Mini Review

Relevance of signaling molecules for apoptosis induction on influenza A virus replication

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A B S T R A C T

Apoptosis is an important mechanism to maintain homeostasis in mammals, and disruption of the apoptosis regulation mechanism triggers a range of diseases, such as cancer, autoimmune diseases, and developmental disorders. The severity of influenza A virus (IAV) infection is also closely related to dysfunction of apoptosis regulation. In the virus infected cells, the functions of various host cellular molecules involved in regulation of induction of apoptosis are modulated by IAV proteins to enable effective virus replication. The modulation of the intracellular signaling pathway inducing apoptosis by the IAV infection also affects extracellular mechanisms controlling apoptosis, and triggers abnormal host responses related to the disease severity of IAV infections. This review focuses on apoptosis related molecules involved in IAV replication and pathogenicity, the strategy of the virus propagation through the regulation of apoptosis is also discussed.

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1. Introduction

Apoptosis is classified into type-I programmed cell-death, where morphological features of the cells ongoing apoptosis are subject to cytoplasmic shrinkage, plasma membrane blebbing, DNA fragmentation, and chromatin condensation. Finally, the cells form cell fragments, termed apoptotic bodies, and are removed by phagocytic cells. Apoptosis is able to remove cells without a trace, and is an important physiological mechanism to maintain homeostasis in mammals. Because of its physiological significance, the execution of apoptosis must be strictly regulated, and a large number of molecules are involved in controlling apoptosis.

Apoptosis is closely related to a number of aspects of influenza A virus (IAV) infection. For instance, apoptosis plays a pivotal role in IAV elimination through the removal of the virus infected cells, and tissue damage during the course of IAV infection including multiple organ dysfunction is caused by apoptosis [1,2]. Further, abnormal induction of lymphocyte apoptosis is related in the disease symptoms of influenza, and apoptosis is also important to terminate inflammation through the induction of activation-induced cell death (AICD). In this review, focusing on the relationship between IAV proteins and apoptosis related host cellular molecules, strategies of IAV for effective viral propagation by the regulation of apoptosis are discussed.

2. Major pathways for apoptosis induction

Normally, apoptosis induction is accompanied by activation of caspases (cysteine–aspartic acid proteases) [3]. Caspases are classified into initiator caspases and effector caspases. Initiator caspases are responsible for initiating apoptosis through the activation of downstream effector caspases by proteolytic cleavage, and effector caspases are necessary for activation or inactivation of molecules, such as PARP (poly (ADP-ribose) polymerase) [4] and CAD (caspase-activated DNase) [5] to execute apoptosis. There are two major pathways to activate caspase cascades for apoptosis induction, one is the death receptor pathway, and the other is the mitochondrial pathway (Fig. 1).

Death receptors, such as TNFαR1 (tumor necrosis factor α receptor 1), Fas, DR4 (death receptor 4, also called TRAILR1) and
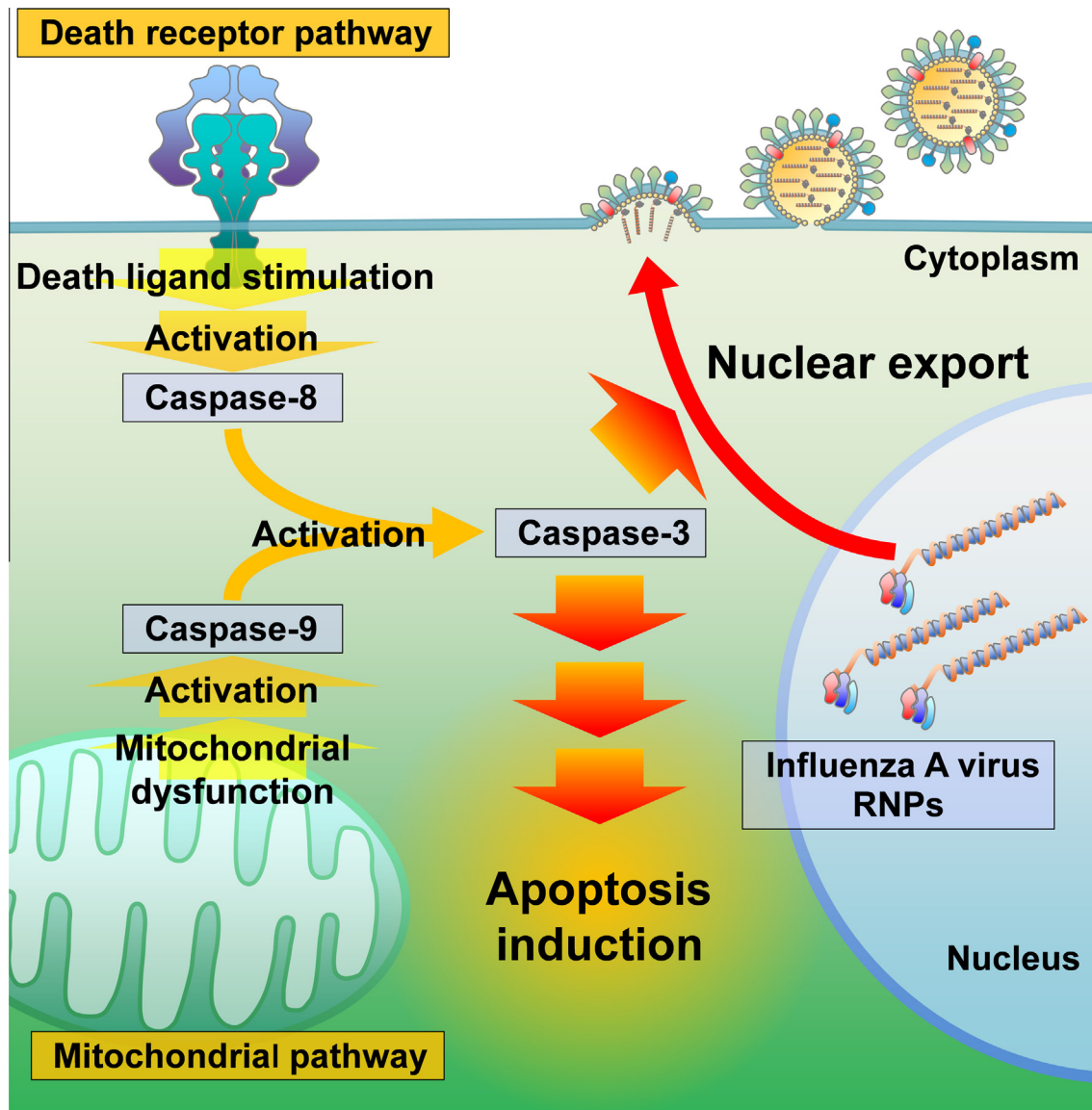
Fig. 1. Two major pathways for induction of apoptosis and involvement of caspase-3 activation for IAV replication. Death receptor pathway and mitochondria pathway are crucial for the activation of caspase-8 and caspase-9 respectively. Disruption of mitochondrial membrane potential causes cytochrome c release, and activates caspase-9 by the complex formation with cytochrome c recognition protein, Apaf-1. After the activation of these pathways, both activated caspase-8 and caspase-9 activate caspase-3 by proteolytic cleavage.

DR5 (death receptor 5, also called TRAILR2), are defined by the death domain of its cytoplasmic region. The death domain is responsible for activating caspase-8. After the stimulation with the ligands of death receptors, FADD (Fas-associated death domain) is directly or indirectly bound to the death receptors, and then caspase-8 is activated by FADD through the activation of a self proteolytic cleavage. Therefore, FADD plays a pivotal role in death receptor-mediated apoptosis induction. It has been reported that Fas is able to directly bind to FADD [6], TNFαR1 requires TRADD (tumor necrosis factor receptor type 1-associated death domain protein) [7], and DR4 and DR5 require DAP3 (death-associated protein 3) for recruitment of FADD [8].

Mitochondria are an important organelle in determining cell destiny, and generally the mitochondrial membrane potential is disrupted in the course of apoptosis induction. After disruption of the mitochondrial membrane potential, the cytochrome c in the mitochondrial inner membrane is released into the cytoplasm, and caspase-9 is activated by Apaf-1 (apoptotic protease activating

factor 1) which is known to be a cytoplasmic sensor molecule for cytochrome c [9]. The mitochondria membrane potential is mainly regulated by Bcl-2 (B-cell lymphoma 2) family proteins [10], a family of proteins characterized by BH (Bcl-2 homology) domains, and Bcl-2 are classified into three types. One is a pro-apoptotic multi-domain sub-family of proteins including Bax (Bcl-2-associated x protein) and Bak (Bcl-2 homologous antagonist killer). These proteins have BH1, BH2, and BH3 domains, and activate apoptosis induction through the increment of permeability of the mitochondrial outer membrane. Another is the anti-apoptotic sub-family proteins which have BH1, BH2, BH3, and BH4 domains, and include Bcl-2 and Bcl-xL (B-cell lymphoma-extra large). These proteins exhibit anti-apoptotic functioning through the inhibition of the pro-apoptotic multidomain Bcl-2 sub-family function. The third is pro-apoptotic BH3 only proteins, such as Bid (BH3 interacting-domain death agonist) and Bad (Bcl-2-associated death promoter). These proteins are antagonists to the anti-apoptotic Bcl-2 subfamily protein function, and promote apoptosis.

Both activated caspase-8 and caspase-9 activate common downstream caspases, mainly caspase-3, by proteolytic cleavage, and then the apoptosis takes place. Importantly, apoptosis through these two major pathways is crucial for the elimination of IAV through the removal of the virus infected cells from the body, as well as it is involved in the effective replication of the IAV. Previous study has demonstrated that activation of caspase-3 is important for the effective replication of the IAV through the activation of exportation of the viral RNP (ribonucleoprotein) complex from the nucleus to the cytoplasm [11]. This may indicate that the IAV utilizes apoptosis signaling molecules, crucial for host immune response to eliminate the virus, conversely for the effective replication of the IAV.

3. Death receptor mediated signaling pathway

The death receptor-mediated signaling pathway is thought to be closely related to the pathology of IAV infection, and TNFα, FasL (Fas ligand), and TRAIL (TNF-related apoptosis inducing ligand) are known to be death ligands, and recognized by TNFαR1, Fas, DR4, and DR5, respectively. Abnormally elevated expression of these death ligands is frequently found in lethal IAV infections, and aberrant induction of apoptosis caused by these death ligands is

thought to be related in the onset of the multi organ disorders occurring in severe IAV infections. Death receptors play pivotal roles in the activation of caspase-8, and also work to activate NF-κB (nuclear factor-κB) and JNK (c-Jun amino-terminal kinase) like other non-death receptors belonging to the TNF-superfamily receptors (Fig. 2). Overall, death receptor-mediated signaling pathway contributes to apoptosis induced by IAV infection through the activation of caspases mediated by FADD and JNK, and death receptor-mediated activation of NF-κB is crucial for enhancement of death receptor-mediated signaling in both autocrine and paracrine manner.

Generally, NF-κB activation increases cell viability, and competes with apoptosis induction. It has been reported that the NS1 (non-structural protein 1) protein encoded in the IAV genome, is involved in the activation of NF-κB through the activation of the PI3K (phosphatidylinositol-3 kinase)/Akt (v-akt murine thymoma viral oncogene homolog 1) pathway [12,13]. In addition, IAV neuraminidase (NA) protein is also involved in activation of Akt through binding with CEACAM6 (carcinoembryonic antigen-related cell adhesion molecule 6) protein which is known to be related in activation of Src (sarcoma viral oncogene homolog)/Akt signaling pathway [14]. At the same time NF-κB is also an important transcriptional factor for activation of the immune response through
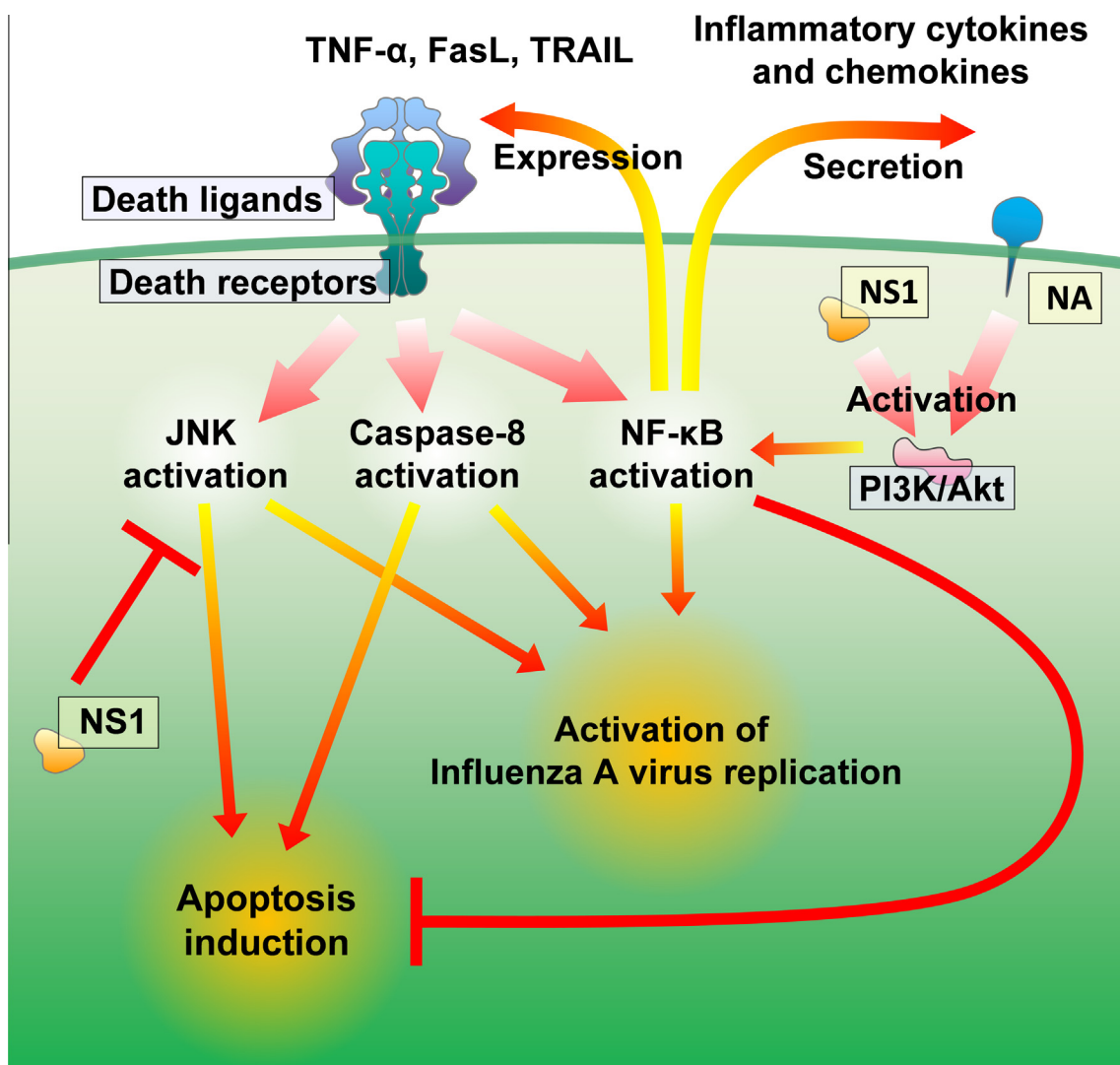

Fig. 2. Modulation of IAV replication by death receptor-mediated signaling pathway. In addition to caspase 8 activation, death receptors activate NF-κB and JNK signaling pathways. IAV NS1 and NA are involved in activation of NF-κB through the activation of Akt, and NS1 also has a function to inhibit the JNK activation.
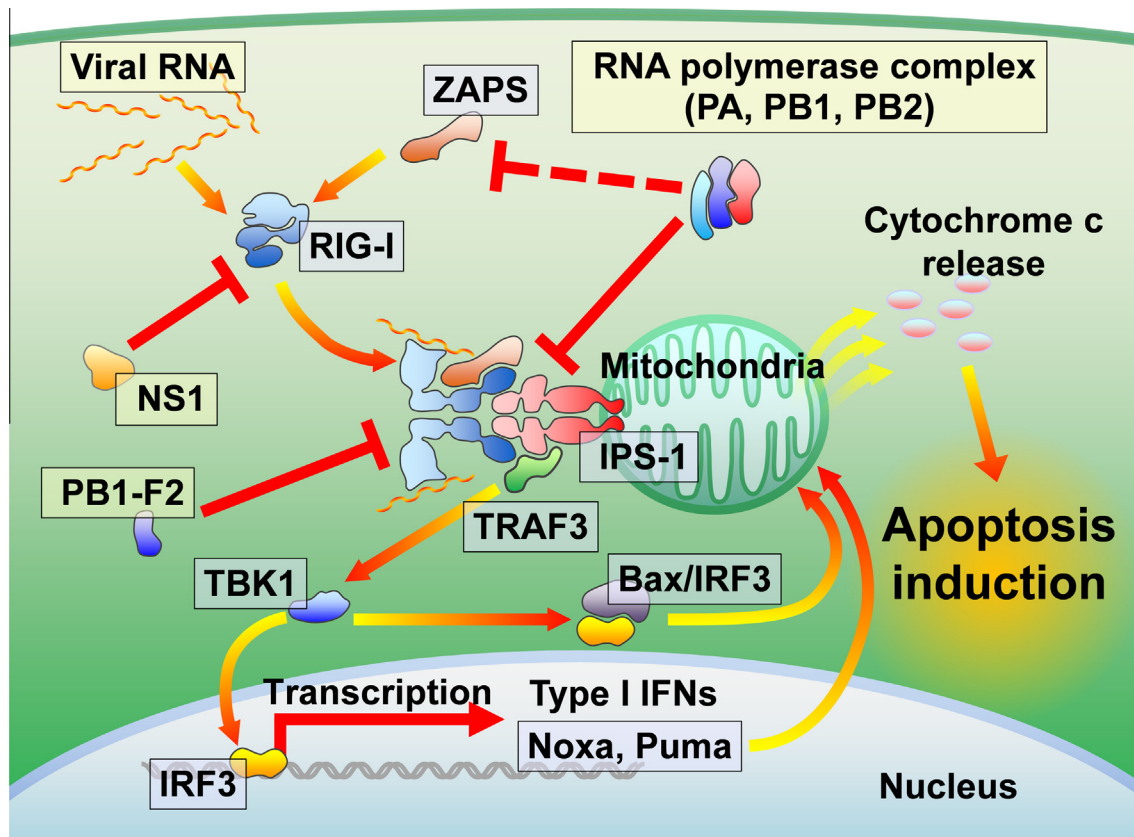
Fig. 3. IPS-1-mediated apoptosis induction pathway activated by IAV infection. IPS-1 is responsible to activate a transcriptional factor, IRF3. IRF3 induces the transcription of pro-apoptotic proteins, Noxa and Puma. IPS-1-mediated phosphorylation of IRF3 leads binding of IRF3 to Bax, and promotes Bax-induced apoptosis. Functions of IPS-1 are inhibited by IAV proteins, NS1, blocking the function of RIG-I, and the viral polymerase complex.

the induction of a number of inflammatory cytokines including TNF-α, FasL, and TRAIL. Previously, the importance of NF-κB-dependent expressions of TRAIL, Fas, and FasL has been reported [15]. Therefore, activation of NF-κB is thought to be important to prevent immediate execution of apoptosis and to increase cell viability for effective virus replication, as well as it is crucial for death ligand expression to enhance caspase activation.

The JNK is known to be an important kinase which regulates expression of genes involved in stress responses. Previous reports demonstrated that JNK activation is involved in production of type I interferons (IFNs), and is that JNK activation is inhibited by the influenza virus NS1 protein [16,17]. It has also been reported that treatment with JNK inhibitor exhibits antiviral activity against IAV infections [18]. Generally, the JNK signaling pathway is related to stress induced apoptosis through activation of the mitochondrial pathway. However, JNK activation is also implicated in cell proliferation and survival under some conditions. It is assumed that transient activation of JNK is involved in increasing cell viability, and that sustained activation of JNK is associated with apoptosis induction. The dual phased function of JNK might explain these controversial phenomena. In addition, since JNK activation emphasizes death receptor mediated apoptosis induction, the inhibition of JNK activation could be effective to protect from the apoptosis caused by abnormally elevated expressions of inflammatory cytokines including death ligands after IAV infection [19].

4. RIG-I like receptor mediated signaling pathway

The RIG-I (retinoic acid-inducible gene-I) is known to be an intracellular pattern recognition receptor responsible for recogniz-

ing the viral RNA in IAV-infected cells, and is crucial for activation of host anti-virus responses through the induction of type I IFNs and inflammatory cytokines. The RIG-I recognizes viral 5′-tri-phosphorylated RNAs, and is activated through conformational changes and then binds to IPS-1 (IFN-β promoter stimulator protein 1; also called MAVS, Cardif, or VISA) [20], an adapter protein localized in the mitochondria outer membrane. The IPS-1 is responsible for activating downstream signaling molecules for the induction of type I IFNs and inflammatory cytokines. Further, IPS-1 is also involved in apoptosis induced by viral infection [21,22]. The IRF3 (IFN regulatory factor 3), the downstream transcriptional factor activated by IPS-1, is involved in IPS-1-mediated apoptosis induction. The IPS-1-mediated activation of IRF3 leads to the expression of Noxa/Puma. Noxa/Puma inhibits the function of mitochondrial anti-apoptotic Bcl-2 family proteins by binding, and induces apoptosis through the destruction of the mitochondrial membrane potential. Further, IRF3 is able to induce apoptosis independently from the function as a transcriptional factor. The IPS-1-mediated IRF3 phosphorylation leads to the IRF3 binding to Bax, and activates the Bax-mediated apoptosis induction.

The IPS-1-mediated signaling pathway for the production of type I IFNs is critical to the activation of the early defensive mechanism of the host against viral infections. Because of the physiological significance of IPS-1-mediated signaling pathway, this pathway is inhibited by many viruses, such as hepatitis C virus, Ebora virus, and severe acute respiratory syndrome coronavirus [22,23]. Inhibition of the IPS-1-mediated signaling pathway is also assumed to be important for the effective replication of IAV. The IAV has several viral components to inhibit the IPS-1-mediated signaling pathway (Fig. 3). The NS1 protein of the IAV binds to RIG-I and inhibits RIG-I functioning through its RNA
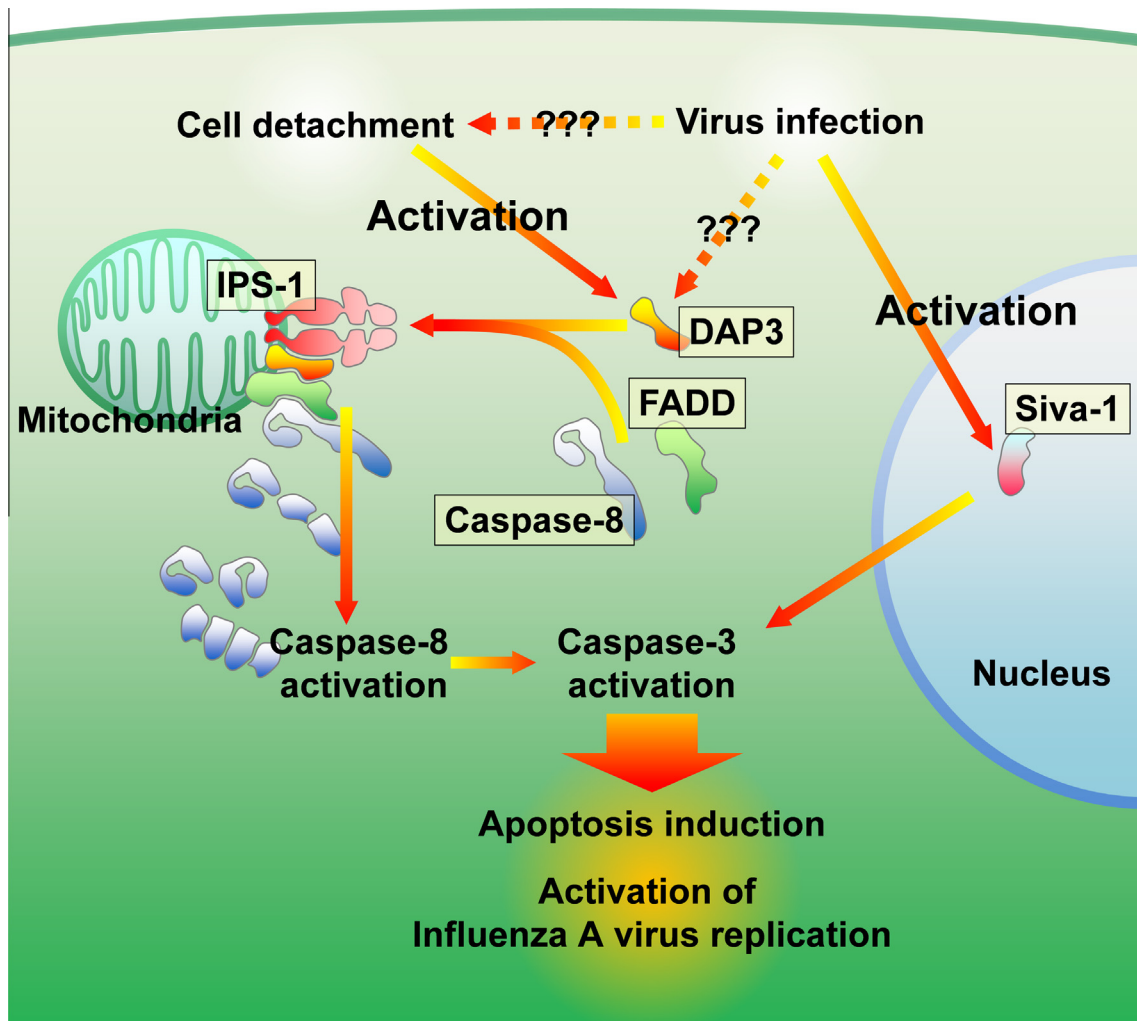
Fig. 4. Other apoptosis induction factors involved in IAV replication. Siva-1 is involved in the effective IAV replication through the activation of caspases. DAP3 is essential for death receptor-mediated apoptosis induction and IPS-1-induced anoikis, suggesting that DAP3 is an important molecule to regulate apoptosis induced by IAV infection.

binding activity [24]. In addition, the function of TRIM25 (tripartite motif-containing protein 25), the E3 ubiquitin ligase crucial for the RIG-I mediated IFN production, is also inhibited by the NS1 protein [25]. The viral polymerase complex binds to IPS-1 and inhibits the IPS-1 function for type I IFN production [26]. Further, PB1-F2, a viral protein encoded in the second open reading frame of IAV segment 2 mRNA, is also involved in the inhibition of the IPS-1-mediated production of type I IFN by binding to IPS-1 [27]. Results of the comprehensive proteomic analysis indicate that the viral polymerase complex may bind to ZAPS (zinc finger antiviral protein, short form) [28], the positive regulator of the IPS-1-mediated signaling pathway by binding to RIG-I [29]. This finding suggests that the viral polymerase complex may modulate its function.

Although the functions of these viral molecules on IPS-1-mediated induction of apoptosis have not been well confirmed, these molecules are thought to inhibit the function of IPS-1 leading to induction of apoptosis and also the induction of type I IFNs. A previous report has demonstrated that overexpression of Bcl-2 effectively inhibits IAV replication [30]. Bcl-2 is an anti-apoptotic protein, functional against the pro-apoptotic proteins such as Bax, Noxa, and Puma. These results suggest that the IPS-1-mediated activation of the mitochondrial pathway for apoptosis induction may be also functional for the effective replication of the IAV.

5. Other signaling molecules for controlling apoptosis

A previous report demonstrated that the Siva-1, a pro-apoptotic protein, is crucial for effective replication of the IAV [31]. Since the function of Siva-1 in the virus replication completely disappears after treatment with a pan-caspase inhibitor, Z-VAD fmk, the Siva-1 appears to modulate IAV replication through the controlling activation of caspases (Fig. 4). Several apoptosis-related molecules involved in Siva-1 mediated apoptosis induction were reported, and one of these is XIAP (X-linked inhibitor of apoptosis protein) [32]. The XIAP is known to be an anti-apoptotic protein, and it directly inhibits proteolytic activity of caspases including caspase-3 by binding [33]. Siva-1 is considered to be involved in the inhibition of XIAP function, and a previous report demonstrated that overexpression of XIAP inhibits IAV replication [11]. This may suggest the significance of the Siva-1-mediated signaling pathway on the virus propagation.

Some molecules involved in the death receptor mediated signaling pathway are also important for the IPS-1-mediated signaling pathway. For instance, FADD, an adaptor molecule responsible for activating caspase-8 in the death receptor signaling pathway, is important for NF-κB activation in the IPS-1-mediated signaling pathway [34]. The TRADD, an adapter molecule crucial for the recruitment of FADD to TNFαR1, is also involved in the activation of the IPS-1-mediated signaling pathway for type I IFN

production [35]. In addition, DAP3 is known to be crucial for apoptosis induced by TRAIL stimulation through the recruitment of FADD to DR4 and DR5, and is also related to other IPS-1 functions. A previous report has demonstrated that IPS-1 is also involved in induction of anoikis [36], which is known to be a form of apoptosis induced by anchorage-dependent cells detaching from the surrounding extracellular matrix. In anoikis induction, DAP3 binds to IPS-1 and recruits FADD for activation of caspase-8, and then apoptosis is executed. The DAP3 function in anoikis induction is inhibited by Akt-dependent phosphorylation [37], and as described in the previous section, AKT is activated by the NS1 protein of IAV. Therefore, the DAP3 function inducing anoikis is thought to be inhibited in IAV infected cells. The role of the DAP3 and IPS-1-mediated signaling pathway for apoptosis induction on IAV infection is not fully understood. However, DAP3 is also crucial for apoptosis induced by TNF-α, FasL, and TRAIL stimulation [8,38]. Therefore, DAP3 and DAP3 related molecules, such as LKB1 (liver kinase B1) [39], and DELE (death ligand signal enhancer) [40], are thought to be implicated in the virus replication and regulation of apoptosis caused by the IAV infection.

It has been reported that matrix protein (M) 1 and 2 of influenza A virus are involved in regulation of apoptosis induction [41,42]. IAV M1 protein is involved in cell susceptibility to apoptosis through binding to an anti-apoptotic protein, Hsp70, and M2 protein is indirectly involved in apoptosis induction through inhibition of type II programmed cell death, macroautophagy. Further, involvement of IAV PB1-F2 and NP (nucleoprotein) proteins for apoptosis induction was reported [43,44]. PB1-F2 protein induces apoptosis through direct disruption of mitochondrial membrane potential, and NP protein is indirectly involved in apoptosis induction through binding to a host-cellular anti-apoptotic protein, clusterin. These virus proteins and host-cellular molecules are thought to be also important for controlling apoptosis induced by IAV infection.

This review has mainly discussed intracellular mechanisms for the regulation of apoptosis by IAV. Induction of apoptosis is thought to be important for both inhibition and activation of IAV propagation, and the issues involved in a full understanding of the viral strategy for effective propagation by controlling apoptosis appear to be complicated. Further investigation of the molecular mechanism regulating apoptosis by IAV is required, and may provide insights to enable the development of novel anti-virus drugs.

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