Virus Genes (2019) 55:433–439
https://doi.org/10.1007/s11262-019-01665-z

REVIEW PAPER

Signaling pathways involved in regulating apoptosis induction in host cells upon PRRSV infection

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Received: 19 February 2019 / Accepted: 14 April 2019 / Published online: 19 April 2019

Abstract
Porcine reproductive and respiratory syndrome virus (PRRSV) is the etiologic agent of porcine reproductive and respiratory syndrome (PRRS), a devastating disease of swine that poses a serious threat to the swine industry worldwide. The induction of apoptosis in host cells is suggested to be the key cellular mechanism that contributes to the pathogenesis of PRRS. Various signaling pathways have been identified to be involved in regulating PRRSV-induced apoptosis. In this review, we summarize the potential signaling pathways that contribute to PRRSV-induced apoptosis, and propose the issues that need to be addressed in future studies for a better understanding of the molecular basis underlying the pathogenesis of PRRS.

Keywords PRRSV · Apoptosis · Signaling pathways · Mitochondrial pathway · Death receptor pathway

Introduction

Cell death can occur by either the programmed or the non-programmed pathway [1, 2]. A number of types of programmed cell death have been identified; these include apoptosis [3], autophagic cell death [4, 5], and necroptosis [6, 7]. Of them, apoptosis is the most common type of programmed cell death defined by a series of typically morphological nuclear changes, such as chromatin condensation and nuclear fragmentation, and it plays a critical role in development and tissue homeostasis [8]. There are two major types of apoptosis pathways. One is the mitochondrial pathway (intrinsic pathways) characterized by mitochondrial outer membrane permeabilization (MOMP) and subsequent release of apoptotic factors such as cytochrome c into the cytoplasm to form the apoptosome and activate initiator caspase-9. The other one is the death receptor pathway (extrinsic pathway) characterized by the formation of a death-inducing signaling complex (DISC) and subsequently activating initiator caspases (caspases-8 and -10). The cross-talk among these two pathways can occur through the truncated form of Bid (t-Bid) mitochondrial translocation [9]. The dysregulation of apoptosis is involved in numerous pathological processes including viral infection and replication [10].

Porcine reproductive and respiratory syndrome (PRRS) is a devastating disease of swine that poses a serious threat to the swine industry worldwide. Porcine reproductive and respiratory syndrome virus (PRRSV), a member of the positive-strand RNA virus family Arteriviridae was determined to be the etiologic agent of PRRS in the early 1990s [11]. It has been well documented that PRRSV infection induces apoptosis in host cells both in vitro and in vivo [12–17]. The apoptosis induction in host cells is a major cellular mechanism contributing to the pathogenesis of PRRS [18–20]. A number of signaling pathways have been identified to be involved in regulating PRRSV-induced apoptosis; these include Bcl-2 family protein-regulated mitochondrial pathway, TNFR1/Fas-mediated death receptor pathway and the up-stream regulators of these pathways such as c-Jun N-terminal kinase (JNK), unfolded protein response (UPR), oxidative stress, p53, and autophagy-related signals.

Edited by Juergen A Richt.

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Signaling pathways involved in PRRSV-induced apoptosis

Involvement of both mitochondrial and death receptor pathways

The activation of mitochondrial pathway (intrinsic pathway) is suggested to play an important role in PRRSV-induced apoptosis [21, 22]. The disruption of mitochondrial membrane potential (MMP) is a hallmark of mitochondrial pathway activation. Mitochondrial membrane potential is tightly controlled by Bcl-2 family proteins including multidomain pro-apoptotic proteins Bax (Bcl-2-associated X protein) and Bak (Bcl-2 antagonist killer 1), BH3-only pro-apoptotic proteins Bid (BH3-interacting domain death agonist), Bim (Bcl-2 interacting mediator of cell death), Bik (Bcl-2-interacting killer), Bad (Bcl-2 associated agonist of cell death), Bmf (Bcl-2 Modifying Factor), Hrk (harakiri), Puma (p53 up-regulated modulator of apoptosis), etc. and anti-apoptotic proteins Bcl-2 (B-cell lymphoma-2), Bcl-xL(B-cell lymphoma-extra-large), Bcl-w (Bcl-2-like protein 2), A1(Bcl-2 related gene A1), Mcl-1 (myeloid cell leukemia 1), etc. Activation of multidomain pro-apoptotic Bax and Bak resulted in permeabilization of mitochondria, which in turn leads to induction of mitochondrial dependent apoptosis. The pro-survival Bcl-2 proteins are the key players in the inhibition of Bax and Bak, whereas the BH3-only molecules (BH3s) trigger apoptosis by either activating Bax/Bak or inhibiting anti-apoptotic Bcl-2 proteins [23]. The balance between pro-apoptotic and anti-apoptotic proteins is essential to keep mitochondrial membrane potential at normal levels. Lee and Kleiboeker [21] demonstrated that the pro-apoptotic Bax expression is up-regulated by PRRSV infection, followed by the disruption of mitochondrial membrane potential, cytochrome c release, and subsequent caspase-9 activation. The authors also revealed that the expression of TNFR1 and FasL are increased in response to PRRSV infection, suggesting that the death receptor pathway may also contribute to PRRSV-induced apoptosis. Furthermore, Bid is cleaved to form the active form t-Bid upon PRRSV infection, indicating that a crosstalk between the extrinsic and intrinsic pathways took place in PRRSV-induced apoptotic process [21, 24]. In addition to the involvement of Bax and t-Bid, studies by us or others show that the decreased expression of anti-apoptotic protein Mcl-1 and Bcl-xl, and increased pro-apoptotic Bim makes an additional contribution to PRRSV-induced mitochondrial activation [24, 25].

The role of MAPKs in regulating PRRSV-induced apoptosis

The mitogen-activated protein kinase (MAPK) cascades are evolutionary conserved intracellular signal transduction pathways that play a pivotal role in transmitting cell-surface signals to the regulatory targets. It has been shown to be involved in regulating various cellular processes such as proliferation, differentiation, and cell death [26]. There are three major mammalian MAPK pathways have been identified: extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38. Each cascade consists of three enzymes that are sequentially activated through phosphorylation: a MAPK, a MAPK kinase (MAPKK), and a MAPK kinase kinase (MAPKKK). The activation of MAPKs, especially the stress-activated kinase JNK, is a common event in response to viral infection [27–29]. A number of studies show that JNK is activated by PRRSV infection evidenced by increased phosphorylation of JNK and its substrate c-jun [24, 25, 30–33]. Inhibition of JNK activation by its specific inhibitor SP600125 leads to an abolishment of PRRSV-induced apoptosis, accompanied by the restoration of anti-apoptotic protein Mcl-1 and Bcl-xl expression. These results suggest that the JNK activation functions as a critical mediator to trigger apoptosis through down-regulating anti-apoptotic Bcl-2 family proteins [25]. The JNK activation by PRRSV has been demonstrated to be attributed to ROS generation and ER stress induction [25, 31]. In addition, the activation of JNK has been found contributing the cytokine production induced by PRRSV infection [24, 30, 33].

The contribution of UPR in apoptosis induction by PRRSV infection

The endoplasmic reticulum (ER) is an important organelle and serves multiple functions such as lipid synthesis, calcium storage, protein synthesis, folding, and maturation. Many cellular disturbances, such as redox imbanlane, cause accumulation of misfolded proteins or unfolded proteins, which in turn leads to activation of an evolutionary conserved signaling pathway called the unfolded protein response (UPR). The final outcome of UPR is mitigation of ER stress via blocking protein translation, increasing protein folding capacity and promoting ubiquitination mediated mis/unfolded protein degradation, and to re-establish the homeostasis [34]. However, severe or prolonged activation of the UPR can cause cell death induction that is involved in the pathogenesis of various diseases, including vital infection [35, 36]. In response to PRRSV infection, the two branches of UPR signaling pathways IRE1-XBP1 and PERK–eIF2α are activated evidenced by the elevated phosphorylation levels of these kinases and the activation of their respective substrate XBP1 and eIF2α. The induction of UPR has been found not only contributing to PRRSV-induced apoptosis in host cells [24, 31], but also involving in the regulation of virus replication and dysregulation of alveolar macrophage cytokine production [37]. Mechanistically, the activation of

UPR promotes apoptosis of host cells through triggering JNK-mediated mitochondrial pathway [31].

Induction of oxidative stress promotes PRRSV-induced apoptosis

Redox imbalance due to increased oxidative-free radicals and/or decreased anti-oxidative capacity will cause oxidative stress. Redox balance is controlled by a battery of enzymes, non-enzymatic compounds, and redox-sensitive transcriptional factors. The oxidative stress-related enzymes include superoxide dismutases (SODs), catalase, glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), thioredoxins (TRXs), peroxiredoxins (PRXs), glutaredoxins, cytochromes P450 (CYPs), and Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, whereas the non-enzymatic redox-related molecules include mainly glutathione (GSH), ascorbic acid, and tocopherols/tocotrienols. The major transcriptional factors involved in redox regulation include Nrf2, Nrf1, p53, and FoxO [38, 39]. Changes in redox homeostasis in vital infected cells are one of the key events that is linked to the pathogenesis of viral infections [40]. It has been shown that oxidative stress is induced in response to PRRSV infection both in vitro and in vivo models [21, 25, 41, 42]. Inhibition of ROS generation by anti-oxidant protects the cells from PRRSV-induced apoptosis through suppressing JNK activation [25]. Regarding the mechanisms of PRRSV-induced oxidative stress, Yan et al. [42] revealed that the increased ROS generation by PRRSV infection is likely attributable to the elevated inducible nitric oxide synthase (iNOS), which is associated with the changes of heat shock protein 90 (HSP90) and caveolin-1 (Cav-1) expression. In addition, a study by Stukelj et al. [43] demonstrates that the decreased GPX activity is observed in PRRSV-infected pigs, suggesting inhibition of anti-oxidant enzyme activity may also contribute to oxidative stress induction by PRRSV infection.

p53 activation protects the host cells from PRRSV-induced apoptosis

p53 is a nuclear transcription factor that was discovered in 1979. It has a broad range of biological functions, primarily regulation of apoptosis, cell cycle, and DNA repair. In most cases, the activation of p53 provokes pro-death signaling to trigger apoptosis through either transcriptional-dependent or -independent mechanisms. For transcriptional pathway, the activated p53 protein translocates into the nuclei and functions as transcriptional activator to activate its transcriptional targets that are involved in apoptosis induction such as pro-apoptotic proteins Bax, puma and NOXA [44]. For transcriptional-independent pathway, the activated p53 protein translocates into the mitochondria, leading to the activation of mitochondrial pathway through forming complexes with the anti-apoptotic Bcl-2 family proteins [45]. In addition, cytosolic p53 can also directly trigger Bax activation and apoptosis [46]. However, cumulating evidence suggests that p53 may also exert pro-survival activity to suppress apoptosis induction in certain model systems [47]. Proposed mechanisms contributing the anti-apoptotic function of p53 include: p53 inhibits pro-apoptotic JNK activation [48]; p53 induces pro-survival p21 up-regulation [49]; p53 functions as anti-oxidant to counteract ROS-mediated apoptosis [50]. It has been shown that p53 is activated in response to PRRSV infection evidenced by the increased p53 phosphorylation at Ser15 and up-regulation of it transcriptional target p21 [31, 51]. To examine the functional role of p53 activation in apoptosis induction by PRRSV, nutlin-3, a specific p53 activator, was employed to activate p53. Under such condition, the changes of apoptosis induction were measured and the results demonstrate that the apoptosis induction by PRRSV is decreased in the presence of nutlin-3, accompanied by reduced JNK activation [31]. These data suggest that p53 activation protects the host cells from PRRSV-induced apoptosis through inhibiting JNK-mediated apoptotic signaling.

Autophagy regulates virus replication and apoptosis

Autophagy is an intracellular cytoplasmic content (long-lived proteins and damaged organelles) degradation process [52]. Autophagy has been found to play an important role in regulating multiple physiological processes including apoptosis induction [53]. Autophagy can either suppress apoptosis or promote cell death depending on the context [54]. The dysregulation of autophagy has been proposed to contribute to the development of numerous diseases including vital infectious diseases [55]. Vital infection can cause either autophagy activation or inhibition in host cells. Regarding the influences of PRRSV infection on autophagy, a number of studies demonstrate that the numbers of autophagosomes are elevated during PRRSV infection evidenced by the increase of double- or single-membrane vesicles, LC3 fluorescence puncta and LC-3 I/II conversion [56–63]. Inhibition of autophagosome formation by its inhibitor 3-methyladenine (3-MA) or silencing LC3 gene by siRNA leads to decreased yield of PRRSV [56] and increased apoptosis [61]. These results suggest that the autophagy induction by PRRSV promotes virus replication and protects the host cells from the virus-induced apoptosis. Further mechanistic investigations uncover that the autophagy induction by PRRSV exerts the pro-survival function associated with the formation of a complex between the autophagy-related gene Beclin1 and the pro-apoptotic protein Bad [61].

The activation of PI3K/Akt pathway facilitates viral replication and inhibits PRRSV-induced apoptosis

PI3Ks are heterodimeric lipid kinases that can be activated by receptor tyrosine kinases. The well-known downstream target for PI3K is AKT kinase which regulates various cellular processes, such as cell growth, proliferation, differentiation, transcription, translation, and apoptosis [64]. Akt exerts its anti-apoptotic and pro-survival effects through either inhibitory phosphorylation of some pro-apoptotic Bcl-2 family proteins such as Bax, Bad, and caspase-9, or activating some transcription factors which can up-regulate anti-apoptotic genes, such as CREB (cAMP response element-binding protein), IKB (inhibitor of kappa B) kinase, Bcl-2, MDM2 (murine double minute 2), Forkhead family [65]. It has been well documented that viruses and viral proteins interact with the PI3K/Akt signaling pathway during different steps of the viral life cycle, leading to effective viral replication [66]. A number of studies have demonstrated that the PI3K/Akt pathway is activated in response to PRRSV infection at the early stage [31, 59, 67–71]. The activation of PI3K/Akt is required for virus entry and promotes virus replication. Regarding the role of PI3K/Akt pathway in PRRSV-induced apoptosis, studies demonstrate that the Akt activation by PRRSV inhibited host cell apoptosis early in infection through negatively regulating the JNK pathway [31] and inhibitory phosphorylation of pro-apoptotic Bad [68]. Mechanistic investigations on PI3K/Akt activation by PRRSV reveal that both FAK [70] and EGFR [71] are induced by PRRSV, which in turn contributed to the activation of PI3K/Akt pathway.

Conclusion remarks

As discussed above, multiple signaling pathways have been suggested to be involved in regulating PRRSV-induced apoptosis in host cells (Fig. 1). These include Bcl-2 family protein-regulated mitochondrial pathway, TNFR1/Fas-mediated death receptor pathway and the up-stream regulators of these pathways such as JNK, UPR, oxidative stress, p53, autophagy-related signals, and PI3K/Akt pathway. Understanding of the molecular basis involved in PRRSV-induced apoptosis will promote the development of mechanism-based approach to manage this devastating infectious disease. To this end, a number of issues that need to addressed in future studies.

The mechanisms of JNK inhibition by p53

p53 plays a dual role not only in the regulation of cell death, but also in the modulation of redox. As mentioned above, the p53 activation protects the host cells from PRRSV-induced apoptosis through suppressing JNK activation. We hypothesize that the p53 activation by PRRSV infection exerts anti-oxidant activity, which in turn leads to the inhibition of ROS-JNK axis. Alternatively, p53 may directly bind to JNK and inhibit its activation. The first hypothesis can be tested by measuring the changes of p53-regulated redox-related proteins such as MnSOD, GPX1, Sestrins in the presence or absence of the activated p53 in response to PRRSV infection. Immunoprecipitation can be employed to examine the direct interaction of p53 with JNK to determine the contribution of the second hypothesis.

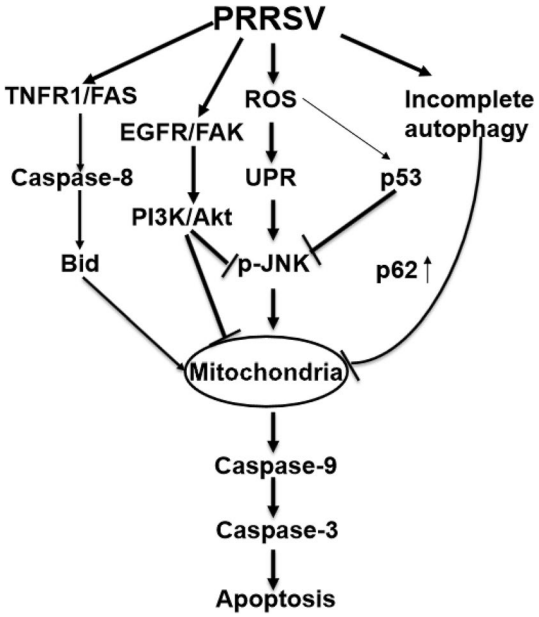

Fig. 1 Both Bcl-2 family protein-regulated mitochondrial pathway and TNFR1/Fas-mediated death receptor pathway are activated in response to PRRSV infection. The activation of oxidative stress, UPR and JNK triggers the activation of mitochondrial pathway, whereas the induction of p53, PI3K/Akt and autophagy inhibits PRRSV-induced apoptosis via suppressing the activation of JNK or mitochondrial pathway (*PRRSV* porcine reproductive and respiratory syndrome virus, *TNF* tumor necrosis factor; *ROS* reactive oxygen species, *UPR* unfolded protein response, *JNK* c-Jun N-terminal kinase, *EGFR* epidermal growth factor receptor, *FAK* focal adhesion kinase; arrow means activation; blunt line means inhibition; thick line means strong evidence; thin line means weak evidence)

The role of p62 in regulating PRRSV-mediated apoptosis

p62 is a multifunctional adaptor protein implicated in regulating autophagy, apoptosis, and oxidative stress. As an autophagy substrate, autophagosome degradation inhibition leads to accumulation of p62. It has been shown that PRRSV infection suppresses the fusion between autophagosomes and lysosomes, leading to accumulation of autophagosomes [57]. This suppression is supposed to cause p62 accumulation,

which may produce significant impact on PRRSV-induced apoptosis. Further studies may start with investigating the changes of p62 expression in response to PRRSV infection. If p62 is up-regulated by PRRSV, the functional role of p62 can be evaluated via genetic manipulation of p62 expression.

In vivo validation

The most findings mentioned above have been reported in cell culture models only; validation of the in vitro findings is necessary to ensure the clinical relevance and therapeutic significance. For examples, the activation of p53, JNK, and PI3K/Akt was observed in in vitro, it would be desirable to determine the contribution of these signaling pathways in PRRSV-infected pig model.

Acknowledgements This work was funded by grants from National Natural Science Foundation of China (NSFC, 31671945).

Compliance with ethical standards

Conflicts of interest The author has no conflicts of interest to disclosure.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals This is a review article and the article does not contain any studies with human participants or animals performed by the author.

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