarbanti, R.; De Chiara, G.; Garaci, E. Influenza virus and redox mediated cell signaling: a complex network of virus/host interaction. *New Microbiol.* **2007**, 30, 367-375.
60. Checconi, P.; Salzano, S.; Bowler, L.; Mullen, L.; Mengozzi, M.; Hanschmann, E.M.; Lillig, C.H.; Sgarbanti, R.; Panella, S.; Nencioni, L.; Palamara, A.T.; Ghezzi, P. Redox proteomics of the inflammatory secretome identifies a common set of redoxins and other glutathionylated proteins released in inflammation, influenza virus infection and oxidative stress. *PLoS One* **2015**, 10, e0127086. doi: 10.1371/journal.pone. 0127086. eCollection 2015.
61. Buffinton, G.D.; Christen, S.; Peterhans, E.; Stocker, R. Oxidative stress in lungs of mice infected with influenza A virus. *Free radical research communications* **1992**, *16*, 99-110.
62. He, G.; Dong, C.; Luan, Z.; McAllan, B.M.; Xu, T.; Zhao, L.; Qiao, J. Oxygen free radical involvement in acute lung injury induced by H5N1 virus in mice. *Influenza and other respiratory viruses* **2013**, *7*, 945-953, doi:10.1111/irv.12067.
63. de Jong, MD.; Simmons, C.P.; Thanh, T.T.; Hien, V.M.; Smith, G.J.; Chau, T.N.; Hoang, D.M.; Chau, N.V.; Khanh, T.H.; Dong, V.C.; Qui, P.T.; Cam, B.V.; Ha do, Q.; Guan, Y.; Peiris, .JS.; Chinh, N.T.; Hien, T.T.; Farrar. J. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med.* **2006**, 12, 1203-1207.
64. Vlahos, R.; Stambas, J.; Selemidis, S. Suppressing production of reactive oxygen species (ROS) for influenza A virus therapy. *Trends in pharmacological sciences* **2012**, *33*, 3-8, doi:10.1016/j.tips.2011.09.001.
65. Khomich, O.A.; Kochetkov, S.N.; Bartosch, B.; Ivanov, A.V. Redox bilogy of respiratory viral infecion, *Viruses*, **2018**, 10, 392; doi: 10.3390/v10080392.
66. Maurizi, C.P. Influenza caused epidemic encephalitis (encephalitis lethargica): the circumstantial evidence and a challenge to the nonbelievers. *Medical hypotheses* **2010**, *74*, 798-801, doi:10.1016/j.mehy.2009.12.012.
67. Sellers, S.A.; Hagan, R.S.; Hayden, F.G.; Fischer, W.A., 2nd. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. *Influenza and other respiratory viruses* **2017**, *11*, 372-393, doi:10.1111/irv.12470.
68. Toovey, S. Influenza-associated central nervous system dysfunction: a literature review. *Travel medicine and infectious disease* **2008**, *6*, 114-124, doi:10.1016/j.tmaid.2008.03.003.
69. Ng, Y.P.; Lee, S.M.; Cheung, T.K.; Nicholls, J.M.; Peiris, J.S.; Ip, N.Y. Avian influenza H5N1 virus induces cytopathy and proinflammatory cytokine responses in human astrocytic and neuronal cell lines. *Neuroscience* **2010**, *168*, 613-623, doi:10.1016/j.neuroscience.2010.04.013.
70. Wang, G.; Zhang, J.; Li, W.; Xin, G.; Su, Y.; Gao, Y.; Zhang, H.; Lin, G.; Jiao, X.; Li, K. Apoptosis and proinflammatory cytokine responses of primary mouse microglia and astrocytes induced by human H1N1 and avian H5N1 influenza viruses. *Cellular & molecular immunology* **2008**, *5*, 113-120, doi:10.1038/cmi.2008.14.
71. Lin, X.; Wang, R.; Zhang, J.; Sun, X.; Zou, Z.; Wang, S.; Jin, M. Insights into Human Astrocyte Response to H5N1 Infection by Microarray Analysis. *Viruses* **2015**, *7*, 2618-2640, doi:10.3390/v7052618.
72. Siegers, J.Y.; van de Bildt, M.W.G.; Lin, Z.; Leijten, L.M.; Lavrijssen, R.A.M.; Bestebroer, T.; Spronken, M.I.J.;

De Zeeuw, C.I.; Gao, Z.; Schrauwen, E.J.A., et al. Viral Factors Important for Efficient Replication of Influenza A Viruses in Cells of the Central Nervous System. *Journal of virology* **2019**, *93*, doi:10.1128/jvi.02273-18.

73. Lee, N.; Wong, C.K.; Hui, D.S.; Lee, S.K.; Wong, R.Y.; Ngai, K.L.; Chan, M.C.; Chu, Y.J.; Ho, A.W.; Lui, G.C., et al. Role of human Toll-like receptors in naturally occurring influenza A infections. *Influenza and other respiratory viruses* **2013**, *7*, 666-675, doi:10.1111/irv.12109.
74. Liu, Y.; Chen, H.; Sun, Y.; Chen, F. Antiviral role of Toll-like receptors and cytokines against the new 2009 H1N1 virus infection. *Molecular biology reports* **2012**, *39*, 1163-1172, doi:10.1007/s11033-011-0846-7.
75. Pan, H.Y.; Yano, M.; Kido, H. Effects of inhibitors of Toll-like receptors, protease-activated receptor-2 signalings and trypsin on influenza A virus replication and upregulation of cellular factors in cardiomyocytes. *The journal of medical investigation : JMI* **2011**, *58*, 19-28.
76. Song, B.M.; Kang, Y.M.; Kim, H.S.; Seo, S.H. Induction of inflammatory cytokines and toll-like receptors in human normal respiratory epithelial cells infected with seasonal H1N1, 2009 pandemic H1N1, seasonal H3N2, and highly pathogenic H5N1 influenza virus. *Viral immunology* **2011**, *24*, 179-187, doi:10.1089/vim.2010.0125.
77. Zhang, R.; Ai, X.; Duan, Y.; Xue, M.; He, W.; Wang, C.; Xu, T.; Xu, M.; Liu, B.; Li, C., et al. Kaempferol ameliorates H9N2 swine influenza virus-induced acute lung injury by inactivation of TLR4/MyD88-mediated NF-kappaB and MAPK signaling pathways. *Biomedicine & pharmacotherapy*, **2017**, *89*, 660-672, doi:10.1016/j.biopha.2017.02.081.
78. Guillot, L.; Le Goffic, R.; Bloch, S.; Escriou, N.; Akira, S.; Chignard, M.; Si-Tahar, M. Involvement of toll-like receptor 3 in the immune response of lung epithelial cells to double-stranded RNA and influenza A virus. *The Journal of biological chemistry* **2005**, *280*, 5571-5580, doi:10.1074/jbc.M410592200.
79. Le Goffic, R.; Balloy, V.; Lagranderie, M.; Alexopoulou, L.; Escriou, N.; Flavell, R.; Chignard, M.; Si-Tahar, M. Detrimental contribution of the Toll-like receptor (TLR)3 to influenza A virus-induced acute pneumonia. *PLoS pathogens* **2006**, *2*, e53, doi:10.1371/journal.ppat.0020053.
80. Marchant, D.; Singhera, G.K.; Utokaparch, S.; Hackett, T.L.; Boyd, J.H.; Luo, Z.; Si, X.; Dorscheid, D.R.; McManus, B.M.; Hegele, R.G. Toll-like receptor 4-mediated activation of p38 mitogen-activated protein kinase is a determinant of respiratory virus entry and tropism. *Journal of virology* **2010**, *84*, 11359-11373, doi:10.1128/jvi.00804-10.
81. Shirey, K.A.; Lai, W.; Scott, A.J.; Lipsky, M.; Mistry, P.; Pletneva, L.M.; Karp, C.L.; McAlees, J.; Gioannini, T.L.; Weiss, J., et al. The TLR4 antagonist Eritoran protects mice from lethal influenza infection. *Nature* **2013**, *497*, 498-502, doi:10.1038/nature12118.
82. Creagh, E,M,; O'Neill, L.A. TLRs, NLRs, and RLRs: a trinity of pathogen sensors that cooperate in innate immunity. *Treands Immunol*. **2006**, 27, 352-357.
83. Kirkpatrick, C.T.; Wang, Y.; Leiva Juarez, M.M.; Shivshankar, P.; Pantaleón García, J.; Plumer, A.K.; Kulkarni, V.V.; Ware, H.H.; Gulraiz, F.; Chavez Cavasos, M.A.; Martinez Zayas, G.; Wali, S.; Rice, A.P.; Liu, H.; Tour, J.M.; Sikkema, W.K.A.; Cruz Solbes, A.S.; Youker, K.A.;Tuvim, M.J.; Dickey, B.F., Evans, S.E. Inducible Lung Epithelial Resistance Requires Multisource Reactive Oxygen Species Generation To Protect against Viral Infections. *MBio.* 2018, 9. pii: e00696-18. doi: 10.1128/mBio.00696-18.
84. Yeo, S.J.; Kim, S.J.; Kim, J.H.; Lee, H.J.; Kook, Y.H. Influenza A virus infection modulates the expression of type IV collagenase in epithelial cells. *Arch Virol*. **1999**, 144, 1361-1370.
85. Wang, S.; Quang, Le, T.; Chida, J.; Cisse, Y.; Yano, M.; Kido, H. Mechanisms of matrix metalloproteinase-9 upregulation and tissue destruction in various organs in influenza A virus infection. *J Med Invest.* **2010**, 57, 26-34.
86. Lee, Y.H.; Lai, C.L.; Hsieh, S.H.; Shieh, C.C.; Huang, L.M.; Wu-Hsieh, B.A. Influenza A virus induction of oxidative stress and MMP-9 is associated with severe lung pathology in a mouse model. *Virus research* **2013**, *178*, 411-422, doi:10.1016/j.virusres.
87. Bradley, L.M.; Douglass, M.F.; Chatterjee, D.; Akira, S.; Baaten, B.J. Matrix metalloprotease 9 mediates neutrophil migration into the airways in response to influenza virus-induced toll-like receptor signaling. *PLoS Pathog.* **2012**, 8, e1002641. doi: 10.1371/journal.ppat.1002641.
88. Tang, F.S.; Van Ly, D.; Spann, K.; Reading, P.C.; Burgess, .JK.; Hartl, D.; Baines, K.J.; Oliver, B.G. Differential

neutrophil activation in viral infections: Enhanced TLR-7/8-mediated CXCL8 release in asthma**.** *Respirology.* **2016**, 21, 172-179. doi: 10.1111/resp.12657.

89. Uchide, N.; Obatake, K.; Yamada, R.; Sadanari, H.; Matsubara, K.; Murayama, T.; Ohyama, K. Regulation of Matrix Metalloproteinases-2 and -9 Gene Expression in Cultured Human Fetal Membrane Cells by Influenza Virus Infection. *Biological & pharmaceutical bulletin* **2016**, *39*, 1912-1921, doi:10.1248/bpb.b16-00093.
90. Betakova, T.; Kostrabova, A.; Lachova, V., Turianova, L. Cytokines Induced During Influenza Virus Infection. Curr Pharm Des. 2017, 3, 2616-2622. doi: 10.2174/1381612823666170316123736.
91. Lam, W.Y., Teyng, A.C., Chu, I.M., Chan, P.K. Profiles of cytokine and chemokine gene expression in human pulmonary epithelial cells induced by human and avian influenza viruses. Virol J. 2010, 7, 344. doi: 10.1186/1743-422X-7-344.
92. Nencioni, L.; Sgarbanti, R.; De Chiara, G.; Garaci, E.; Palamara, A.T. Influenza virus and redox mediated cell signaling: a complex network of virus/host interaction. *The new microbiologica* **2007**, *30*, 367-375.
93. Wong, E.T.; Tergaonkar, V. Roles of NF-kappaB in health and disease: mechanisms and therapeutic potential. *Clinical science (London, England : 1979)* **2009**, *116*, 451-465, doi:10.1042/cs20080502.
94. Zhu, L.; Ly, H.; Liang, Y. PLC-gamma1 signaling plays a subtype-specific role in postbinding cell entry of influenza A virus. *Journal of virology* **2014**, *88*, 417-424, doi:10.1128/jvi.02591-13.
95. Lamichhane, P. P.; Samarasinghe, A.E. The Role of Innate Leukocytes during Influenza Virus Infection. *J Immunol Res.* 2019, 2019:8028725. doi: 10.1155/2019/8028725.
96. Atkin-Smith, G.K.; Duan, M.; Chen, W.; Poon, I.K.H. The induction and consequences of Influenza A virus-induced cell death. *Cell Death Dis.* 2018, 9, 1002. doi: 10.1038/s41419-018-1035-6.
97. Jung, K.I., KO, D.H., Shin, N., Pyo, C.W., Choi, S.Y. Endoplasmic reticulum-associated degradation potentiates the infectivity of influenza A virus by regulating the host redox state. Free Radic Biol Med. 2019, 135, 293-305.
98. Hassan, I.H.; Zhang, M.S.; Powers, L.S.; Shao, J.Q.; Baltrusaitis, J.; Rutkowski, D.T.; Legge, K.; Monick, M.M. Influenza A viral replication is blocked by inhibition of the inositol-requiring enzyme 1 (IRE1) stress pathway. *The Journal of biological chemistry* **2012**, *287*, 4679-4689, doi:10.1074/jbc.M111.284695.
99. Medina, R.A.; Garcia-Sastre, A. Influenza A viruses: new research developments. *Nature reviews. Microbiology* **2011**, *9*, 590-603, doi:10.1038/nrmicro2613.
100. Tscherne, D.M.; Garcia-Sastre, A. Virulence determinants of pandemic influenza viruses. *The Journal of clinical investigation* **2011**, *121*, 6-13, doi:10.1172/jci44947.
101. Teske, S.; Bohn, A.A.; Regal, J.F.; Neumiller, J.J.; Lawrence, B.P. Activation of the aryl hydrocarbon receptor increases pulmonary neutrophilia and diminishes host resistance to influenza A virus. *American journal of physiology. Lung cellular and molecular physiology* **2005**, *289*, L111-124, doi:10.1152/ajplung.00318.2004
102. Lim, J.Y.; Oh, E.; Kim, Y.; Jung, W.W.; Kim, H.S.; Lee, J.; Sul, D. Enhanced oxidative damage to DNA, lipids, and proteins and levels of some antioxidant enzymes, cytokines, and heat shock proteins in patients infected with influenza H1N1 virus. *Acta virologica* **2014**, *58*, 253-260.
103. Mileva, M.; Bakalova, R.; Tancheva, L.; Galabov, A.; Ribarov, S. Effect of vitamin E supplementation on lipid peroxidation in blood and lung of influenza virus infected mice. *Comparative immunology, microbiology and infectious diseases* **2002**, *25*, 1-11.
104. Shibutani, S.; Takeshita, M.; Grollman, A.P. Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG. *Nature* **1991**, *349*, 431-434, doi:10.1038/349431a0.
105. Kwak, M.K.; Itoh, K.; Yamamoto, M.; Kensler, T.W. Enhanced expression of the transcription factor Nrf2 by cancer chemopreventive agents: role of antioxidant response element-like sequences in the nrf2 promoter. *Molecular and cellular biology* **2002**, *22*, 2883-2892, doi:10.1128/mcb.22.9.2883-2892.2002.
106. Sies, H. Oxidative stress: oxidants and antioxidants. *Experimental physiology* **1997**, *82*, 291-295.
107. Kosmider, B.; Messier, E.M.; Janssen, W.J.; Nahreini, P.; Wang, J.; Hartshorn, K.L.; Mason, R.J. Nrf2 protects human alveolar epithelial cells against injury induced by influenza A virus. *Respiratory research* **2012**, *13*, 43, doi:10.1186/1465-9921-13-43.
108. Yamada, Y.; Limmon, G.V.; Zheng, D.; Li, N.; Li, L.; Yin, L.; Chow, V.T.; Chen, J.; Engelward, B.P. Major shifts

in the spatio-temporal distribution of lung antioxidant enzymes during influenza pneumonia. *PloS one* **2012**, *7*, e31494, doi:10.1371/journal.pone.0031494.

109. Ludwig, S.; Planz, O.; Pleschka, S.; Wolff, T. Influenza-virus-induced signaling cascades: targets for antiviral therapy? *Trends in molecular medicine* **2003**, *9*, 46-52.
110. Simon, P.F.; McCorrister, S.; Hu, P.; Chong, P.; Silaghi, A.; Westmacott, G.; Coombs, K.M.; Kobasa, D. Highly Pathogenic H5N1 and Novel H7N9 Influenza A Viruses Induce More Profound Proteomic Host Responses than Seasonal and Pandemic H1N1 Strains. *Journal of proteome research* **2015**, *14*, 4511-4523, doi:10.1021/acs.jproteome.5b00196.
111. Jacoby, D.B.; Choi, A.M. Influenza virus induces expression of antioxidant genes in human epithelial cells. *Free radical biology & medicine* **1994**, *16*, 821-824, doi:10.1016/0891-5849(94)90198-8
112. Lin, L.T.; Richaqrdson, C.D. The Host Cell receptors fro Measles Virus and Their Intercation with the Viral Hemagglutinin (H) Protein. Viruss 2016, 8, doi:10.3390/v8090250.
113. Huang, Y.; Zaas, A.K.; Rao, A.; Dobigeon, N.; Woolf, P.J.; Veldman, T.; Oien, N.C.; McClain, M.T.; Varkey, J.B.; Nicholson, B., et al. Temporal dynamics of host molecular responses differentiate symptomatic and asymptomatic influenza a infection. *PLoS genetics* **2011**, *7*, e1002234, doi:10.1371/journal.pgen.1002234.
114. Erkekoglu, P.; Asci, A.; Ceyhan, M.; Kizilgun, M.; Schweizer, U.; Atas, C.; Kara, A.; Kocer Giray, B. Selenium levels, selenoenzyme activities and oxidant/antioxidant parameters in H1N1-infected children. *The Turkish journal of pediatrics* **2013**, *55*, 271-282.
115. Soliman, H.; MedIVilla-Varela, M.; Antonia, S. Indoleamine 2,3-dioxygenase: is it an immune suppressor? *Cancer journal (Sudbury, Mass.)* **2010**, *16*, 354-359, doi:10.1097/PPO.0b013e3181eb3343.
116. Choi, A.M.; Knobil, K.; Otterbein, S.L.; Eastman, D.A.; Jacoby, D.B. Oxidant stress responses in influenza virus pneumonia: gene expression and transcription factor activation. *The American journal of physiology* **1996**, *271*, L383-391, doi:10.1152/ajplung.1996.271.3.L383.
117. Biswas, M.; Chan, J.Y. Role of Nrf1 in antioxidant response element-mediated gene expression and beyond. *Toxicology and applied pharmacology* **2010**, *244*, 16-20, doi:10.1016/j.taap.2009.07.034.
118. Ki, Y.W.; Park, J.H.; Lee, J.E.; Shin, I.C.; Koh, H.C. JNK and p38 MAPK regulate oxidative stress and the inflammatory response in chlorpyrifos-induced apoptosis. *Toxicology letters* **2013**, *218*, 235-245, doi:10.1016/j.toxlet.2013.02.003.
119. Meineke, R.; Rimmelzwaan, G.F.; Elbahesh, H. Influenza Virus Infections and Cellular Kinases. *Viruses* **2019**, *11*, doi:10.3390/v11020171. .
120. Hiscott, J.; Kwon, H.; Genin, P. Hostile takeovers: viral appropriation of the NF-kappaB pathway. *The Journal of clinical investigation* **2001**, *107*, 143-151, doi:10.1172/jci11918.
121. Liu, G.H.; Qu, J.; Shen, X. NF-kappaB/p65 antagonizes Nrf2-ARE pathway by depriving CBP from Nrf2 and facilitating recruitment of HDAC3 to MafK. *Biochimica et biophysica acta* **2008**, *1783*, 713-727, doi:10.1016/j.bbamcr.2008.01.002.
122. Torres, M.; Forman, H.J. Redox signaling and the MAP kinase pathways. *BioFactors (Oxford, England)* **2003**, *17*, 287-296.
123. Leslie, N.R. The redox regulation of PI 3-kinase-dependent signaling. *Antioxidants & redox signaling* **2006**, *8*, 1765-1774, doi:10.1089/ars.2006.8.1765.
124. McCubrey, J.A.; Lahair, M.M.; Franklin, R.A. Reactive oxygen species-induced activation of the MAP kinase signaling pathways. *Antioxidants & redox signaling* **2006**, *8*, 1775-1789, doi:10.1089/ars.2006.8.1775.
125. Nencioni, L.; De Chiara, G.; Sgarbanti, R.; Amatore, D.; Aquilano, K.; Marcocci, M.E.; Serafino, A.; Torcia, M.; Cozzolino, F.; Ciriolo, M.R., et al. Bcl-2 expression and p38MAPK activity in cells infected with influenza A virus: impact on virally induced apoptosis and viral replication. *The Journal of biological chemistry* **2009**, *284*, 16004-16015, doi:10.1074/jbc.M900146200.
126. Shin, Y.K.; Liu, Q.; Tikoo, S.K.; Babiuk, L.A.; Zhou, Y. Effect of the phosphatidylinositol 3-kinase/Akt pathway on influenza A virus propagation. *The Journal of general virology* **2007**, *88*, 942-950, doi:10.1099/vir.0.82483-0.
127. Li, Y.; Lin, Z.; Guo, M.; Zhao, M.; Xia, Y.; Wang, C.; Xu, T.; Zhu, B. Inhibition of H1N1 influenza virus-induced apoptosis by functionalized selenium nanoparticles with amantadine through ROS-mediated AKT signaling

pathways. *International journal of nanomedicine* **2018**, *13*, 2005-2016, doi:10.2147/ijn.S155994.

128. Ehrhardt, C.; Marjuki, H.; Wolff, T.; Nurnberg, B.; Planz, O.; Pleschka, S.; Ludwig, S. Bivalent role of the phosphatidylinositol-3-kinase (PI3K) during influenza virus infection and host cell defence. *Cellular microbiology* **2006**, *8*, 1336-1348, doi:10.1111/j.1462-5822.2006.00713.x.
129. Neff-LaFord, H.; Teske, S.; Bushnell, T.P.; Lawrence, B.P. Aryl hydrocarbon receptor activation during influenza virus infection unveils a novel pathway of IFN-gamma production by phagocytic cells. *Journal of immunology (Baltimore, Md. : 1950)* **2007**, *179*, 247-255, doi:10.4049/jimmunol.179.1.247.
130. Wheeler, J.L.; Martin, K.C.; Lawrence, B.P. Novel cellular targets of AhR underlie alterations in neutrophilic inflammation and inducible nitric oxide synthase expression during influenza virus infection. *Journal of immunology (Baltimore, Md. : 1950)* **2013**, *190*, 659-668, doi:10.4049/jimmunol.1201341.
131. Yamada, T.; Horimoto, H.; Kameyama, T.; Hayakawa, S.; Yamato, H.; Dazai, M.; Takada, A.; Kida, H.; Bott, D.; Zhou, A.C., et al. Constitutive aryl hydrocarbon receptor signaling constrains type I interferon-mediated antiviral innate defense. *Nature immunology* **2016**, *17*, 687-694, doi:10.1038/ni.3422.
132. Gaelings, L.; Soderholm, S.; Bugai, A.; Fu, Y.; Nandania, J.; Schepens, B.; Lorey, M.B.; Tynell, J.; Vande Ginste, L.; Le Goffic, R., et al. Regulation of kynurenine biosynthesis during influenza virus infection. *The FEBS journal* **2017**, *284*, 222-236, doi:10.1111/febs.13966.
133. Wheeler, J.L.; Martin, K.C.; Resseguie, E.; Lawrence, B.P. Differential consequences of two distinct AhR ligands on innate and adaptive immune responses to influenza A virus. *Toxicological sciences : an official journal of the Society of Toxicology* **2014**, *137*, 324-334, doi:10.1093/toxsci/kft255.
134. Boule, L.A.; Burke, C.G.; Jin, G.B.; Lawrence, B.P. Aryl hydrocarbon receptor signaling modulates antiviral immune responses: ligand metabolism rather than chemical source is the stronger predictor of outcome. *Scientific reports* **2018**, *8*, 1826, doi:10.1038/s41598-018-20197-4.
135. Miyamoto S, Ronsein GE, Prado FM, Uemi M, Corrêa TC, Toma IN, Bertolucci A, Oliveira MC, Motta FD, Medeiros MH, Mascio PD. Biological hydroperoxides and singlet molecular oxygen generation. IUBMB Life. **2007**, *59*, 322-331.
136. Stanley, C.P.; Maghzal, G.J.; Ayer, A.; Talib, J.; Giltrap, A.M.; Shengule, S.; Wolhuter, K.; Wang, Y.; Chadha, P.; Suarna, C., et al. Singlet molecular oxygen regulates vascular tone and blood pressure in inflammation. *Nature* **2019**, *566*, 548-552, doi:10.1038/s41586-019-0947-3.
137. Gutierrez-Vazquez, C.; Quintana, F.J. Regulation of the Immune Response by the Aryl Hydrocarbon Receptor. *Immunity* **2018**, *48*, 19-33, doi:10.1016/j.immuni.2017.12.012.
138. Head, J.L.; Lawrence, B.P. The aryl hydrocarbon receptor is a modulator of anti-viral immunity. *Biochemical pharmacology* **2009**, *77*, 642-653, doi:10.1016/j.bcp.2008.10.031.
139. Hazafa, A.; Rehman, K.U.; Jahan, N.; Jabeen, Z. The Role of Polyphenol (Flavonoids) Compounds in the Treatment of Cancer Cells. *Nutrition and cancer* **2019**, 10.1080/01635581.2019.1637006, 1-12, doi:10.1080/01635581.2019.1637006.
140. Garozzo, A.; Tempera, G.; Ungheri, D.; Timpanaro, R.; Castro, A. N-acetylcysteine synergizes with oseltamivir in protecting mice from lethal influenza infection. *International journal of immunopathology and pharmacology* **2007**, *20*, 349-354, doi:10.1177/039463200702000215.
141. Geiler, J.; Michaelis, M.; Naczk, P.; Leutz, A.; Langer, K.; Doerr, H.W.; Cinatl, J., Jr. N-acetyl-L-cysteine (NAC) inhibits virus replication and expression of pro-inflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus. *Biochemical pharmacology* **2010**, *79*, 413-420, doi:10.1016/j.bcp.2009.08.025.
142. Ghezzi, P.; Ungheri, D. Synergistic combination of N-acetylcysteine and ribavirin to protect from lethal influenza viral infection in a mouse model. *International journal of immunopathology and pharmacology* **2004**, *17*, 99-102, doi:10.1177/039463200401700114.
143. Zhang, R.H.; Li, C.H.; Wang, C.L.; Xu, M.J.; Xu, T.; Wei, D.; Liu, B.J.; Wang, G.H.; Tian, S.F. N-acetyl-l-cystine (NAC) protects against H9N2 swine influenza virus-induced acute lung injury. *International immunopharmacology* **2014**, *22*, 1-8, doi:10.1016/j.intimp.2014.06.013.
144. Garigliany, M.M.; Desmecht, D.J. N-acetylcysteine lacks universal inhibitory activity against influenza A viruses. *Journal of negative results in biomedicine* **2011**, *10*, 5, doi:10.1186/1477-5751-10-5.

145. Nencioni, L.; Iuvara, A.; Aquilano, K.; Ciriolo, M.R.; Cozzolino, F.; Rotilio, G.; Garaci, E.; Palamara, A.T. Influenza A virus replication is dependent on an antioxidant pathway that involves GSH and Bcl-2. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology* **2003**, 17, 758-760, doi:10.1096/fj.02-0508fje.
146. Braakman, I.; Helenius, J.; Helenius, A. Role of ATP and disulphide bonds during protein folding in the endoplasmic reticulum. *Nature*. **1992**, 356, 260-262.
147. Limongi, D.; Baldelli, S.; Checconi, P.; Marcocci, M.E.; De Chiara, G.; Fraternale, A.; Magnani, M.; Ciriolo, M.R.; Palamara, A.T. GSH-C4 Acts as Anti-inflammatory Drug in Different Models of Canonical and Cell Autonomous Inflammation Through NFκB Inhibition. *Front Immunol*. **2019**, 10, 155. doi: 10.3389/fimmu.2019.00155. eCollection 2019.
148. Jung, K.I.; Ko, D.H.; Shin, N.; Pyo, C.W.; Choi, S.Y. Endoplasmic reticulum-associated degradation potentiates the infectivity of influenza A virus by regulating the host redox state. *Free Radic Biol Med* **2019**, 135, 293-305. doi: 10.1016/j.freeradbiomed.2019.03.021.
149. Episcopio, D.; Aminov, S.; Benjamin, S.; Germain, G.; Datan, E.; Landazuri, J.; Lockshin, R.A.; Zakeri, Z. Atorvastatin restricts the ability of influenza virus to generate lipid droplets and severely suppresses the replication of the virus. *FASEB J* **2019**, 33, 9516-9525. doi: 10.1096/fj.201900428RR
150. Peterhans, E. Oxidants and antioxidants in viral diseases: disease mechanisms and metabolic regulation. *The Journal of nutrition* **1997**, *127*, 962s-965s, doi:10.1093/jn/127.5.962S.
151. Gasparini, R.; Amicizia, D.; Lai, P.L.; Bragazzi, N.L.; Panatto, D. Compounds with anti-influenza activity: present and future of strategies for the optimal treatment and management of influenza. Part II: Future compounds against influenza virus. *Journal of preventive medicine and hygiene* **2014**, *55*, 109-129.
152. Sgarbanti, R.; Amatore, D.; Celestino, I.; Marcocci, M.E.; Fraternale, A.; Ciriolo, M.R.; Magnani, M.; Saladino, R.; Garaci, E.; Palamara, A.T., et al. Intracellular redox state as target for anti-influenza therapy: are antioxidants always effective? *Current topics in medicinal chemistry* **2014**, *14*, 2529-2541.
153. Michaelis, M.; Sithisarn, P.; Cinatl, J., Jr. Effects of flavonoid-induced oxidative stress on anti-H5N1 influenza a virus activity exerted by baicalein and biochanin A. *BMC research notes* **2014**, *7*, 384, doi:10.1186/1756-0500-7-384.
154. Sheridan, P.A.; Zhong, N.; Carlson, B.A.; Perella, C.M.; Hatfield, D.L.; Beck, M.A. Decreased selenoprotein expression alters the immune response during influenza virus infection in mice. *The Journal of nutrition* **2007**, *137*, 1466-1471, doi:10.1093/jn/137.6.1466.
155. Ling, J.X.; Wei, F.; Li, N.; Li, J.L.; Chen, L.J.; Liu, Y.Y.; Luo, F.; Xiong, H.R.; Hou, W.; Yang, Z.Q. Amelioration of influenza virus-induced reactive oxygen species formation by epigallocatechin gallate derived from green tea. *Acta pharmacologica Sinica* **2012**, *33*, 1533-1541, doi:10.1038/aps.2012.80.
156. Song, J.M.; Lee, K.H.; Seong, B.L. Antiviral effect of catechins in green tea on influenza virus. *Antiviral research* **2005**, *68*, 66-74, doi:10.1016/j.antiviral.2005.06.010.
157. Wu, W.; Li, R.; Li, X.; He, J.; Jiang, S.; Liu, S.; Yang, J. Quercetin as an Antiviral Agent Inhibits Influenza A Virus (IV) Entry. *Viruses* **2015**, *8*, doi:10.3390/v8010006.
158. Awogbindin, I.O.; Olaleye, D.O.; Farombi, E.O. Mechanistic perspective of the oxido-immunopathologic resolution property of kolaviron in mice influenza pneumonitis. *APMIS : acta pathologica, microbiologica, et immunologica Scandinavica* **2017**, *125*, 184-196, doi:10.1111/apm.12640.
159. Bergmann, S.; Elbahesh, H. Targeting the proviral host kinase, FAK, limits influenza a virus pathogenesis and NFkB-regulated pro-inflammatory responses. *Virology* **2019**, *534*, 54-63, doi:10.1016/j.virol.2019.05.020.
160. Jiang, H.; Shen, S.M.; Yin, J.; Zhang, P.P.; Shi, Y. Sphingosine 1-phosphate receptor 1 (S1PR1) agonist CYM5442 inhibits expression of intracellular adhesion molecule 1 (ICAM1) in endothelial cells infected with influenza A viruses. *PloS one* **2017**, *12*, e0175188, doi:10.1371/journal.pone.0175188.
161. Lee, J.Y.; Abundo, M.E.C.; Lee, C.W. Herbal Medicines with Antiviral Activity Against the Influenza Virus, a Systematic Review. *The American journal of Chinese medicine* **2018**, *46*, 1663-1700, doi:10.1142/s0192415x18500854.
162. Planz, O. Development of cellular signaling pathway inhibitors as new antivirals against influenza. *Antiviral research* **2013**, *98*, 457-468, doi:10.1016/j.antiviral.2013.04.008.

163. Wang, L.; Jiang, H.; Shen, S.M.; Wen, C.X.; Xing, Z.; Shi, Y. Inhibition of autophagy and chemokine induction by sphingosine 1-phosphate receptor 1 through NF-kappaB signaling in human pulmonary endothelial cells infected with influenza A viruses. *PloS one* **2018**, *13*, e0205344, doi:10.1371/journal.pone.0205344.
164. McCarty, M.F.; Barroso-Aranda, J.; Contreras, F. Practical strategies for targeting NF-kappaB and NADPH oxidase may improve survival during lethal influenza epidemics. *Medical hypotheses* **2010**, *74*, 18-20, doi:10.1016/j.mehy.2009.04.052.
165. van den Berg, R.; Haenen, G.R.; van den Berg, H.; Bast, A. Transcription factor NF-kappaB as a potential biomarker for oxidative stress. *The British journal of nutrition* **2001**, *86 Suppl 1*, S121-127, doi:10.1079/bjn2001340
166. Heaton, B.E.; Kennedy, E.M.; Dumm, R.E.; Harding, A.T.; Sacco, M.T.; Sachs, D.; Heaton, N.S. A CRISPR Activation Screen Identifies a Pan-avian Influenza Virus Inhibitory Host Factor. *Cell reports* **2017**, *20*, 1503-1512, doi:10.1016/j.celrep.2017.07.060.
167. Saito, S.; Lin, Y.C.; Nakamura, Y.; Eckner, R.; Wuputra, K.; Kuo, K.K.; Lin, C.S.; Yokoyama, K.K. Potential application of cell reprogramming techniques for cancer research. *Cellular and molecular life sciences : CMLS* **2019**, *76*, 45-65, doi:10.1007/s00018-018-2924-7.
168. Saito, S.; Lin, Y.C.; Tsai, M.H.; Lin, C.S.; Murayama, Y.; Sato, R.; Yokoyama, K.K. Emerging roles of hypoxia-inducible factors and reactive oxygen species in cancer and pluripotent stem cells. *The Kaohsiung journal of medical sciences* **2015**, *31*, 279-286, doi:10.1016/j.kjms.2015.03.002.
169. Wu, H.; Song, W.; Gao, X.; Liu, N.; Wang, P.; Chen, H.; Cai, Z. Proteomics study of N-acetylcysteine response in H1N1-infected cells by using mass spectrometry. *Rapid communications in mass spectrometry : RCM* **2014**, *28*, 741-749, doi:10.1002/rcm.6840.
170. Sgarbanti, R.; Nencioni, L.; Amatore, D.; Coluccio, P.; Fraternale, A.; Sale, P.; Mammola, C.L.; Carpino, G.; Gaudio, E.; Magnani, M., et al. Redox regulation of the influenza hemagglutinin maturation process: a new cell-mediated strategy for anti-influenza therapy. *Antioxidants & redox signaling* **2011**, *15*, 593-606, doi:10.1089/ars.2010.3512.
171. Uchide, N.; Ohyama, K.; Bessho, T.; Yuan, B.; Yamakawa, T. Effect of antioxidants on apoptosis induced by influenza virus infection: inhibition of viral gene replication and transcription with pyrrolidine dithiocarbamate. *Antiviral research* **2002**, *56*, 207-217.
172. Uchide, N.; Ohyama, K.; Bessho, T.; Toyoda, H. Inhibition of influenza-virus-induced apoptosis in chorion cells of human fetal membranes by nordihydroguaiaretic Acid. *Intervirology* **2005**, *48*, 336-340, doi:10.1159/000085103.
173. Miyamoto, D.; Kusagaya, Y.; Endo, N.; Sometani, A.; Takeo, S.; Suzuki, T.; Arima, Y.; Nakajima, K.; Suzuki, Y. Thujaplicin-copper chelates inhibit replication of human influenza viruses. *Antiviral research* **1998**, *39*, 89-100.
174. Palamara, A.T.; Nencioni, L.; Aquilano, K.; De Chiara, G.; Hernandez, L.; Cozzolino, F.; Ciriolo, M.R.; Garaci, E. Inhibition of influenza A virus replication by resveratrol. *The Journal of infectious diseases* **2005**, *191*, 1719-1729, doi:10.1086/429694.
175. Huang, Y.L.; Loke, S.H.; Hsu, C.C.; Chiou, W.F. (+)-Vitisin A inhibits influenza A virus-induced RANTES production in A549 alveolar epithelial cells through interference with Akt and STAT1 phosphorylation. *Planta medica* **2008**, *74*, 156-162, doi:10.1055/s-2007-993786.
176. Yang, B.; Yao, D.F.; Ohuchi, M.; Ide, M.; Yano, M.; Okumura, Y.; Kido, H. Ambroxol suppresses influenza-virus proliferation in the mouse airway by increasing antiviral factor levels. *The European respiratory journal* **2002**, *19*, 952-958, doi:10.1183/09031936.02.00253302.
177. Wang, H.; Xu, R.; Shi, Y.; Si, L.; Jiao, P.; Fan, Z.; Han, X.; Wu, X.; Zhou, X.; Yu, F., et al. Design, synthesis and biological evaluation of novel L-ascorbic acid-conjugated pentacyclic triterpene derivatives as potential influenza virus entry inhibitors. *European journal of medicinal chemistry* **2016**, *110*, 376-388, doi:10.1016/j.ejmech.2016.01.005.
178. Kim, Y.; Kim, H.; Bae, S.; Choi, J.; Lim, S.Y.; Lee, N.; Kong, J.M.; Hwang, Y.I.; Kang, J.S.; Lee, W.J. Vitamin C Is an Essential Factor on the Anti-viral Immune Responses through the Production of Interferon-alpha/beta at the Initial Stage of Influenza A Virus (H3N2) Infection. *Immune network* **2013**, *13*, 70-74, doi:10.4110/in.2013.13.2.70.

179. Cai, Y.; Li, Y.F.; Tang, L.P.; Tsoi, B.; Chen, M.; Chen, H.; Chen, X.M.; Tan, R.R.; Kurihara, H.; He, R.R. A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice. *BioMed research international* **2015**, *2015*, 675149, doi:10.1155/2015/675149.
180. Sharma, R.A.; McLelland, H.R.; Hill, K.A.; Ireson, C.R.; Euden, S.A.; Manson, M.M.; Pirmohamed, M.; Marnett, L.J.; Gescher, A.J.; Steward, W.P. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* **2001**, *7*, 1894-1900.
181. Barzegar, A.; Moosavi-Movahedi, A.A. Intracellular ROS protection efficiency and free radical-scavenging activity of curcumin. *PloS one* **2011**, *6*, e26012, doi:10.1371/journal.pone.0026012.
182. Dai, J.; Gu, L.; Su, Y.; Wang, Q.; Zhao, Y.; Chen, X.; Deng, H.; Li, W.; Wang, G.; Li, K. Inhibition of curcumin on influenza A virus infection and influenzal pneumonIVia oxidative stress, TLR2/4, p38/JNK MAPK and NF-kappaB pathways. *International immunopharmacology* **2018**, *54*, 177-187, doi:10.1016/j.intimp.2017.11.009.
183. Dai, J.P.; Wang, Q.W.; Su, Y.; Gu, L.M.; Zhao, Y.; Chen, X.X.; Chen, C.; Li, W.Z.; Wang, G.F.; Li, K.S. Emodin Inhibition of Influenza A Virus Replication and Influenza Viral PneumonIVia the Nrf2, TLR4, p38/JNK and NF-kappaB Pathways. *Molecules (Basel, Switzerland)* **2017**, *22*, doi:10.3390/molecules22101754.
184. Dai, J.P.; Wang, Q.W.; Su, Y.; Gu, L.M.; Deng, H.X.; Chen, X.X.; Li, W.Z.; Li, K.S. Oxymatrine Inhibits Influenza A Virus Replication and Inflammation via TLR4, p38 MAPK and NF-kappaB Pathways. *International journal of molecular sciences* **2018**, *19*, doi:10.3390/ijms19040965.
185. Zhou, B.; Yang, Z.; Feng, Q.; Liang, X.; Li, J.; Zanin, M.; Jiang, Z.; Zhong, N. Aurantiamide acetate from baphicacanthus cusia root exhibits anti-inflammatory and anti-viral effects via inhibition of the NF-kappaB signaling pathway in Influenza A virus-infected cells. *Journal of ethnopharmacology* **2017**, *199*, 60-67, doi:10.1016/j.jep.2017.01.038.
186. Antanasijevic, A.; Cheng, H.; Wardrop, D.J.; Rong, L.; Caffrey, M. Inhibition of influenza H7 hemagglutinin-mediated entry. *PloS one* **2013**, *8*, e76363, doi:10.1371/journal.pone.0076363.
187. Antanasijevic, A.; Hafeman, N.J.; Tundup, S.; Kingsley, C.; Mishra, R.K.; Rong, L.; Manicassamy, B.; Wardrop, D.; Caffrey, M. Stabilization and Improvement of a Promising Influenza Antiviral: Making a PAIN PAINless. *ACS infectious diseases* **2016**, *2*, 608-615, doi:10.1021/acsinfecdis.6b00046.
188. Nagai, T.; Miyaichi, Y.; Tomimori, T.; Yamada, H. Inhibition of mouse liver sialidase by plant flavonoids. *Biochemical and biophysical research communications* **1989**, *163*, 25-31, doi:10.1016/0006-291x(89)92093-7.
189. Nagai, T.; Miyaichi, Y.; Tomimori, T.; Suzuki, Y.; Yamada, H. Inhibition of influenza virus sialidase and anti-influenza virus activity by plant flavonoids. *Chemical & pharmaceutical bulletin* **1990**, *38*, 1329-1332, doi:10.1248/cpb.38.1329.
190. Nagai, T.; Miyaichi, Y.; Tomimori, T.; Suzuki, Y.; Yamada, H. In vivo anti-influenza virus activity of plant flavonoids possessing inhibitory activity for influenza virus sialidase. *Antiviral research* **1992**, *19*, 207-217.
191. Nagai, T.; Suzuki, Y.; Tomimori, T.; Yamada, H. Antiviral activity of plant flavonoid, 5,7,4'-trihydroxy-8-methoxyflavone, from the roots of Scutellaria baicalensis against influenza A (H3N2) and B viruses. *Biological & pharmaceutical bulletin* **1995**, *18*, 295-299, doi:10.1248/bpb.18.295.
192. Nagai, T.; Moriguchi, R.; Suzuki, Y.; Tomimori, T.; Yamada, H. Mode of action of the anti-influenza virus activity of plant flavonoid, 5,7,4'-trihydroxy-8-methoxyflavone, from the roots of Scutellaria baicalensis. *Antiviral research* **1995**, *26*, 11-25.
193. Kuzuhara, T.; Iwai, Y.; Takahashi, H.; Hatakeyama, D.; Echigo, N. Green tea catechins inhibit the endonuclease activity of influenza A virus RNA polymerase. *PLoS currents* **2009**, *1*, Rrn1052.
194. Choi, H.J.; Song, J.H.; Park, K.S.; Kwon, D.H. Inhibitory effects of quercetin 3-rhamnoside on influenza A virus replication. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences* **2009**, *37*, 329-333, doi:10.1016/j.ejps.2009.03.002.
195. Kim, Y.; Narayanan, S.; Chang, K.O. Inhibition of influenza virus replication by plant-derived isoquercetin. *Antiviral research* **2010**, *88*, 227-235, doi:10.1016/j.antiviral.2010.08.016.
196. Gangehei, L.; Ali, M.; Zhang, W.; Chen, Z.; Wakame, K.; Haidari, M. Oligonol a low molecular weight polyphenol of lychee fruit extract inhibits proliferation of influenza virus by blocking reactive oxygen species-

dependent ERK phosphorylation. *Phytomedicine : international journal of phytotherapy and phytopharmacology* **2010**, *17*, 1047-1056, doi:10.1016/j.phymed.2010.03.016.

197. Kim, D.H.; Park, G.S.; Nile, A.S.; Kwon, Y.D.; Enkhtaivan, G.; Nile, S.H. Utilization of Dianthus superbus L and its bioactive compounds for antioxidant, anti-influenza and toxicological effects. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* **2019**, *125*, 313-321, doi:10.1016/j.fct.2019.01.013.
198. Formica, J.V.; Regelson, W. Review of the biology of Quercetin and related bioflavonoids. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* **1995**, *33*, 1061-1080, doi:10.1016/0278-6915(95)00077-1.
199. Zhao, Y.; Wang, J.; Ballevre, O.; Luo, H.; Zhang, W. Antihypertensive effects and mechanisms of chlorogenic acids. *Hypertension research : official journal of the Japanese Society of Hypertension* **2012**, *35*, 370-374, doi:10.1038/hr.2011.195.
200. Shen, W.; Qi, R.; Zhang, J.; Wang, Z.; Wang, H.; Hu, C.; Zhao, Y.; Bie, M.; Wang, Y.; Fu, Y., et al. Chlorogenic acid inhibits LPS-induced microglial activation and improves survival of dopaminergic neurons. *Brain research bulletin* **2012**, *88*, 487-494, doi:10.1016/j.brainresbull.2012.04.010.
201. Pica, N.; Palese, P. Toward a universal influenza virus vaccine: prospects and challenges. *Annual review of medicine* **2013**, *64*, 189-202, doi:10.1146/annurev-med-120611-145115.
202. Nabar, G.M.; Mahajan, K.D.; Calhoun, M.A.; Duong, A.D.; Souva, M.S.; Xu, J.; Czeisler, C.; Puduvalli, V.K.; Otero, J.J.; Wyslouzil, B.E., et al. Micelle-templated, poly(lactic-co-glycolic acid) nanoparticles for hydrophobic drug delivery. *International journal of nanomedicine* **2018**, *13*, 351-366, doi:10.2147/ijn.S142079.
203. Lin, Z.; Li, Y.; Gong, G.; Xia, Y.; Wang, C.; Chen, Y.; Hua, L.; Zhong, J.; Tang, Y.; Liu, X., et al. Restriction of H1N1 influenza virus infection by selenium nanoparticles loaded with ribavirin via resisting caspase-3 apoptotic pathway. *International journal of nanomedicine* **2018**, *13*, 5787-5797, doi:10.2147/ijn.S177658.
204. Kode, S.S.; Pawar, S.D.; Tare, D.S.; Keng, S.S.; Hurt, A.C.; Mullick, J. A novel I117T substitution in neuraminidase of highly pathogenic avian influenza H5N1 virus conferring reduced susceptibility to oseltamivir and zanamivir. *Veterinary microbiology* **2019**, *235*, 21-24, doi:10.1016/j.vetmic.2019.06.005.
205. Chen, T.Y.; Chen, D.Y.; Wen, H.W.; Ou, J.L.; Chiou, S.S.; Chen, J.M.; Wong, M.L.; Hsu, W.L. Inhibition of enveloped viruses infectivity by curcumin. *PLoS One* **2013**, 8, e62482. doi: 10.1371/journal.pone.0062482.
206. Ye, S.; Lowther, S.; Stambas J. Inhibition of reactive oxygen species production ameliorates inflammation induced by influenza A viruses via upregulation of SOCS1 and SOCS3. *J Virol*. **2015** 89, 2672-2683. doi: 10.1128/JVI.03529-14.
207. Mehrbod, P.; Abdalla, M. A.; Fotouchi, F.; Aro, A.O.; Eloff, J. N.; McGaw, L. J., Fasina, F.O. Immunomodulatory properties of quercetin-3-O-α-L-rhamnopyranoside from *Rapanea melanophloeos* against influenza a virus. *BMC Complement Altern Med*. **2018**, 8, 184. doi: 10.1186/s12906-018-2246-1.
208. Episcopio, D.; Aminov, S.; Benjamin, S.; Germain, G.; Datan, E.; Landazuri, J.; Lockshin, R.A.; Zakeri, Z. Atorvastatin restricts the ability of influenza virus to generate lipid droplets and severely suppresses the replication of the virus. *FASEB J*. **2019** 33, 9516-9525. doi: 10.1096/fj.201900428RR.
209. To, E.E.; Luong, R.; Diao, J.; O' Leary, J.J.; Brooks, D.A.; Vlahos, R.; Selemidis, S. Novel endosomal NOX2 oxidase inhibitor ameliorates pandemic influenza A virus-induced lung inflammation in mice. *Respirology*. **2019**, 24, 1011-1017. doi: 10.1111/resp.13524.
210. Kim, H.O.; Yeom, M.; Kim, J.; Kukreja, A.; Na, W.; Choi, J.; Kang, A.; Yun, D.; Lim, J.W.; Song, D.; Haam, S. Reactive Oxygen Species-Regulating Polymersome as an Antiviral Agent against Influenza Virus. *Small*. **2017** 13, doi: 10.1002/smll.201700818.
211. Takahashi, E.; Indalao, I.L.; Sawabuchi, T.; Mizuno, K.; Sakai, S.; Kimoto, T.; Kim, H.; Kido H. Clarithromycin suppresses induction of monocyte chemoattractant protein-1 and matrix metalloproteinase-9 and improves pathological changes in the lungs and heart of mice infected with influenza A virus. *Comp Immunol Microbiol Infect Dis*. **2018**, 56: 6-13. doi: 10.1016/j.cimid.2017.11.002.
212. Tomozawa, T.; Hoshino, K.; Yamashita, M.; Kubo, S. Efficacy of laninamivir octanoate in mice with advanced inflammation stage caused by infection of highly lethal influenza virus. *J Infect Chemother*. **2019**, 25, 584-588.

doi: 10.1016/j.jiac.2019.02.023.

213. Zhang, J.; Hu, Y.; Hau, R.; Musharrafieh, R.; Ma, C.; Zhou, X.; Chen, Y.; Wang, J. Identification of NMS-873, an allosteric and specific p97 inhibitor, as a broad antiviral against both influenza A and B viruses. *Eur J Pharm Sci.* **2019**, 133, 86-94. doi: 10.1016/j.ejps.2019.03.020.
214. O'Hanlon, R.; Shaw, M.L. Baloxavir marboxil: the new influenza drug on the market. *Curr Opin Virol*. **2019**, 35, 14-18. doi: 10.1016/j.coviro.2019.01.006.
215. Alves Galvão, M.G.; Rocha Crispino Santos, M.A.; Alves da Cunha, A,J. Amantadine and rimantadine for influenza A in children and the elderly. *Cochrane Database Syst Rev.* **2014**, 11, CD002745. doi: 10.1002/14651858.CD002745.
216. Scott, L.J. Peramivir: A Review in Uncomplicated Influenza. *Drugs.* **2018**, 78,1363-1370. doi: 10.1007/s40265-018-0981-8.
217. Liu, T.; Liu, M.; Chen, F.; Chen, F.; Tian, Y.; Huang, Q.; Liu, S.; Yang, J. A Small-Molecule Compound Has Anti-influenza A Virus Activity by Acting as a "PB2 Inhibitor".*Mol Pharm.* **2018**, 5, 4110-4120. doi: 10.1021/acs.molpharmaceut.8b00531.
218. Jang, Y.; Shin, J.S.; Yoon, Y.S.; Go, Y.Y.; Lee, H.W.; Kwon, O.S.; Park, S.; Park, M.S.; Kim M. Salinomycin Inhibits Influenza Virus Infection by Disrupting Endosomal Acidification and Viral Matrix Protein 2 Function. *J Virol.* **2018**, 92(24). pii: e01441-18. doi: 10.1128/JVI.01441-18.
219. Hu, Y.; Hau, R.K.; Wang, Y.; Tuohy, P.; Zhang, Y.; Xu, S.; Ma, C.; Wang, J. Structure-Property Relationship Studies of Influenza A Virus AM2-S31N Proton Channel Blockers. *ACS Med Chem Lett.* **2018** 9, 1111-1116. doi: 10.1021/acsmedchemlett.8b00336.
220. Li, Y.; Lin, Z.; Guo, M.; Zhao, M.; Xia, Y.; Wang, C.; Xu, T.; Zhu, B. Inhibition of H1N1 influenza virus-induced apoptosis by functionalized selenium nanoparticles with amantadine through ROS-mediated AKT signaling pathways. *Int J Nanomedicine.* **2018**, 13, 2005-2016. doi: 10.2147/IJN.S155994.
221. Goldhill, D.H.; Te Velthuis, A.J.W.; Fletcher, R.A.; Langat, P.; Zambon, M.; Lackenby, A.; Barclay, W.S. The mechanism of resistance to favipiravir in influenza. *Proc Natl Acad Sci U S A.* **2018**, 115, 11613-11618. doi: 10.1073/pnas.1811345115.
222. Lee, A.C.Y.; To, K.K.W.; Zhang, A.J.X.; Zhu, H.; Li, C.; Zhang, R.R.; Hung, I.F.N.; Kao, R.Y.T.; Chan, K.H.; Yuen, K.Y. Triple combination of FDA-approved drugs including flufenamic acid, clarithromycin and zanamivir improves survival of severe influenza in mice. *Arch Virol*. **2018**, 163, 2349-2358. doi:10.1007/s00705-018-3852-4.