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Metabolic host response and therapeutic approaches to influenza infection

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Abstract

Based on available metabolomic studies, influenza infection affects a variety of cellular metabolic pathways to ensure an optimal environment for its replication and production of viral particles. Following infection, glucose uptake and aerobic glycolysis increase in infected cells continually, which results in higher glucose consumption. The pentose phosphate shunt, as another glucose-consuming pathway, is enhanced by influenza infection to help produce more nucleotides, especially ATP. Regarding lipid species, following infection, levels of triglycerides, phospholipids, and several lipid derivatives undergo perturbations, some of which are associated with inflammatory responses. Also, mitochondrial fatty acid β-oxidation decreases significantly simultaneously with an increase in biosynthesis of fatty acids and membrane lipids. Moreover, essential amino acids are demonstrated to decline in infected tissues due to the production of large amounts of viral and cellular proteins. Immune responses against influenza infection, on the other hand, could significantly affect metabolic pathways. Mainly, interferon (IFN) production following viral infection affects cell function via alteration in amino acid synthesis, membrane composition, and lipid metabolism. Understanding metabolic alterations required for influenza virus replication has revealed novel therapeutic methods based on targeted inhibition of these cellular metabolic pathways.

Keywords: Influenza, Glycolysis, Fatty acid synthesis, Metabolism, Indoleamine-2,3-dioxygenase

Background

Influenza virus infection (IVI) is one of the most common infectious agents, capable of infecting a variety of avian and mammalian species. The virus is responsible for seasonal epidemics, leading to 3–5 million severe infections and 250,000–500,000 deaths annually [1, 2]. Despite the annual vaccination program, the high mortality rate caused by influenza infection and its various complications, including chronic lung disease, cardiac disease, asthma, and metabolic disorders, is yet to be adequately addressed [3–5].

In 1956, Eagle et al. first indicated that the addition of glucose to HeLa cell medium could promote the generation of poliovirus progeny [6]. Results of a published study showed that the replication of the influenza virus depends on host cellular metabolism

such that metabolites including nucleic acids, proteins, glycoproteins, and lipids are crucially required for the life cycle of the influenza virus [7]. Recent research on a mouse model showed that influenza infection could affect more than 100 metabolite markers in serum, lung, and bronchoalveolar lavage fluid [8]. Acquiring the required materials from the host cell to self-replicate, the virus can disrupt biochemical processes such as glycolysis, fatty acid (FA) synthesis, and glutamine pathways [9]. It is of particular importance for scientists to broaden their horizon on the metabolic changes during influenza infection, which in turn paves the way for preventing life-threatening consequences.

Influenza infection actively provokes the pro-oxidant condition in the host cell to facilitate viral proliferation and pathogenesis. Increased expression of influenza M2 protein can activate protein kinase C and increase reactive oxygen species (ROS) production [10]. On the other hand, PB1-F2 decreases superoxide anion dismutase 1 (SOD1) expression and consequently disrupts the ROS scavenging process [11]. In people with influenza infection, increased levels of DNA, lipid, and protein oxidation products are found in plasma and urine [12–14]. Also, increased levels of ROS and inducible nitric oxide synthase (iNOS) have been observed as markers of oxidative stress in the lungs of people who died due to pandemic influenza infection [15]. ROS-producing enzymes induced by influenza infection mainly include NADPH oxidase (Nox) and xanthine oxidase, upregulation of which causes the impaired defensive function of antioxidants [16]. An increase in ROS production, along with impaired antioxidant function, ultimately leads to a profound change in redox homeostasis of the cell [16–19]. Nox2 is a phagocytic enzyme that is involved in the production of ROS induced by influenza virus [19–22], and impaired Nox2 expression results in a lack of increased RNS and ROS production following influenza infection [20]. Xanthine oxidase is also an ROS-producing enzyme that is induced by influenza infection [23, 24], and its inhibition can hinder ROS increase in the cell.

On the other hand, increased expression of SOD1 reduces influenza virus titers within the cell [25]. It is also reported that influenza infection significantly increases ROS production by inducing Nox4, and the proliferation of this virus in lung epithelial cells is dependent on redox-sensitive pathways activated by Nox4-derived ROS [16]. Glutathione (GSH) is a vital antioxidant in the cell, and its cellular content is inversely related to influenza virus replication in the cell [26, 27]. It is indicated that higher levels of GSH, antioxidant enzymes such as glutathione peroxidase, and the anti-apoptotic protein Bcl-2 in the lungs of female mice result in superior resistance of these mice to influenza infection. In contrast, male mice are more susceptible to this infection due to higher expression of Nox4. This difference is due primarily to the higher ability of female mice to maintain cellular redox homeostasis [28]. Amatore et al. also showed that an increase in GSH content in organs by affecting GSH-dependent antiviral pathways strengthens the immune system, in particular Th1 cell response, and decreases viral replication [29]. However, GSH depletion results in a deviation of the response towards Th2 cells [30].

Furthermore, oxidative stress following infection can induce the transcription factor NF-kB, which subsequently leads to increased levels of inflammatory cytokines, including interleukin (IL)-1β, IL-6, IFN, and TNF [31, 32]. IFNs are one of these cytokines that trigger and affect T cell metabolism via mediating glucose uptake, glycolysis, and lipid synthesis. IFN can also exert its function on metabolic changes by producing several mediators including indoleamine-2,3-dioxygenase (IDO) and nitric oxide (NO), both of which

appear to have either an inducible or an inhibitory role in viral replication [33]. Since tryptophan is critical for T cell proliferation, depletion of this amino acid by IDO suppresses the immune system through the stimulation of T regulatory cells. NO, on the other hand, inhibits viral replication via changes in the structure of viral proteins [34]. In this review, we first discuss the metabolic abnormalities during influenza infection and then shed light on the role of immunometabolites that regulate cellular metabolism. The following sections summarize recent evidence about the novel therapeutic approaches that target metabolic pathways in influenza infection.

Metabolic perturbations in influenza infection

Viruses take advantage of various cellular mechanisms to replicate efficiently. Vital metabolic pathways of host cells are one of the most widely used mechanisms targeted by viruses, resulting in considerable changes. In this context, studies have revealed that various human viruses, such as cytomegalovirus [35–37], rubella [38, 39], dengue [40], mumps [41], poliovirus [42, 43] and reovirus [44] can strongly affect host cell glycolysis, lipid metabolism, and glutaminolysis. Furthermore, a review by Sanchez and Lagunoff delineated the activation of these metabolic processes by several viruses [45]. As will be discussed in this section, influenza as a highly pathogenic human virus interferes tremendously with the host metabolic cycles and thereby forces them to produce viral particles more efficiently.

Glucose metabolism

The metabolism and concentration of glucose in the cell play a cardinal role in the homeostasis of cellular metabolic procedures [46]. Shortly after the onset of IVI, the rate of glucose uptake by infected cells increases continually, and the subsequently enhanced glycolysis results in higher glucose consumption, production of viral particles [47, 48], and extracellular concentration of lactate. The relationship between glycolysis and IVI has shown that influenza infection at a higher multiplicity of infection (MOI) raises the glycolytic activity of the cells [49]. In a study by Kohio and Adamson, a dose-specific increase in influenza infection was associated with higher glucose levels, whereas the treatment of cells with glycolysis inhibitors remarkably suppressed the viral replication. However, the viral infection could be retriggered by adding ATP to the cell environment. This study revealed that enhancing vacuolar-type ATPase (a proton pump essential for influenza uncoating) via increasing glucose metabolism and, as a result, higher available ATP resources, augments the virus infection [50]. The observations, as mentioned above, reveal a significant increase in ATP and glucose consumption within cells following influenza infection and also highlight the dependence of the influenza virus on the glycolysis pathway for energy production. The viral replication has the highest use of ATP during influenza infection, releasing large quantities of energy in the form of heat. This process can increase the temperature of infected cells by 4–5 °C. As viral proliferation increases, the cellular ATP level drops sharply, resulting in reduced potential and stability of the mitochondrial membrane [51]. Based on available results, patients with metabolic disorders can develop more severe influenza infection compared to healthy hosts. There have been several studies showing that diabetes can increase the risk of influenza infection, the severity of the disease, and the fatal consequences of this infection [52–55]. About 90% of patients with type 2 diabetes are overweight, and

obesity is a significant risk factor for severe influenza infection [56]. This reinforcing effect of diabetes on influenza may be due to the inhibitory effect of hyperglycemia on the immune system [57–59]. It has been shown that this hyperglycemia-associated immunosuppression and susceptibility to influenza infection can be alleviated by insulin administration and diabetes control [60]. On the other hand, the pentose phosphate pathway (PPP), as another glucose-consuming pathway reported to be enhanced by IVI [61], contributes to a higher yield of nucleotides and ATP for viral replication [62]. Significant up-regulation of the PPP key enzymes in influenza-infected cells, including glucose 6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD), was reported by Janke et al. [63]. G6PD enzyme is also responsible for the generation of NADPH [64], a critical component of fatty acid biosynthesis. The level of G6PD activity specifies the ability of the cell to clear the accumulated ROS. Cells with an average G6PD level can retain the appropriate GSH/GSSG ratio and keep the ROS production at a tolerably low level, indicating that G6PD activity has an inverse correlation with cellular ROS level [65]. Disruption of redox balance has been shown to contribute to replication and virulence of several viruses [66–68], and G6PD deficiency can cause this disruption. Despite the results reported by Janke et al., G6PD activity seems to have an inverse relation with some other respiratory viral infections. For example, in an in vitro study, after infection with human coronavirus (HCoV) 229E, the production of viral particles in G6PD-deficient or G6PD-knockdown cells was higher than in healthy cells, and this was correlated with increased oxidant production [67].

Molecular mechanisms through which the virus can control the metabolic pathways have been thoroughly identified. Smallwood et al. have shown that an increase in glucose uptake, glycolysis, and glutaminolysis following influenza infection may be related to the loss of PI3K/AKT/mTOR pathway homeostasis and subsequent increase in c-Myc expression in the infected cells [9]. Regarding the available results, the mechanistic target of rapamycin complex 1 (mTORC1) and mTORC2 signaling can be activated by a variety of influenza virus proteins. The viral hemagglutinin (HA) protein, along with virus replication, can upregulate PDPK1-mediated phosphorylation and activate AKT, which is required for induction of the mTORC1 signaling pathway by the influenza virus. On the other hand, influenza M2 protein is capable of down-regulation of the mTORC1 inhibitor REDD1, thereby enhancing the mTORC1 activation [69]. mTORC1 signaling, in turn, promotes c-Myc expression at the translational level [70]. Additionally, the NS1 protein can effectively promote the activity of mTORC2, which, in turn, upregulates c-Myc through FoxO inhibition [71]. Moreover, AKT-dependent inactivation of FoxOs can increase glycolysis [72, 73] by removing the suppressive force of c-Myc [74–76]. Myc enhances glycolysis by upregulating expression of the glucose transporter GLUT1, glycolytic genes, and lactate dehydrogenase (LDH), as the converter of pyruvate to lactate [77, 78]. mTORC1 also mediates upregulation of hypoxia-inducible factor-1α (HIF-1α), a factor that increases the expression of various genes [79], including several glycolytic enzymes, glucose transporters, and LDH [80–82]. AKT is able to promote the expression and membrane localization of GLUT1 as well as the function of phosphofructokinase [83, 84]. Furthermore, AKT is demonstrated to activate SREBP in an mTORC1-dependent manner [85] and to upregulate SREBP by enhancing the stability of its processed form [86]. SREBP1 is shown to be required for the mTORC1-induced increase in the expression of G6PD, which is the rate-limiting enzyme of the PPP oxidative branch [79].

In addition to the above-mentioned metabolic pathways, the influenza virus exhibits disruptive effects on some other metabolic processes, which gives rise to metabolic disorders and ATP crisis. Previous studies have found that the influenza infection increases the cellular synthesis of fatty acids [87], with some of their derivatives, including eicosanoids [88], and these molecules are natural endogenous ligands and stimulators of peroxisome proliferation-activated receptors (PPARs) [88–90]. PPARs are a group of nuclear receptor proteins that act as transcription factors and regulate the expression of different genes [91] involved in cellular differentiation and metabolism of carbohydrates, lipids, and proteins [92]. Furthermore, all types of PPARs discovered so far are able to suppress the activity of the pyruvate dehydrogenase (PDH) enzyme (known as a catalyzer of the oxidative decarboxylation of pyruvate leading to acetyl-CoA production) in various organs through the upregulation of pyruvate dehydrogenase kinase (PDK)-4 [93]. In this respect, extremely low PDH enzyme activity has been found after influenza infection in vitro. Enhanced PDK4-mediated inhibition of PDH has been found in the lung tissue of influenza-infected mice. This enzyme inhibition contributes to an erroneous process, which causes significant disruption of glucose oxidation, cellular respiration, and lipid metabolism (Fig. 1) [7, 94].

Lipid metabolism

Following infection, levels of phospholipids and several lipid derivatives undergo perturbations. Several lines of evidence have shown that in obese mice due to abnormalities in the

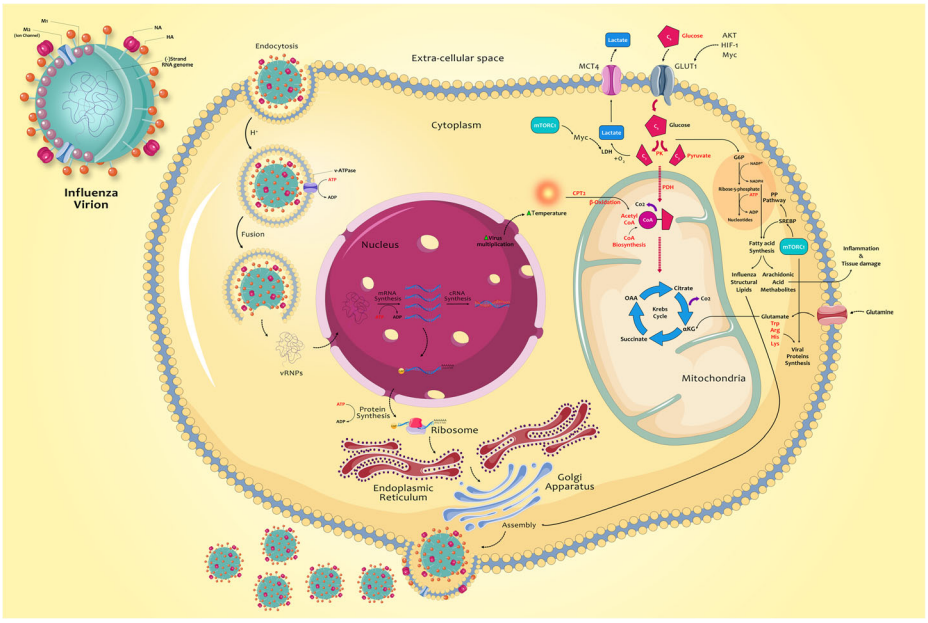

Fig. 1 Metabolic changes caused by influenza infection and related mechanisms. Several anabolic and catabolic processes can be affected: higher glucose uptake and metabolism in glycolysis and pentose phosphate pathways, higher nucleotide catabolism, increase in biosynthesis of fatty acids including arachidonic acid, the precursor of proinflammatory lipids, and also enhanced glutaminolysis and protein synthesis. Activation of mTORC1&2 signaling and downstream factors by influenza infection may have an essential role in the upregulation of these metabolic processes. In addition, high ATP consumption and reduced β-oxidation, as well as glucose oxidation by influenza infection, contribute to the ATP crisis and hence influenza-related multi-organ failure

metabolism of fatty acids and phospholipids, induction of influenza infection produces a more severe inflammatory response in comparison with non-obese mice [95]. These findings indicate a direct link between influenza-mediated inflammation and the abundance of lipids and their metabolism in the body. According to a study, diacyl glycerophosphocholine (PC) and diacyl glycerophosphoethanolamine (PE) species (containing 20:4 or 22:6 as precursors of docosahexaenoic acid (DHA) and arachidonic acid (AA) respectively) are associated with influenza-related diseases. Interestingly, glycerophospholipid species (PC (18:1/20:4) and PC (16:0/22:6)) yields increase during the influenza infection. In addition, upsurge in PC (18:1/20:4) and PE (18:0/22:4) species is associated with tissue lesions in the lungs and trachea. Several phospholipids containing 20:4, especially PC (18:1/20:4), serve as AA reservoirs in cells, breakdown of which increases the cellular levels of AA [96]. This influenza-mediated elevation of AA, consistent with inflammation, has also been reported in the same study [97]. The accumulation of the above-mentioned proinflammatory lipids in the cell leads to the promoted synthesis of eicosanoids and inflammatory mediators, thus exacerbating post-infection necrosis, inflammation, and tissue damage in the lungs [96]. In a prospective cohort study on influenza-infected subjects, lipid inflammatory mediators in serum samples of patients were mainly AA-derived oxylipins, including TXB2, 15-deoxy-12,14-PGD2, 20-HETE, 5,6-DHET, 5-oxoETE, LTE4, and 12-HpETE. Although all of these metabolites were shown to be elevated shortly after the infection, 5,6-DHET and 5-oxoETE levels remained considerably high up to 4 weeks post-infection, indicating a constant pulmonary inflammation [98].

The pulmonary surfactant system, which is involved in suppressing influenza infection in the respiratory tracts [99], can be disrupted due to significant influenza-induced changes in the abundance of different types of PC and PE species as the major components of surfactants [96, 100]. Tanner et al. proposed a principal correlation between influenza replication and choline lipids metabolism. They found an IVI-mediated reduction in ester-linked PC species as well as an increased level of sphingomyelin (SM) [101], probably connected with expending cellular choline stores for SM synthesis. This led to an increase in SM species within the infected cell. SM and short-chain fatty acid-containing ether-linked PC (ePC) species were found in higher amounts in both infected cells and virions and therefore appeared to be involved in viral morphogenesis. On the other hand, long-chain fatty acid-containing ePC was increased in infected cells while having low levels in the structure of the virion, highlighting the role of this phospholipid in replication of the virus [101].

Evidently, higher production of these complex lipids in the cell will require increased biosynthesis of fatty acids. In this regard, the results of a study revealed that influenza infection could induce fatty acid biosynthesis and cholesterol metabolism in human lung basal epithelial tumor cells [87]. Since SREBPs are thoroughly identified as stimulators of expression of many genes involved in lipid and sterol biosynthesis, including fatty acid synthase [102–104], their upregulation by the influenza virus (through induction of mTORC1 signaling, as discussed earlier) may logically explain the increased rate of lipogenesis [105]. A coincidence between increased fatty acid synthesis and a decline in fatty acid β-oxidation has been found during influenza infection, which is attributed to a variety of mechanisms directly or indirectly related to viral replication. For instance, the sharp increase of proinflammatory cytokines during influenza infection [106] causes decreased hepatic fatty acid β-oxidation both in vitro and in vivo [107, 108], most likely through excessive nitric oxide and other related free radicals [109]. In

addition, increased temperature of cells during infection (which could be the result of virus replication and fever) causes heat stress which in turn can considerably downregulate carnitine palmitoyltransferase II (CPT II) activity and reduce the β-oxidation and ATP levels in fibroblasts of influenza-associated encephalopathy patients and healthy volunteers [110]. A study on influenza-infected mice demonstrated a significant depression in long hepatic chain fatty acid β-oxidation at both the mRNA and protein level, as several β-oxidation essential enzymes were reduced by > 50% [97]. A significant decrease in mitochondrial fatty acid β-oxidation simultaneously with increased biosynthesis of fatty acids and membrane lipids may reflect the fact that the virus stores structural lipids to produce more infectious particles. In addition to impaired metabolism in mitochondria, influenza infection induces severe peroxisomal lipid metabolism disorders, which can be inferred from abnormal levels of several specific long-chain fatty acids [101] (Fig. 1).

Other metabolites

The aforementioned metabolic processes are not the only pathways affected by influenza virus infection. This virus has the ability to induce higher consumption rates of glutamine during glutaminolysis, which can be attributed to transient c-Myc overexpression [9]. Myc acts to regulate glutamine uptake and its utilization in the cell [111]. It has been demonstrated that catalytic activity of glutaminase, as the key enzyme in glutaminolysis, greatly increases following the infection [63]. Moreover, essential amino acids, especially tryptophan, are other materials whose quantities have been shown to decline in infected tissues [112]. mTORC1 can up-regulate protein synthesis through several downstream factors [113]. Thus, induction of mTORC1 signaling by the influenza virus leads to higher usage of essential amino acid storages for concurrent production of large amounts of viral and cellular proteins. Infection of influenza virus can also alter the cellular level and metabolism of purines and pyrimidines [8, 98, 100], and is associated with both increased activities of nucleotide catabolism core enzymes including adenosine deaminase (ADA) and xanthine oxidase (XO) and elevated levels of inosine, hypoxanthine, xanthine, and uric acid in serum and bronchoalveolar lavage fluid. Enhanced catabolic degradation of nucleotides and their metabolites can facilitate the production of superoxide and contribute to the pathogenesis of influenza infection [23].

Immunometabolites and their role in influenza infection

Interferons are well-known cytokines with a powerful capability of altering the cellular functions following viral infections. These alterations affect protein synthesis, composition of the membrane, cellular proliferation, and nutritional status [34]. Interferon stimulated genes (ISGs) are the effector components whose transcription could be induced by type I IFNs and IFNγ [114, 115].

IFNs and energy metabolism

Studies have recently underscored the general effect of IFNs on the energy metabolism of cells, mostly by promoting glycolysis. For instance, IFNβ has been shown to induce the glucose uptake of embryonic fibroblasts in a PI3/AKT-dependent manner, thereby

increasing ATP production [116]. It has also been demonstrated that type I IFN can stimulate oxygen consumption in a range of cells, including conventional dendritic cells (DCs), keratinocytes, and memory T cells [117]. Indeed, the high yield of ATP and mitochondrial fitness guarantee the host cell's need for energy in plasmacytoid DCs (pDCs) and non-hematopoietic cells following challenges with viral pathogens [118]. These studies emphasized the mediatory effect of type I IFN on glycolysis induction via IFNAR1, Tyk2, and STAT1. It has also been shown that influenza infection stimulates pDCs to enhance their glycolysis and develop a Warburg-like remodeling of energy metabolism. This enhanced glycolysis leads to higher IFN production and, consequently, more potent antiviral activity [118]. IFNγ induces metabolic reprogramming of M1 macrophages as a rapid increase in aerobic glycolysis, followed by a reduction in oxidative phosphorylation. This metabolic reprogramming maintains cell viability and the inflammatory response while reducing dependence on mitochondrial oxidative metabolism. Excessive production of pro-inflammatory cytokines and chemokines in human monocytes/macrophages can be blocked by inhibition of aerobic glycolysis [119]. Also, activation of macrophages by IFNγ induces expression of the ATP-citrate lyase enzyme (ACLY), and blockage of ACLY activity reduces the production of ROS and nitric oxide [120].

There is a strong consensus that influenza replication is crucially dependent on fatty acids [97], which makes it a fascinating target for therapeutic modalities [45]. Thus, the ability of IFN to channel the FAs from biosynthesis to catabolism via fatty acid oxidation (FAO) is currently known as a promising antiviral strategy in pDCs [117], which requires further research for more elucidation. Several lines of current evidence have revealed the antiviral activity of type I IFN to be exerted through hampering glucose-derived cholesterol and fatty acid synthesis [121, 122]. Sterol regulatory binding protein 2 (SREBP2), along with SREBP1, is known as the leading transcription factor which orchestrates the biosynthesis pathway of sterol, whose inhibited transcription and expression can be strongly mediated by IFNs via IFNAR1 [123] (Fig. 2).

Innate immune cells can recognize influenza A viruses and their infected cells by toll-like receptors (TLRs) [124]. This recognition can lead to the induction of an inflammatory response that, in turn, controls the replication and spread of the virus [31]. H5N1, H7N7, and H7N9 were correlated with increased transcription of the cytokine response in mice. Severe infection with H7N9, H7N7, H5N1, or 1918 virus can lead to upregulation of inflammatory cytokine genes along with downregulation of lipid metabolism and coagulation genes [125]. This uncontrolled proinflammatory response accompanied by an inadequate anti-inflammatory response is referred to as the cytokine storm [31]. Monocytes/macrophages, neutrophils, and lung epithelial cells have useful roles in the cytokine storm developed by influenza infection [126]. Severe cytokine storm, with greater levels of interferons and tumor necrosis factors, has been recognized in patients hospitalized due to influenza infection [127]. Such influenza-induced cytokine storms, together with viral virulence, can develop severe lung injury in patients [128, 129]. It is believed that the level of the cytokine storm is directly associated with the severity of the disease caused by influenza infection [130, 131]. Some specific polymorphisms in immune system genes have determinative roles in the outcome of influenza infection. Our previous studies have shown a relationship between cytokine gene polymorphisms and severity of the influenza disease. Several cytokines were evaluated after influenza A/H3N2 virus infection, among which IL-17 rs2275913 GG and AG,

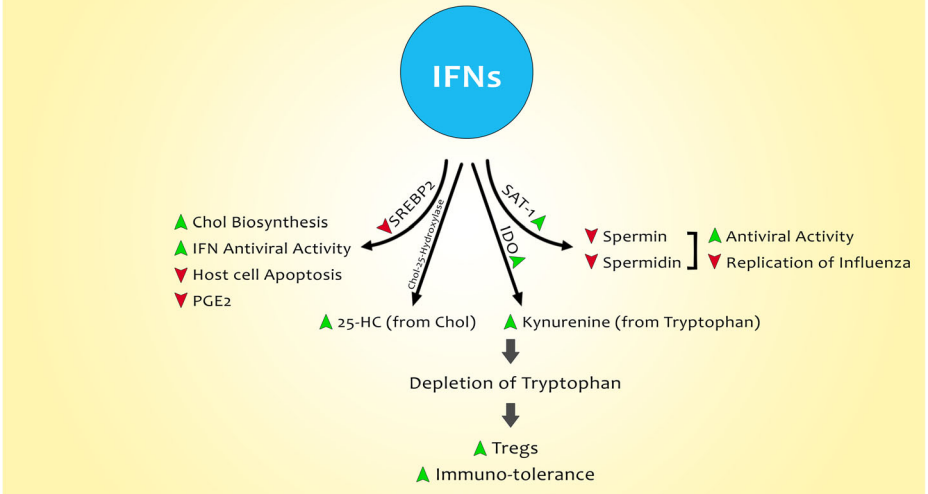

Fig. 2 Role of IFNs in host cell metabolic changes following infection with influenza. IFNs affect the lipid metabolism through downregulation of SREBP-2, leading to higher cholesterol biosynthesis, and suppressed host cell apoptosis and PGE-2 production. They can also enhance the level of 25-HC arisen from cholesterol (via activation of Chol-25 hydroxylase) and IDO. SAT-1 can be upregulated by IFNs, lowering the levels of spermidine and spermine and thereby dampening influenza replication

GG and GT of IL-10 (rs1800872) and IL-28 (rs8099917) genotype TT polymorphisms were associated with increased risk of influenza infection.

In contrast, IL-1β (rs16944) (GG) and IL-28 (rs8099917) GG and TG genotypes were associated with reduced risk of infection [132]. In another study, an association between IL-1β rs16944 and IL-17 rs2275913 genotypes and severe influenza disease was found while IL-10 rs1800872 and IL-28 rs8099917 polymorphisms were not associated with influenza disease. Also, lacking an A allele in IL-17 rs2275913 could increase the risk of influenza A (H1N1) infection [2]. Such polymorphisms in immune system genes may be associated with some metabolic changes and, in turn, may reinforce the metabolic disorders following influenza infection. However, additional studies are needed in this field to confirm or reject this opinion.

IFNs and amino acid metabolism and the role of IDO

IFNs are known to be capable of depletion of polyamines to limit virus replication. Polyamines are small ornithine-derived polycationic molecules which encompass three molecules: putrescine, spermidine, and spermine. Spermidine and spermine depletion is one of the compelling mechanisms through which IFNs produce their antiviral effects on the replication of RNA viruses. Mechanistically speaking, polyamines appear to play a pivotal role in the processes of RNA transcription and protein translation of viruses, making them a promising target to combat viral infections [133].

L-tryptophan is one of the nine essential amino acids with a remarkable role in immunosuppression and tolerance and is also essential in protein, kynurenine, and serotonin synthesis [122]. IDO is an intracellular enzyme that induces production of

kynurenine from L-tryptophan, thereby acting to deplete tryptophan and modulate the immune system following viral infections [134]. Having two IFN-stimulated response elements and three IFNγ-activated sites in the promoter of IDO, IFNγ acts as the most powerful inducer of IDO1 expression [135]. IDO has also been shown to be expressed during influenza infection [136]. Dendritic cells, macrophages, and epithelial cells can express IDO [137, 138], and since the primary target for replication of influenza is primarily found to be respiratory epithelial cells, understanding the role of IDO during influenza infection is of particular importance. There exists a coincidence of peak IDO1 and IFN-k expression during influenza infection. Also, mouse lung airways considerably express IFN type I and III following infection with influenza [139]. These findings emphasize that there is upregulated expression and enhanced function of IDO during influenza infection, which is found to be induced by IFN-I. Moreover, IFN-I is thought to signal the adjacent cells via IFN-IR and stimulate them to produce IDO [140].

Nonetheless, the IFN-mediated IDO induction during influenza infection generally has undesirable consequences and establishes immune tolerance [136]. Indeed, an inhibitory effect of tryptophan depletion on T cell responses has been confirmed. Also, IDO induces kynurenine derivation from tryptophan, leading to stimulation of regulatory T cells [141].

Nowadays, IDO is hypothesized to be part of the "metabolic, immune regulation," which plays a protective role in immune responses and inhibits the overreaction of these responses against influenza infection. A pleiotropic role has been attributed to IDO during infections, which gives rise to the opposing outcomes (Fig. 3) [142].

Research on the role of IDO in influenza infection has been mainly focused on the murine models of influenza infection, emphasizing the increased IDO activity and its maximum expression correlated with increased lymphocyte numbers in the respiratory tract [143].

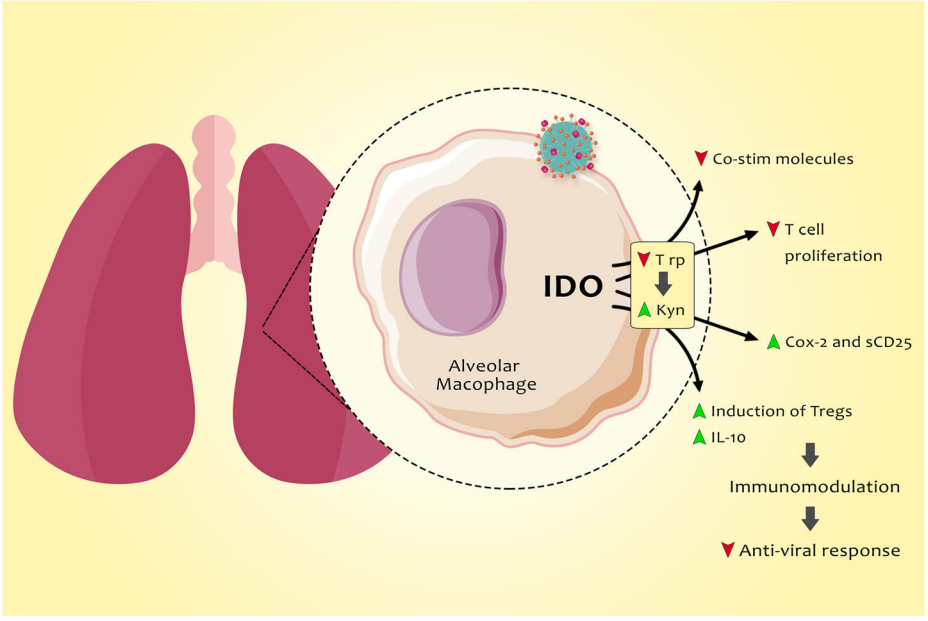

Fig. 3 Role of IFN in IDO activation. IFNs also induce activity of IDO, an enzyme that mediates the production of kynurenine from tryptophan. This event results in tryptophan depletion, which in turn develops the immune tolerance and generates Tregs

IFNs and nitric oxide induction

Nitric oxide (NO) is a gaseous free radical with accessible vasodilatory and microbicidal functions [144]. However, the antiviral effect of NO has also been documented, leading to reduced viral load and more efficient clearance of infection [145]. Nitrosylation of viral molecules has been offered as an antiviral mechanism employed by NO [146]. Also, NO synthase-mediated generation of NO leads to the depletion of L-arginine, thereby reducing the level of polyamines. Thus, IFN-induced NOS2 represents antiviral activities, and this, in turn, may exhibit another mechanism through which IFNs hinder viral infections such as influenza [34]. Despite existing data regarding the antiviral activity of NO, many studies have considered NO as a double-edged sword with both pathogenic and viricidal effects. The role of NO in the pathogenesis of pneumonia caused by influenza virus infection has been described in mice. The IFNγ response induces greatly increased levels of iNOS in the lungs of infected mice, leading to the production of a significant amount of NO and peroxynitrite species, which are among the most important pathogenic factors in influenza virus-induced pneumonia in mice [147]. Uetani et al. also observed overexpression of the iNOS gene in human airway epithelial cells induced by influenza A virus infection [148]. In addition, NO produced by phagocytic cells has antiviral activity that is simultaneous with nonspecific damage of host cells and viral pathogenesis [149]. In a survey by Nin et al. on pandemic A/H1N1 influenza infection, all cases showed increased levels of iNOS protein, tyrosine nitration, and oxygen free radicals, indicating the production of peroxynitrite. Their results revealed the involvement of oxidative and nitrative stress in the pathogenesis of H1N1 influenza virus-induced acute respiratory distress syndrome (ARDS) [15]. Influenza-induced cytokines such as IFNγ stimulate NO release from human airway epithelial cells [150–152]. As mentioned previously, the influenza infection induces upregulation of HIF-1α.

Interestingly HIF-1α-knockout macrophages show decreased expression of iNOS after IFNγ stimulation [153], indicating the possible involvement of HIF-1α in influenza pathogenesis. It has been shown that infection of H5N1 and 1918 viruses induces higher levels of NO in mice compared to the seasonal H1N1 virus and, as a result, they develop more intense pathogenic outcomes, while mice with iNOS deficiency showed reduced morbidity, mortality, and cytokine production in the lungs following H5N1 and 1918 virus infection. Also, systemic administration of NOS inhibitor could postpone weight loss and death among 1918 virus-infected mice [154]. In another survey, the delivery of NO to influenza-infected mice could not improve the lung infection and survival of mice, indicating that NO administration was not a suitable treatment strategy for influenza although this was probably due to the difficulty of determining concentrations of NO that are both viricidal and safe in host airways [155]. Also, it is reported that NO released from *S*-nitroso-*N*-acetylpenicillamine (SNAP) reduces the replication of influenza virus in a dose-dependent manner. The production of NO in airway epithelial cells can lead to antiviral rather than harmful effects following influenza infection provided that its production is precisely controlled [156].

Novel therapeutic approaches by targeting metabolic pathways

Since the influenza virus affects about 20% of the world population annually, preventive and therapeutic approaches require much closer attention. Therapeutic drugs for

influenza infection fall into three groups: 1) neuraminidase inhibitors (zanamivir, oseltamivir, laninamivir, peramivir), 2) M2 inhibitors (rimantadine and amantadine), and 3) polymerase inhibitors (favipiravir) [157, 158]. Antiviral drug resistance has recently emerged as a global problem which can bring about a remarkable financial and social burden [159]. Therefore, further research is urgently needed to develop novel and promising antiviral drugs. Many of the metabolic pathways in influenza infections are increasingly changing, dampening of which appears to hamper the virus replication. One of the newly developed strategies aiming to hinder influenza infection is targeting metabolic pathways and restoration of hemostasis in cells (Table 1).

The PI3K/mTOR signaling pathway has been shown to play a pivotal role in a variety of cellular pathways, including proliferation and nutrient uptake, and its activation increases the glucose uptake through the up-regulation of cell surface glucose transporter [163]. BEZ235 alters glucose metabolism via blockage of the PI3K/mTOR pathway, and some clinical trials are underway to assess this strategy in cancer therapy (Smith et al., 2012). On the other hand, several lines of evidence have demonstrated that siRNA targets the PI3K-AKT-mTOR pathway, thereby warding off influenza infection [164]. In a new study by Smallwood et al., it was found that although BEZ235 did not interfere with the early stages of the infection, it could finally reduce the viral progeny and result in prolonged survival in mice challenged by the influenza virus. Indeed, BEZ235 induced hemostasis in the PI3K/mTOR pathway via phosphorylation of p85 and 4E-BP1 and through reconstitution of metabolic status, which was already altered by the virus [9].

It has been found that there is an elevated level of PDK4 in lung, liver, and heart during influenza infection, while the levels of ATP and PDH, a key enzyme in the regulation of glucose, lipid and ATP levels in human cells, are shown to be reduced [156]. Furthermore, dichloroacetate (DCA) is a pyruvate dehydrogenase kinase inhibitor with anti-tumor activity in a variety of carcinomas. Studies have also indicated that diisopropylamine dichloroacetate (DADA) could ameliorate the metabolism of hepatocytes in chronic liver disease [165]. In a study by Yamane et al. attempting to evaluate the effect of DADA on influenza-infected mice (PR8), oral administration of DADA was found to not only restore the activity of PDH and ATP in affected organs but also suppress cytokine storm and viral replication [94].

Table 1 Characteristics of some metabolic pathway blockers in influenza infection

Agent	Target	Outcome	Model	Reference
BEZ235	PI3K/mTOR	Reconstitution of metabolic status and decreased viral replication	In vivo	[9]
Hochuekkito	Effect on mitochondrial and glycolysis	Ameliorates metabolism and intensifies the symptoms	In vitro	[160]
Simvastatin	Sterol synthesis	Decreased influenza replication and cytokine production	In vitro	[161]
DADA	Pyruvate dehydrogenase kinase	Suppresses cytokine storm and viral replication	In vivo	[94]
MJWQH	amino acid, fatty acid and arachidonic acid pathway	Improved weight loss, lung index, biomarkers and inflammatory mediators such as prostaglandin E2	In vivo	[162]
Bezafibrate	Carnitine palmitoyltransferase II	Restores the ATP levels in cells and intensifies the symptoms	In vivo	[110]
AM580	Sterol regulatory element binding protein (SREBP) pathways	Inhibited influenza virus replication through interference with SREBP paths	In vivo	[105]

DADA Diisopropylamine dichloroacetate, *MJWQH* Modified Jiu Wei Qiang Huo

Sterols are intermediate metabolites that play an essential role in a broad spectrum of biological pathways, including inflammation. Research has shown that interferon production following the immune response in viral infection regulates sterol production paths. Blanc et al. revealed that sterol metabolism pathway regulators such as simvastatin, Zometa (zoledronic acid), and FPT inhibitor III could effectively hinder H5N1 influenza replication and cytokine production, which makes them promising therapeutic candidates in acute patients [121, 161].

On the other hand, as mentioned earlier, SREBPs are transcription factors that have a critical role in the process of lipogenesis. Studies have shown that these factors can play a variety of roles, such as energy supply and post-translational protein modification, as well as in the propagation of various groups of viruses such as influenza viruses. A study has shown that the AM580 compound, which is a retinoid derivative, inhibits SREBP-linked pathways, and it has antiviral activity against influenza A and coronavirus in vitro and in vivo [105].

Concerning the fact that mitochondria and glycolysis are two sources of energy production, they play vital roles in the regulation of innate immunity responses. During the immune system response, and especially the cytokine storm, following influenza infection, ATP synthesis in the mitochondria decreases, leading to weakened innate immune responses (Dengbing Yao). Studies have revealed that traditional herbal medicines have an important role in improving influenza-like symptoms in infected patients. Results of a study demonstrated that pre-treatment of infected cells with Hochuekkito (a traditional Japanese herbal medicine) could activate both mitochondrial and glycolytic energy metabolism and thereby intensify symptoms [160]. Also, the effects of traditional Chinese medicine (modified Jiu Wei Qiang Huo) on H1N1 infected mice were evaluated in another study. The results showed that this herbal medicine could ameliorate weight loss and inflammatory mediators in infected mice through the regulation of amino acid, fatty acid, and arachidonic acid pathways [162].

Conclusion

Based on recent studies, influenza virus infection can interfere with cellular metabolic pathways either directly or indirectly via stimulation of immune system mediators. Through enhancing the activity of the mTORC1 complex, the influenza virus strengthens several metabolic pathways, including glycolysis, glutaminolysis, pentose phosphate, and fatty acid synthesis, to provide more ATP and structural materials for viral replication. On the other hand, β-oxidation suppression following viral infection can help to supply essential fatty acids for the synthesis of structural lipids. However, exhausting cellular ATP resources due to virus replication, as well as an increase in pro-inflammatory lipid synthesis, will ultimately lead to irreversible cell damage. Innate immune responses following influenza infection play a crucial role in metabolic alterations. IFN is one of these mediators that acts on several metabolites such as IDO and NO and thereby affects lipid and amino acid pathways. Since the drug resistance in influenza infection is a global concern, research on designing novel therapeutic modalities to tackle pandemics is of particular importance. Thus, a clear understanding of the metabolic alterations during influenza infection would be tremendously helpful for therapeutic purposes.

Abbreviations
6PGD: 6-phosphogluconate dehydrogenase; AA: Arachidonic acid; ADA: Adenosine deaminase; CPT: Carnitine palmitoyltransferase; DADA: Diisopropylamine dichloroacetate; DCA: Dichloroacetate; DHA: Docosahexaenoic acid; FA: Fatty acid; FAO: Fatty acid oxidation; IDO: Indoleamine-2,3-dioxygenase; ISGs: Interferon stimulated genes; IVI: Influenza virus infection; MOI: Multiplicity of infection; mTORC1: Mechanistic target of rapamycin complex 1; NHBE: Normal human bronchial epithelial; NO: Nitric oxide; PDH: Pyruvate dehydrogenase; PDK: Pyruvate dehydrogenase kinase; PPARs: Peroxisome proliferation-activated receptors; PPP: Pentose phosphate pathway; SM: Sphingomyelin; SREBP2: Sterol regulatory binding protein 2; XO: Xanthine oxidase

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