ejpmr, 2025, 12(5), 706-713

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

VIRAL MANIPULATION OF HOST CELL DEATH PATHWAYS: EVASION OF APOPTOSIS, PYROPTOSIS, AND NECROPTOSIS

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Article Received on 25/03/2025 **Article Revised on 15/04/2025** **Article Published on 04/05/2025**

ABSTRACT

Host cell death pathways are designed processes programmed to maintain the immune system's homeostasis by monitoring host-pathogen interactions, determining disease severity and cynical progression, as well as clearing of infected host cells to inhibit viral replication and dissemination. Viral adaptiveness has however enabled varied weaponization against cell death pathways to ensure continuous survival. To this end, the host's cell death mechanism consequently adjusts to maintain its balance. Apoptosis is primarily the host's preferred cell death pathways at initial immune response. Reduced tissue damage during apoptotic activation makes it the immune response mechanism in the control of infection. This limits what could eventually result in an inevitable consequence of inflammation that's usually associated with pyroptosis and necroptosis. The three major cell death pathways are explored in this paper, with focus on their morphology and viral manipulative responses to each pathway's activation. The characteristic indexes used by viruses and viral pathogens in manipulating these cell death pathways to ensure survival are also discussed.

KEYWORDS: cell death, viral adaptiveness, inflammatory response, apoptosis, necroptosis, pyroptosis.

II. INTRODUCTION

Viral manipulation and adaptiveness to host's immune responses have helped evolve the viral pathogen activities. As a result, the importance of continuous studies into host-virus relationships becomes even more critical in order to understand viral adaptive strategies against host's responses. Responses are defence mechanisms designed to protect hosts against infections.

Inflammatory pathways, complement system activations, and immune cell recruitment to infected regions are initiated responses armed to neutralize infections.[1]

When initial responses remain unresolved in the host's infected conditions, the removal of infected cells from the organism is activated. This is achieved through the activation of cell death signaling pathways.[2] This is aimed at removing viral replications in isolated intracellular niche of pathogens.[3] Thereby exposing intracellular pathogenic activities to extracellular immune surveillance, before being engulfed by macrophages and dendritic cells.[4] This helps in activation of the adaptive immune system by the presentation of viral antigens to T cells.[5]

The adaptiveness of the immune system to combat viral infections have also contributed to the evolution of viral pathogenic strategies to subvert immune defences and modulate cell death. Inducing and suppression of host cell death are some of the adaptive strategies which may facilitate replications, immune cells elimination and evasion of host's defences.[6] Pore-forming toxins are also weaponized features used by viruses to evade the host's defence. This permits extracellular leakage of enzymes, effector proteins and other cellular components, which are then delivered by specialized secretions systems and immune cells targeting superantigens, into the host's cytosol.[7]

Apoptosis, Pyroptosis and Necroptosis are mechanisms that facilitate programmed cell death (PCD) occurrence. PCD is a regulated death system designed to remove damaged or unwanted cells. As components of the host's defense system, structured against infections such as viruses, cell death modes are distinct in morphological changes and molecule signaling pathways. This essay discusses the distinctness of each cell death mode, their inductive pathophysiological consequences, their biochemical basis, and viral infection modulation.

1.0 Apoptosis

Morphology and Biochemical Features

Apoptosis is programmed way cells self-destruct without harming other surrounding tissues to maintain

homeostasis and ensure proper embryonic development.[7] Plasma membrane blebbing, cell body shrinkage (pyknosis), and fragmentation (karyorrhexis) make up core morphological features of apoptosis.[8]

Its biochemical features are characterized by a decrease in the mitochondria's inner transmembrane potential, activation of selective proteases, cleavage of chromosomal DNA into internucleosomal fragments, selective cleavage of cellular proteins, and phosphatidylserine (PS) transfer within the plasma membrane from the inner chamber to the outer leaflet.[9][10] The apoptotic bodies transferred to the outer leaflet are then phagocytosed in by neighboring cells and resident phagocytes.[11]

The production of inflammatory cytokines by macrophages may be prevented when apoptotic cells are engulfed, suppressing dendritic cell maturation and antigen presentation.[12] The absence of cytoplasmic content spillage into extracellular milieu enables apoptosis activation without eliciting inflammatory response.

The changes in biochemical and morphological features are evidence of its evolutionarily conserved cell suicide mechanism centred around a core family of cysteinyl aspartate-specific proteases (caspases).[13]

1.1 Apoptosis Signaling Pathways

The initiation and execution phases make up the signaling pathway in apoptosis. The initiator caspases containing large predomains are first recruited in a large protein complex. The caspases contained include -2, -8, -9, and -10.[14] They undergo proximity-induced oligomerization and interchain autoprocessing in the protein complex, where they attain maturation for the execution phase.[15]

1.1.1 Initiation Phase

At this stage, initiator caspase activation takes place following a two-stage process, comprising the intrinsic and extrinsic pathways.[16] The activation of initiator caspases is usually masterminded by Death-inducing signaling complex (DISC), and apoptosome complexes.[17] The intrinsic and extrinsic pathways communicate through the activation of Bcl-2 homology domain 3(BH3) - only protein Bid.[18]

a. Extrinsic Pathway

The bending of extracellular death receptor ligands to their respective transmembrane receptors triggers the extrinsic pathway.[19] The death receptor ligands include tumor necrosis factor (TNF), Fasligand (FasL),and TNF-related apoptosis-inducing ligand (TRAIL).[20]

Death receptors are active agents for several immunological processes.[21] An example of such importance can be noted with Fas, where mutation disease is characterized by uncontrolled production of B cells. Receptor aggregation in the gene encoding Fas are apparent in several cases of lymphoproliferative disorder.[22] Epstein-Barr virus (EBV), a common cause of post- transplant lymphoproliferative disorder (PTLD), responds to FasL binding, initiates the formation of the DSC in EBV-infected B cells, where the adaptor molecule F associated death domain (FADD) serves as platform for recruitment and activation of caspases 8 and 10, thereby reducing the burden of PTLD-associated tumors.[23]

b. Intrinsic Pathway

The intrinsic pathway is initiated by the release of apoptogenic proteins from their mitochondrial intermembrane space into the cytosol.[24] Released apoptogenic proteins such as cytochrome c are associated with the adaptor protein Apoptosis protease activating factor-1 (Apaf-1) to form the apoptosome complex.[25] After which the respective initiator caspases proteolytically activate the executioner caspases (caspases -3, -6, and -7). This is achieved by releasing the executioner caspases from their shorts inhibitory prodomain.[26]

Processed executioner caspases are released from their endogenous X-linked inhibitor of apoptosis (XIAP) by mitochondrial death proteins. The presence of its characteristic N-terminal IAP binding motifs (IBM) in mitochondrial death proteins facilitates the isolation of XIAP.[27] Examples of the mitochondrial death proteins include such as HtrA2/Omi and SMAC/Diablo.[28] Viral infections may trigger intrinsic pathway initiation, Chemotherapeutic drugs and UV irradiation can also be a trigger.[29]

1.1.2 Execution Phase

The released mature caspases (-3, -6 and -7) cleave a large set of substrates which is characterized in the morphological and biochemical features of apoptosis.[30]

1.2 Viral Evasion of Apoptosis

Evasion strategy is critical for the continuous survival of viruses. Preventing apoptosis activation facilitates intracellular replication and survival. By using virus-encoded proteins that interfere with caspase activation or inhibit caspase activity, there is a constant evolution of viruses, to tackle the apoptotic adaptiveness.

Encoding of viral protein during regulated death receptor-mediated apoptosis is done in several different ways by viruses. They are, however, targeted at upregulating death receptors or their ligands on the cell surface of the plasma membrane of infected individuals, increasing sensitivity of the cells to death receptor-mediated apoptosis.[31]

HIV-1 patients have shown increased expression of Fas antigens in CD4- and CD8- which alters related cell sensitive FasL/Fas mediated apoptosis.[32] This results in depletion of T- lymphocytes in individuals with HIV

infections.[33] TRAIL mediated apoptosis in primary CD4+ is induced on infection, regulated by IFN-α produced by HIV-1- stimulated plasmacytoma dendritic cells (pDCs).[34]

The upregulation of TRAIL in primary macrophages activates apoptosis in bystander T cells and neuronal cells. Sensitization of T cells to Fas-activating apoptosis is done by HIV-1 proteins Tat, Vpu, gp120 and gp160, contributing to T cell depletion in AIDS.[35]

Hepatitis viruses (HPV) also contribute to significant increase in Fas protein expression on PBMCs of chronic hepatitis virus (HCV)-infected patients.[36] This increase in Fas protein sequentially makes the hepatocytes more sensitive to TRAIL-induced apoptosis due to the increased presence of DR4 and DR5 proteins.[37]

2.0 Necroptosis

Morphology and Signaling Pathway

Viruses can induce necroptosis through several signaling pathways involving ligand–receptor binding including TNF-α/TNFR, Fas ligand/FAS, interferon-gamma (IFN-γ)/IFNAR1, double- stranded RNA/Toll-like receptor 3 (TLR3), and double-stranded DNA/Z-DNA binding protein 1 (ZBP1).[38]

Caspase-8 is generated on homodimerization of pro-caspase-8, which is recruited on binding RIPK1 to FADD.[39] However, FADD and caspase-8 interaction is restricted by the RIPK1 to FADD binding.[40] This restriction is facilitated by Ankyrin repeat domain-containing protein 13a (ANKRD13a) with ubiquitinated-RIPK1.[41] The facilitation is done using the Ub-interacting motif.[42] As a result of cIAP1/2-mediated polyubiquitination at Lys115 and Lys377 of RIPK1, its interaction with ANKRD13a and complex II formation are regulated.[43][44]

RSK1 is activated by the induction of PDK1 via phosphorylation at the Ser221 site of the RSK1 NTKD domain, after which it is recruited to the necrosome where it phosphorylates.[45] Cis- autophosphorylation on necrosome formation activates RIPK3, stimulated by RIPK1.[46] After that, the RHIM domain of RIPK3 mediates its interaction with RIPK1.[47] The resulting RIPK3- RIPK1 complex recruits MLKL.[48]][49] MLKL is the primary necroptosis executor.

The activation of ZBP1 occurs when the Na+/H+ exchanger SLC9A1 elevates cytoplasmic pH, thereby stimulating RIPK3 kinase activity.[50] Activated ZBP1 binds with phosphorylates RIPK3 to recruit phosphorylates MLKL which oligomerizes before binding to phosphatidylinositol and cardiolipin.[51] The whole necrosome is then translocated to the cell membrane or organelle membrane from the cytoplasm, forming permeable pore which leads to the activation of necroptosis on inducing membrane rupture.[52] Thus, phosphorylated MLKL accumulating at intercellular junctions drives necroptosis in neighboring cells.[53]

2.1 Viral Evasion of Necroptosis

Proteins with receptor-interacting protein (RIP) homotypic interaction motifs (RHIMs) are critical in necroptotic signalling.[54] RIP kinase 1 (RIPK1), RIPK3, TIR-domain-containing adapter-inducing IFN-β (TRIF), and Z-DNA-binding protein 1 (ZBP1) are four RHIM-containing protein expressions.[55]

Viruses are however able to block signaling cascades by inhibiting key proteins such as RIPK3. This increases the likelihood to survive and replicate within the host cells, ultimately blocking the host's immune responses.

Herpes simplex virus 1 (HSV1), and HSV2 encode inhibitors that block both caspase-dependent apoptosis and receptor- interacting protein (RIP)-kinase-mediated necroptosis.[56]

3.0 Pyroptosis Pyroptosis Morphology

Pyroptosis, an inflammatory cell death, triggers inflammatory responses in surrounding tissues. Pyroptosis is triggered by inflammatory caspases such as caspase -1/4/5/11, and characterized by cell lysis and inflammation, which results in the cleavage of gasdermin D (GSDMD) and secretion of inactive cytokines interleukin (IL)-18 and IL-1β.[57][58][59] Pattern recognition receptor (PRR) stimulates inflammatory response on recognition of pathogen associated molecular pattern (PAMPs) induced by invading pathogens.[60] Damaged-associated molecular patterns (DAMPs) derived from endogenous pathogens are also recognized by PRR.[61]

On recognizing PAMPs and DAMPs, PRR induces a huge formation of supramolecular assembly of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), which links leucine-rich repeat containing receptors (NLR) to caspase -1.[62] Toll-like receptors (TLRs), nucleotide-binding domain and leucine-rich repeat-containing receptors (NLRs) and absent in melanoma (AIMs) like receptors are some of the members of the PRR family.[63] Amino terminal protein-protein interaction domain such as N-terminal caspase recruitment domain (CARD) or pyrin domain (PYD), intermediary NACHT domain required for nucleotide binding and self-oligomerization, carboxy-terminal leucine rich repeat (LRR) motifs involved sensing viral molecules share a domain organization with the PRR family.[64]

PAMPs represent cell wall components alien to mammalian cells but unique to viruses in their nucleic acid structures.[65] As a result, distinct inflammasomes are assembled depending on the infectious agent. Ipaf, Nlrp1b, Nlrp3 are some of the released inflammasomes upon viral infections.[66]

Cell swelling, rupture of the plasma membrane, the secretion of the intracellular proinflammatory substances, and chromatin fragmentation are characteristic features of pyroptosis.[67] Swelling and osmotic lysis are a result of water influx from inflammation- induced pore formation. Nucleuses also remain intact despite undergoing chromatin condensation and DNA fragmentation.[68]

3.1 Pyroptosis Signaling Pathways

The execution of pyroptosis occurs in two forms. The canonical pathway and the non-canonical pathway.[69]

Inflammasomes, playing a crucial role in the canonical pathway activation, facilitating the cleavage of cell membrane perforating gasdermin D after caspase-1 activation.[70] While the non-canonical pathway uses caspase -4, -5, and -11 activation in activating a cell membrane rupturing gasdermin D cleavage.[71]

3.1.1 Canonical Inflammasome Pathway

It is dependent on the formation of inflammasomes, the activation platform for caspase-1.[72] Activated inflammasomes recruit ASC adaptors while the NLR or AIM2 signaling domains (PYD or CARD) are connected to ASC to form ASC focus by homotypic interactions.[73] The ASC initiates the canonical pathway by recruiting and activating caspase-1 through pro-caspase- 1 autocleavage, resulting in gasdermin D cleavage.[74]

Activated caspase-1 cleaves IL-1β and IL-18 into their forms, cleaving off a C-terminal inhibitory fragment from the pore-forming protein GSDMD, and forming oligomeric pores after the N-terminal part of GSDMD has been transferred to the plasma membrane, resulting in cell lysis.[75][76] Cell lysis and swelling are associated with pyroptosis and are often accompanied by the secretion of the proinflammatory mediators HMGB1 and IL-α, leading to inflammatory reactions.[77]

Canonical inflammasomes include Nod-like receptors (NLRP1, 3, NLRC4) and AIM2. They all possess N-terminal caspase recruitment (CARD) or pyrin domain (PYD).[78] The inflammasomes activates caspase -1 on contacting PRRs with PAMPs and DAMPs.

Inflammasome activation can be induced by specific PAMPs and DAMPs. NLRP1 inflammasome only recognizes anthrax lethal toxin and muramyl dipeptide.[79] NLRC4 inflammasomes only recognizes PAMPs like flagellin and muramyl dipeptide, and AIM 2 inflammasomes are activated specifically by double-stranded DNA (dsDNA), which is endogenous or pathogen-derived.[80][81] NLRP3 inflammasomes can be more accommodating in stimulating species.[82] Reactive oxygen species (ROS), mitochondrial DAMPs, bacterial pore-forming toxins and extracellular RNA, crystalline structures like monosodium urate and cholesterol are stimulating species for NLRP3.[83]

3.1.2 Non-canonical Inflammasome Pathway

This pathway is triggered by caspase-11 on binding with lipopolysaccharide (LPS).[84] LPS are host-derived oxidized phospholipids which on binding to caspase -11, helps induce pyroptosis.[85] Activate caspase -11 can also activate caspase -1 through GSDMD cleavage.[86] The non-canonical Inflammasome pathway can also be induced by caspase -4 and -5 in human beings.[87]

3.2 Viral Evasion of Pyroptosis

The SARS-CoV-2 nucleoprotein binds the GSDMD linker region in order to block GSDMD cleavage[88]. This suppresses GSDMD-mediated pyroptosis and cytokine release.[89] A 3C-like protease of TGEV, like Enterovirus 71 protease 3C, incorrectly cleaves GSDMD, thereby producing a non-functional N-terminal.[90]

The high inflammatory form of programmed cell death makes it an ideal consequence for cytopathic viruses, playing a vital role in the non-lytic secretion of inflammatory cytokine.[91] By inducing non-lytic secretion of inflammatory cytokines, cytopathic viruses are able to trigger immune responses and potentially contribute to disease pathogenesis.[92]

4.0 CONCLUSION

Viral antagonism of apoptosis, necroptosis, and pyroptosis contributes immensely to virulent activities in the host's defensive mechanism.[93] Frequent studies over the years have helped with understanding of host-pathogen interactions. The complex and evolving nature of this interaction however enhances the need for continued research on this interaction in order to maintain a healthy balance between the host's defensive structure and pathogen's virulence mechanism.

Three major death modes - Apoptosis, necroptosis and pyroptosis can each be activated upon viral infections. Pathogen's nature, load, attack mechanism and site of attack determines the programmed cell host pathway deployed against infectious agents.[94] The immunological silence of apoptosis makes it the primary defense mechanism for the host.[95] Consequently, the need for inflammatory interventions leads to the deployment of necroptosis and pyroptosis.[96] Secretion of proinflammatory cytokines and the extracellular release of the cytosolic content are characteristic features of pyroptosis and necroptosis.[97]

While the success of viruses in evading these cell death pathways may negate the progress made in viral studies and elucidated molecular mechanisms of necroptosis and pyroptosis, insights could be analytically structured into modifying current effectiveness, interactive characterization, and characteristics features enabling the evolving nature of viral pathogens in evading cell death pathways.

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