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Review Article

An Overview of Apoptosis in Microbial Infections: Novel Therapeutic Implications and Challenges in Pathogenesis

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Abstract

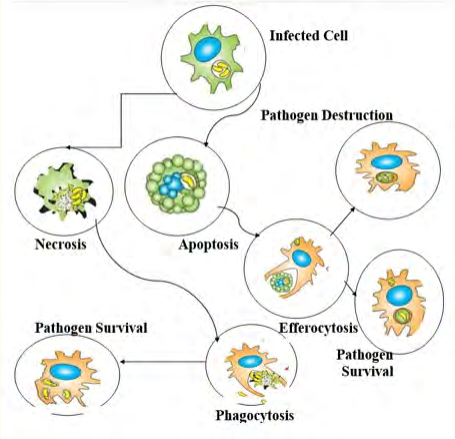
Background: In recent times, there has been a significant increase in studies investigating the mechanisms of microbe-induced host cell death. In addition, pathogens employ several strategies to manipulate host cell death pathways to aid their survival and spread.

Objective: We have described key differences and similarities between the mechanisms used by microbial pathogens to induce apoptotic or anti-apoptotic effects on hostcells.

Review: In this review, these mechanisms were investigated by comparing apoptotic pathways in host cells infected with obligate intracellular, facultative intracellular and extracellular microbes (including bacterial, viral and fungal).

Conclusion: This review paper summarizes what we know recently know about the role of apoptosis in response to a range of microbial infections and examines how cell death pathways may influence immunity against pathogens. However, since apoptosis is also involved in host defense mechanisms against infectious agents, this phenomenon plays an important role in host-pathogen interactions. As apoptosis is a fundamental process in response to such microbial infections, it may be a therapeutic target for the treatment.

Keywords: Apoptosis; Pathogenesis; Microbial Infection; Defence Mecahnisms



Graphical Abstract

Introduction

Apoptosis is defined as cell death activated by a locally regulated self-slaughter program and involves the finely orchestrated disassembly of cellular components designed to eliminate unwanted cells in various physiological processes during embryogenesis. During apoptosis, dead cells are removed with minimal disturbance to the surrounding tissue. However, apoptosis also occurs under pathological conditions and is sometimes accompanied by necrosis [1].

Although suppuratory response of phagocytosis of pathogenic microorganisms and non-inflammatory phagocytosis of each apoptotic cells have been broadly described, the effects of natural immune response of host cells tolerating apoptosis as a interrupted result of infection remain to a certain degree unclear. The ensuing microbial infections the nonspecific immune system is attacked with varied actions, nearing from one and the other of apoptotic tissue and infectious pathogens. Downstream of apoptotic cells is recognition with help of nuclear receptor activation. At the same time during microbial infection, toll-like receptors act as prototypical inflammasome receptors. When the two signals converge, a novel cascade of events occurs, beginning with the modulation of a subset of inflammatory response genes and ending with the induction of an adaptive immune response. This type of immune response is well befitted to clear the infectious agents and regulate the damage to host cells for the time of infection [2].

A different diversity of microbes (Bacteria, Viruses, Fungi and Parasites) occupied cells to make use of cell content materials and replication themselves and also killed infected host cells frequently. The new daughter viral infectious agents conquered others, repeatedly close by cells, thus extending the parasite's life cycle. When a cell detects that it has such an infection and is about to die, it stops the parasite's reproduction by enhancing a mechanism ofprompt cell demise, preventing it from spreading to other associated cells substantially [3]. The goals of a particularized microbe are normally single cells that are similar to the earliest cellular host. Through this system, microbes infected cells undergo apoptosis, preventing the spread of infection to clone mates and other susceptible cells, contributing to broader featuresof survival of the whole microorganism. Dynamic cell demise in response to infection is therefore most of the prompt forms of immune response [4]. Because host microbes' interactions will change effectively, microbes develop mechanisms to deter like prompt cell demise and so enhance their own cell will change quickly and explicative capacity [5].

Currently, there is no proof to as strong support the continuance of a base molecule cycle that mediates apoptosis at single cell microorganisms induced at requital to inflammation. Some microbes have been isolated to undertake cell demise with outermost properties of apoptosis [6], but still whether these mechanisms are relevant to metazoans remains to be seen. However, using the principles of providence and other theories, it is possible to draw conclusions about the properties of cell death in a common ancestor by comparing organisms from different kingdoms. As we acquire a more knowledge of the apoptosis pathways in varying degrees of microorganisms, this type of apoptotic and injured monocytic derivatives are singly enhanced during *Mycobacterium tuberculosis* infection of monocytic derivatives like macrophages [7]. Disease-causing factors affect the degree of hostess cell inflamed and the capability to suppress apoptosis, while other species specific properties enhance the final step of hostess cell inflamed and change the remaining part of apoptosis [8]. In this review, we discuss the key mechanisms used by obligate, intracellular, facultative intracellular and extracellular microbes to induce apoptosis and the relationship between these phenomenons. The molecular characterization of apoptosis and interactions between host and microbial cells are also discussed.

Bacterial infection and apoptosis relationships

Macrophages affected by *Mycobacterium tuberculosis* can suffer both apoptosis and necrosis of cell demise and it has entirely alternate results for the course of infection. Apoptosis is a type of cell death in which a series of molecular steps in a cell lead to its death and consequence in the directive formation of apoptotic vesicles and degradation of cellular contents. It also has been illustrated that apoptotic type death of macrophage affected by is straight relevant to mycobacterial type of killing [9] and can stimulate the consecration of cellmediated immune responses through the antigen presentation switching pathway [10]. Further, necrotic types of cell death are related to disordered, energy independent cell death, despite current studies recommending that necrosis may pursue a rigid managed and programmed sequence of affairs [11]. In *M. tuberculosis* infection, a necrotic death has been detected and

also illustrated to permit the deliverance of living Mycobacterial species followed by re-infection [12]. Necrotic type of cell demise may be a key factor in inflammatory tissue destruction, granuloma formation and eventually bacterial diffusion.

Most of the review reports have shown that virulent *M. tuberculosis* strains use suppression of apoptosis as a pathogenic mechanism and that its consequences depend on the proliferation of the infection and the relative diseases causing strain of the mycobacterial. Virulent *M. tuberculosis* causes low levels of macrophage apoptosis at low diversity of infection than attenuated or saprophytic *M. tuberculosis* complex organisms are demonstrated [13]. On the contrary, *M. tuberculosis* infection induced necrosis-like cell death at high concentrations through a CICD (Caspase Independent Cell Death) mechanism [14] and most of the studies reported that lethal strains of *M. tuberculosis* stimulate macrophage necrotic death [15]. Therefore it has become a distinguished specimen that pathogenic *M. tuberculosis* suppresses apoptosis, as the same time pathogenic *Mycobacterium* stimulatesapoptosis. Moreover, *M. tuberculosis* individual genes intricate have been discovered in apoptosis suppression [16] and when there is no gene, pro-apoptotic phenotype has been observed.

Salmonella species (*Salmonella enteric)* is a most predominant enteric disease causing pathogenic microorganism of human beings, various wild and domestic animals. It can cause localized enteritis and disseminated systemic disease in humans and vertebrates [17]. *Salmonella* species can spread from the gut and cause harmful, once in a while lethal infections along with significant cytopathology in various organs. An amalgamation of cell biology and bacterial genome investigation has demonstrated that *Salmonella* utilize precise virulent mechanisms to stimulate the host cell demise in the course of infection. *Salmonella* has generated one set collection of virulent proteins to propagate intestinal invasiveness activity and another acted upon systemic disease. Notably, each virulence factor mediates a unique process of apoptosis. The *Salmonella* pathogenesis locus gene encodes with a type 3 protein secretary system (TTSS) that provides effective proteins necessary for intestinal invasiveness and production of intestinal inflammation. *Salmonella* pathogenic effectors gene activates caspase-1 factor in macrophages, causing IL-18 and IL-1b release and triggering rapid cell demise by a vital mechanism with characteristic of either apoptosis or necrosis. *Salmonella* requires caspase-1 to affect the GALT like Peyer's patches and spread to multiple organs in mice. *Salmonella* infect to the mice with support of the pathogenesis TTSS and the SpvB cytotoxin and associated effectors proteins progressive. Macrophages apoptosis is detected in the multiple tissues of the liver [18].

Bacterial strains can stimulate either necrosis or apoptosis by various mechanisms directly or indirectly [19]. In many pathogenic reports, a detailed analytical mechanism of cell death has not been carried out due to bacterial infection. By choice, the analytical mechanism has been detected as necrosis or apoptosis based on the cell biological markers. Sometimes, a combined process is oncosis described [20] and programmed necrosis [21].

Key differences and similarities in the mechanisms used by bacteria to induce apoptotic or anti-apoptotic effects on host cells are described. These mechanisms were investigated by comparing apoptotic pathways in host cells infected with obligate intracellular bacteria and facultative intracellular and extracellular bacteria. The key pathogen-induced events discussed here are specific to each pathogen and include activation of caspases, mitochondrial alterations, and activation of MAPK kinases. Elucidation of the signaling pathways, cellular receptors and bacterial factors involved in the induction of apoptosis may reveal new therapeutic targets to inhibit bacterially induced apoptosis. The development of drugs towards such targets should provide us with new tools to treat many diseases caused by bacterial pathogens [22].

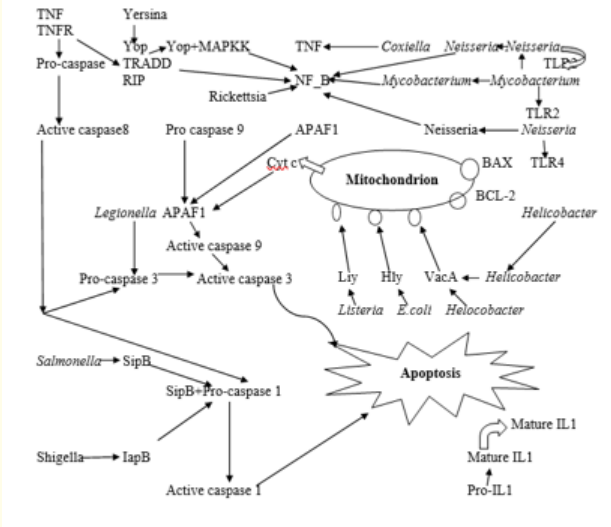


Figure 1: Key Mechanisms bacteria induced cell apoptosis.

Broken lines represent the cellular membrane, which separates the extracellular and intracellular environments. Apoptotic pathways induced by *Helicobacter pylori* (through the action of VacA in mitochondria), *Neisseria* (via NF B activation of the apoptotic mechanism), *Escherichia coli* (apoptosis initiated by the action of hemolysin normally associated with mitochondria) and the pathogens Listeria (Lly action), *Yersinia* (activation of MAPKK and NFκB pathways), apoptotic processes have been shown in *Shigella*, *Salmonella* (caspase 1 activation pathway), *Legionella* (caspase 3 apoptotic activation pathway), *Mycobacterium*, as well as strictly intracellular pathogens and *Coxiella* (similar to the mechanism of *Neisseria*-induced cell apoptosis) (Figure 1) [23].

Viral infection and apoptosis relationships

Viral infection has also been affected by the apoptosis of host cells through tumour necrosis factor stimulation and direct viral cytotoxicity. While Influenza viruses and Adenoviruses induce apoptosis, Baculoviruses can inhibit apoptosis. Chronic Hepatitis C virus (HCV) infection differentially moderate the apoptotic machinery during infection, where the virus induces apoptosis early in the course of infection and apoptosis is modulated as the disease progresses [24]. Although the exact pathogenesis of HCV are not fully observed (such as viral persistence, hepatocyte injury and hepatocarcinogenesis), it suggests that apoptosis of hepatocytes is seriously complicated in pathogenic mechanisms [25]. Apoptosis has maintained cellular homeostasis by damaged cells, eliminating senescent cells and excess new cells [26].

Several studies of Reovirus infection have proven to be a better experimental method for studying the mechanisms of virus stimulated pathogenesis. Reoviruses stimulate apoptosisin target tissues and cultured cells of heart and CNS [27]. *In vivo*, viral infection, necrosis and apoptosis co-localized infections, with disease is induced in the host by apoptosis due to the important mechanism [28]. Several review reports have explored the potential of inhibiting apoptosis as a new ideology to control virus-causing tissue damage mechanisms following infection.

Baculovirus have been inhibitors of apoptosis (IAP) found to suppress apoptosis in tissue response to a large number of stimuli [29]. Several reviews have proven that the Baculovirus and other few virus genes have inhibited IL-1 converting enzymes (ICE) that reduce apoptosis [30]. Additionally, it also promotes the viral pathogenic process by inhibiting the inflammatory response to viral infection [31]. Virus latency is an important factor for example, in Epstain Barr Viral gene is expressed during latency, which upregulates viral gene expression, initiating a beneficial habitat for late infected cells [32]. Moreover, transfection of LMP-1 can be rendered apoptosis-sensitive B cell lines into apoptosis-resistant B cell lines. Sometimes apoptosis can present in severe acute respiratory syndrome (SARS). When this occurs, invasive cells of monocytes in infected tissue may play an important role in the progression of SARS [33]. Moreover, several review reports have proven that during the SARS virus pathogenesis, the Spleen, lung and lymph node being a low number of T and B cells factors. In this situation SARS virus may have an immune related cell killing effect [34].

Viruses can induce apoptosis of infected cells either directly, to aid viral spread, or by inadvertently triggering cellular sensors that initiate cell death. Cellular checkpoints that can act as 'alarm bells' to transmit pro-apoptotic signals in response to viral infections include death receptors, protein kinase R, mitochondrial membrane potential, p53 and endoplasmic reticulum [35]. Many cells undergo apoptosis in response to virus infection, resulting in reduced release of progeny virus. Viruses have therefore evolved many different mechanisms to modulate host cell apoptosis. Viruses can interfere with highly conserved effector mechanisms of programmed cell death or regulatory mechanisms specific to mammalian cells. In addition to providing a selective advantage to the virus, the ability to inhibit apoptosis plays an important role in the transformation of the host cell by oncogenic viruses [36].

AIDS and Apoptosis relationships

Human Immunodeficiency Virus (HIV) is a causative agent of Acquired ImmunoDeficiency Syndrome (AIDS). HIV stimulates the inappropriate induction of CD4+ T cell apoptosis [37]. Genes of mRNA transcription may be infected by viral transcription genes in gene dot cell survival. Thus, the tat gene may protect cells from apoptosis through the gene systematize the expression of the B-Cell lymphoma 2 oncogenic protein [38]. HIV infected individuals have peripheral blood T cells, being an highly susceptible to artificially induced cell death, It is a fact that has been known for a long time and Apoptosis can be rapidly induced by incubating T cells from HIV patients [39] and is accelerated to several degrees by a many

inducers like as mitogens. The number of apoptotic cells may also significantly increase by Superantigens [40]. T cells from lymph nodes and peripheral blood of HIV patients express those which are important factors in the Pre-apoptotic process such as tissue transglutaminase (tTG) and a Ca2+-independent enzyme [41]. It was known that the subset of CD4 play a major role of trigger for apoptosis, furthermore the subset of CD8 cells may also engaged in HIV infections [42]. Compared with control cells expressing activated T lymphocytes, it was observed that they were more prone to apoptosis [43].

Apoptosis is likely to occur not only in infected cells but also in neighbouring cells due to the demonstration of the histopathology of thymus and lymph nodes of HIV patients [44]. Approximately 50% of peripheral blood lymphocytes from HIV patients undergo apoptosis. Thus, the ex vivo experiments proved to be similar to the *in vivo* experiments [45].

S. No	Microorganisms	Apoptosis	Proposed/Demonstrated mechanisms	Cell type
Bacteria				
1	*Pseudomonas aeruginosa*	Induction	Fas/Fas ligand system,Cytochrome c release	Endothelial cells, Epithelial cells
2	*Neisseria gonorrhoeae*	Induction	Increases mitochondrial permeability	Epithelial cells
3	*Shigella flexneri*	Induction	Caspase 1 activation, Extrinsic and intrinsic pathways	Macrophage, Epithelial, endothelial, neurons
4	*Salmonella typhimurium*	Induction	Caspase 1 activation	Macrophages
5	*Listeria monocytogenes*	Induction	Cytochrome c release	Hepatocytes, lymphocytes
6	*Yersinia pseudotuberculosis*	Induction	Inhibits ERK and theNFKB	Macrophage, dendritic cells
7	*Yersinia pestis*	Induction	Caspase 1 activation,Inhibits ERK and the NFKB	Macrophages
8	*Legionella pneumophila*	Induction	Caspase 3	Macrophages, epithelial cells
9	*Escherichia coli*	Induction	Extrinsic and intrinsic pathways	Epithelial cells
10	*Mycobacterium tuberculosis*	Induction	TNF pathway	Macrophages
11	*Helicobacter pylori*	Induction	Action of VacA	Mitochondria
12	*Coxiella*	Induction	Increases mitochondrial permeability	Epithelial cells

Viruses				
13	Hepatitis C virus	Induction	Extrinsic pathway	Cytotoxic T lymphocytes,macrophages
14	HIV-1 gp120 protein	Induction	Fas pathway	CD4+ T cells
15	HIV-1 proteins Env	Induction	p53-dependent genes Puma and Bax	CD4+ T cells
16	HIV Nef	Induction	Extrinsic pathway	CD4+ T cells
17	Rabies virus	Induction	Expression of Bax andcaspase 1, Caspase gene Nedd-2, Activation of caspase 8, Upregulation ofAIF	Neuroblastomacell, Neurons
18	HPV E2 protein	Induction	p53 pathway	HeLa cells
19	HPV E6 protein	Induction	Degradation p53 pathway, Extrinsic pathway, Caspase inactivation	Epithelial cells,Cervical carcinoma cells, fibroblasts, osteosarcoma cells
20	HPV E7 protein	Induction	Retinoblastoma gene	Lens
21	Adenoviral proteins	Induction	p53 pathway	REF52 cells

Table 1: Microorganisms that induce host cell apoptosis [46].

Fungal infections and apoptosis relationships

Apoptosis is a highly complex form of programmed cell death, involving an energy- dependent cascade of molecular and cellular events. It represents a vital part of the immune response to pathogens, which leads to the destruction of the intracellular niche of microbial replication. Furthermore, elimination of pathogen-containing apoptotic bodies by secondary phagocytes and presentation of antigens derived from apoptotic material by dendritic cells (DCs) represent important antimicrobial effector mechanisms [47]. Pathogenic fungi have therefore evolved multiple distinct mechanisms for modulating host cell apoptosis. Notably, the demise of key immune effector cells by apoptosis represents a central mechanism to evade host defences and ensure pathogen survival.

Opportunistic fungal infections and apoptosis relationships

The data support an important role for apoptosis against microbial infections [48]. *Candida*, *Cryptococcus* and *Aspergillus* seem to employ common strategies to manipulate this important pathway to benefit their own survival. The three opportunistic pathogens hijack the host apoptotic machinery to induce the death of immune effector cells and evade host defence. Toxin (e.g., gliotoxin in *Aspergillus* infection), secreted proteases (e.g., Saps in *Candida* infection) or other virulence factors (e.g., capsular constituents in *Cryptococcus* infection) appear capable of directly activating the host apoptotic machinery. However, *C. albicans* and *A. fumigatus* can also activate a PI3K/Akt survival pathway and promote host cell survival. This observation is reminiscent of pro-survival and anti-apoptotic mechanisms that have been described in the context of viral [49] and bacterial infections [50], which appear central to pathogenesis. Therefore, not only viruses and obligate intracellular bacteria, which are highly dependent on host cell survival, but many other human pathogens, activate cell survival pathways in order to maintain their replicative compartment, further suggesting that this may represent a more widespread strategy. *C. albicans* and *A. fumigatus* may activate PI3K/Akt and inhibit apoptosis in order to provide a protective niche for yeast cells/conidial survival and dissemination within the host.

Furthermore, both fungi possess the ability to form filamentous hyphae, which represents the main virulence factor associated with the pathogenesis of *Candida* and *Aspergillus* diseases. Since yeast cells and conidia may be more susceptible to host defence mechanisms than hyphae, it might also be speculated that activation of survival pathways andinhibition of host apoptosis may provide temporary protection against phagocyte killing thus allowing the fungus to filament and escape from immune surveillance [51].

Conclusion

In this review, we have described key differences and similarities between the mechanisms used by microbial pathogens to induce apoptotic or anti-apoptotic effects on hostcells. Pathogen-induced cell death can occur by a variety of complex mechanisms, including apoptosis, necrosis, necroptosis, pyroptosis and etosis.

Host-pathogen interactions and their role in cell death are highly complex, involving a fine balance between pro- and anti-death strategies for both host and pathogen. The study of fungal-induced programmed host cell death suggests that this phenomenon is not a random event during infection, but rather a regulated process with significant implications for disease pathogenesis and host responses. The effect of host cell death on shaping immune responses in the context of fungal infection is highly dependent on many variables such as host cell type, fungal species and strains, specific fungal regions and secreted molecules.

These mechanisms were investigated by comparing apoptotic pathways in host cells infected with obligate intracellular bacteria. The key microbe-induced events discussed here are specific to each pathogen and include activation of caspases, mitochondrial alterations, and activation of MAPK kinases. Elucidation of the signaling pathways, cellular receptors, or bacterial factors involved in the induction of apoptosis may reveal new therapeutic targets for inhibiting bacterial-induced apoptosis. The development of drugs towards such targets should provide us with new tools to treat many diseases caused by bacterial pathogens.

These mechanisms were investigated by comparing apoptotic pathways in host cells infected with obligate intracellular, facultative intracellular and extracellular microbes (including bacterial, viral and fungal).

Apoptosis inhibition helps microbes replicate and survive in the host.

A clear understanding of the molecular basis of apoptosis inhibition or induction is needed.

Elucidation of the mechanisms, cellular receptors or microbial factors involved in modulating apoptosis may reveal insights into the host-pathogen relationship and new therapeutic targets.

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