

# Mechanism of Host Cell Death in Response to Bacterial Infections

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## Abstract

Viral and microbial infections often elicit programmed cell death as part of the host defense system or as a component of the survival strategy of the pathogen. Pathogens have evolved an array of toxins and virulence factors to modulate host cell death pathways. By inducing host cell death, bacteria and viruses eliminate key immune cells and evade host defenses that can compromise their viability. Apoptosis, necrosis, and pyroptosis represent the three major programmed cell death modes during infection, and the choice of death mode depends on a variety of factors, including the nature of the pathogen, pathogen load, and the site of infection. Further insight into the complex relationship between hosts and pathogens will be gained by further elucidating the molecular mechanisms underlying necrosis and pyroptosis, as well as by characterizing new mechanisms by which microbes induce and evade apoptotic, necrotic, and pyroptotic cell death in their hosts.

**Keywords:** Apoptosis; Cell death; Bacterial infection; Factors

## Introduction

Host cell death has been a very significant focus of biological research for years. A broad array of investigations and studies is concerned with this persuasive fact. Death of cells can occur naturally as an obvious phenomenon in cell cycle for the development of tissues and organs systematically to prevent the body from impairment or functional disorder [1]. However, this cell death can also be induced by pathogens like bacteria, viruses etc. Host cells in response to bacterial infections; die as a result of host-microbe interaction (Figure 1) [2]. Cells before undergoing degeneration receive specific chemical signals at particular stages of infection, and these signals trigger the activation of appropriate molecules, which eventually guide the particular cell to death [3]. Bacteria result in damage of host cells by releasing a wide range of virulence factors and suppressing cell growth factors, and thereby interfering with cell growth regulation [4]. Different types of cell death have been demonstrated in past and recent studies. Of these, apoptosis and necrosis are widely elucidated with regard to bacterial pathogenesis. Nonetheless, some other pathways of cell demise have also drawn attention to a large extent [5].

The key objectives of this study are to understand the reasons why a cell is subjected to death and the appropriate machinery implicated in it, and to explore the magnitude of benefits gained from this occurrence by both the host and pathogens.

## Comparative Study of Different Types of Cell Death

### Apoptosis and necrosis

Although both apoptosis and necrosis are forms of cell death, they differ from each other considerably. Apoptosis is considered as an extremely harmonized route of cell death, and is requisite for the growth and homeostasis of multicellular organisms [6]. Furthermore, unlike necrosis, apoptosis does not induce inflammatory response during the process of removal of discrete cells [7]. Vesicles are produced in cells that apoptose without the release of any cellular content. However, death by necrosis is characterized by cell enlargement and lysis, and is able to cause inflammatory responses as a consequence [8]. It is thought that apoptosis is an active, programmed process of independent cellular disintegration, whereas necrosis is a passive, accidental cell death accompanied by uncontrolled discharge of inflammatory cellular contents that takes place due to environmental disturbance [9].

Feature(s)	Apoptosis	Necrosis
DNA	Oligonucleosomal Laddering	Degradation
Nucleus	Chromatin margination	Pyknosis
Membrane Integrity	Conserved	Destroyed
Inflammation	No	Yes
Cell volume	Reduced	Increased ("Oncosis")
Cell fragmentation	Yes (Apoptotic Bodies)	No (Lysis)

**Table 1:** Key characteristics of apoptosis and necrosis.

Morphologically, apoptosis is regarded as a general pathway of shielded cell deletion corresponding to mitosis and cytokinesis that upholds stable populations within tissues. Hence, it is now considered that living cells are genetically programmed to consist of metabolic components leading to cellular demise upon activation [10]. On the contrary, studies reveal that cell necrosis has different mechanisms and outcomes. During necrosis cells first swell, and then the plasma membrane breaks down and cells rapidly undergo lysis. But, during apoptosis cellular shrinkage and corresponding DNA condensation occur initially, and thereafter these cells and nuclei disintegrate into well-enclosed apoptotic bodies [11]. If the apoptotic bodies are not phagocytized, there could be a loss of integrity in apoptotic bodies leading to secondary or apoptotic necrosis. It implies that further degradation of these bodies may possibly take place after the apoptotic course [12]. Table 1 represents certain key characteristics of apoptosis and necrosis.

### Oncosis

It is also known as Early Primary Necrosis. The term oncosis (derived from onkos, meaning swelling) was proposed in 1910 by von

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**Received** June 19, 2012; **Accepted** September 17, 2012; **Published** September 27, 2012

**Citation:** Hossain Z, Farkuddin Md (2012) Mechanism of Host Cell Death in Response to Bacterial Infections. J Clin Cell Immunol 3:128. doi:10.4172/2155-9899.1000128

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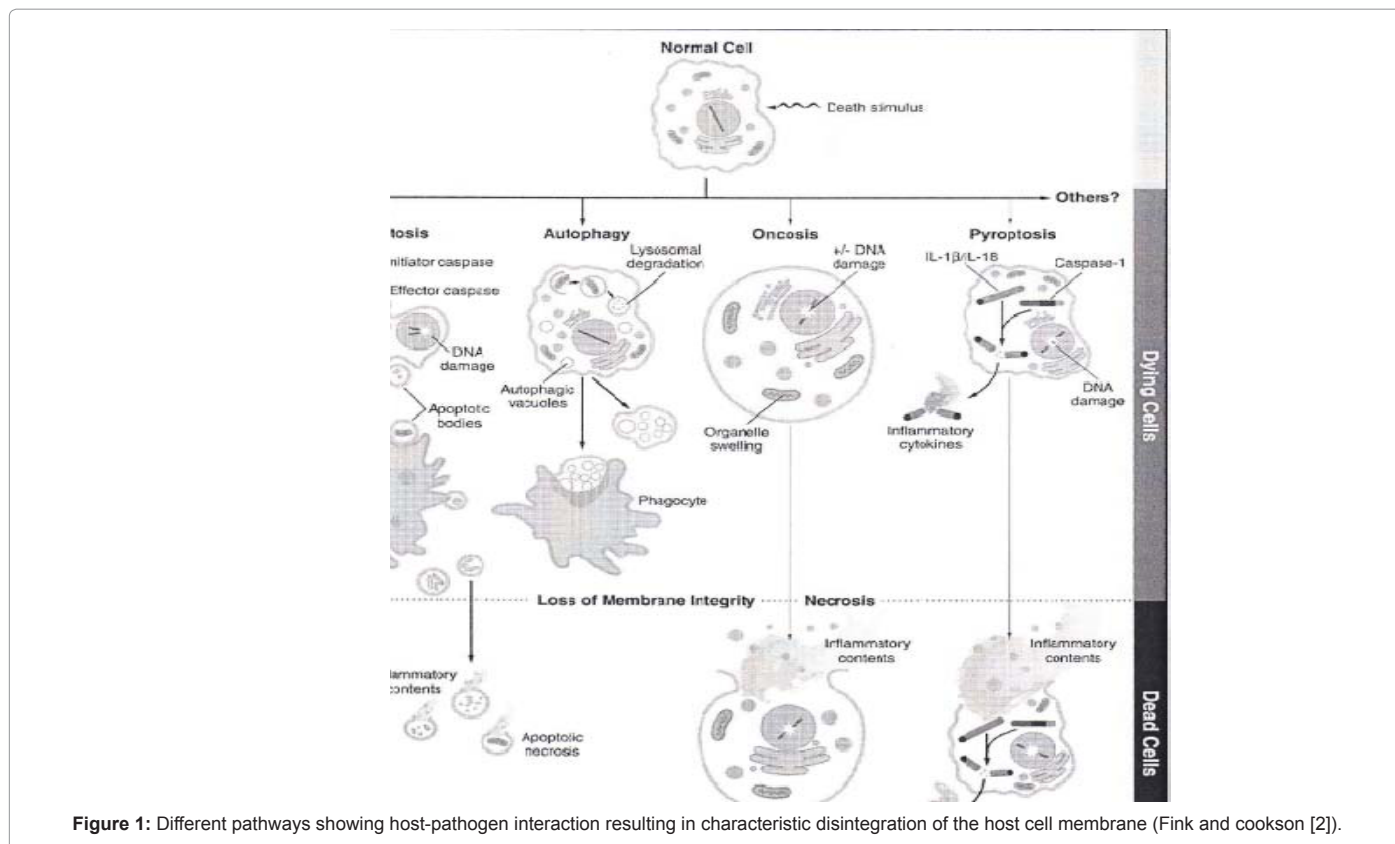


Figure 1: Different pathways showing host-pathogen interaction resulting in characteristic disintegration of the host cell membrane (Fink and Cookson [2]).

Reckling-Hausen exactly to mean cell death with swelling. Cells are directed to necrosis with karyolysis (dissolution of nucleus) by oncosis, while karyorhexis (fragmentation of nucleus) and cell shrinkage are the key characteristics of apoptotic necrosis [13]. In other words, oncosis cell death is measured by cytoplasmic bulging, mechanical rupture of the plasma membrane and expansion of cytoplasmic organelles like mitochondria, endoplasmic reticulum and Golgi apparatus, as well as moderate chromatin condensation [14]. Thus, oncosis fairly resembles necrosis in terms of the cellular destiny. Furthermore, bacteria-induced oncosis has been discerned in many experiments. *Pseudomonas aeruginosa* infection brings about oncosis in infected macrophages and neutrophils. In these cells, swelling, rapid plasma membrane collapse, and inflated nuclei without inter-nucleosomal DNA disintegration are evident [15].

### Autophagy

Autophagy is another mode of cellular disintegration, which is thought to be of great importance in cell life cycle. Autophagy is known as a non-specific degradative pathway that is engaged in the transportation of bulk cytoplasmic components to the vacuole [16]. Perhaps, autophagy is another nature of programmed cell death, which is regarded as Type II PCD (Programmed Cell Death) and is allied with Type I PCD, apoptosis. Apoptosis is followed by the exclusion and degradation of dying cells by phagocytosis, which is a sign of autophagy. The morphological features of autophagy comprise vacuolization, deterioration of cytoplasmic contents, and minor chromatin condensation [17].

### Pyroptosis

Research findings propose that pyroptosis, a new form of death,

occurs in host cells that exhibit apoptotic circumstances. It is generally characterized by the pro-inflammatory nature of cell death process and is believed to have medical significance in infections induced by certain bacteria like *Salmonella typhimurium*. *Salmonella*-induced cell death has been regarded as necrotic in nature based on the cytotoxicity generated by this bacterium [18]. Pyroptosis is now contemplated as a pro-inflammatory programmed cell death because of the requirement of caspase-1 activation and the pro-inflammatory route in this mechanism [19]. Therefore, it should also be noted that pyroptosis is a non-apoptotic programmed cell death because of its exceptional dependence on caspase-1. Caspase-1 is not concerned in orthodox apoptotic cell death pathway and particularly caspase-1 deficient cells react normally to most apoptotic signals [20]. The development of active inflammatory cytokines, IL-1 $\beta$  and IL-18 (interleukins) is a notable role of caspase-1 [21]. Pyroptosis is believed to have further relevance in a diversity of biological approaches due to the observation of caspase-1 activation or dependence during cell death in the immune, central nervous and cardiovascular systems [22].

### Factors Triggering Cell Death

#### Death receptors

Death receptors are transmembrane proteins that belong to tumor necrosis factor (TNF) receptor (TNFR) super family, and localized to the cytoplasmic membrane. The extracellular domains of these receptors are engaged in ligand binding and their "death domains" (DDs) in cytoplasmic tails facilitate apoptotic machinery [23]. Generally, death receptor function can be demonstrated by Fas (CD95/APO-1) as it is a member of the TNFR family. Polymerization of Fas leads to configuration of the death inducing signal complex (DISC). During this mechanism, Fas-associated death domain (FADD) protein, an adaptor

molecule, is engaged through death domains (DDs). FADD also contains two death effector domains (DEDs) that adhere to caspase-8 or its enzymatically inactive homologue, the Fas inhibitor FLICE (FADD-like interleukin-1B converting enzyme) inhibitory protein (FLIP) [24]. Thus, it can be suggested that various cellular receptors can mediate signaling for programmed cell death [25].

### Mitochondria

Mitochondria have been recognized as vital organelles in cell death. The cytosolic assembly of apoptosome (apoptosis inducing caspase activation complex involving Apaf1 and caspase-9) has been observed in mammals upon discharge of mitochondrial cytochrome c [26]. Likewise, mitochondrial swelling, outer membrane rupture and the release of apoptotic mediators can be attributed to mitochondrial permeability transition (mPT) [27]. For this reason, mitochondria play an important role in programmed cell death [28].

### Caspases

As discussed earlier, in certain types of cell death, such as apoptosis and pyroptosis, caspase molecules are largely influential. They constitute a group of cysteine proteases that cleave at caspase-specific sites [29]. Apoptosis seems to be caspase-mediated cell death because an array of caspases (caspase-2,-3,-6,-7,-8,-9, and -10) is recruited in the route of apoptotic cell death [2]. In addition, pyroptosis is a caspase-1 dependent pathway of cellular termination. Despite that, the argument according to previous research data that programmed cell death (PCD) can also pursue the caspase-independent pathway has raised conflicting interest in the factual efficacy of these enzymes in this phenomenon [30].

### Proteins of the Bcl-2 family

It is undoubtedly established that proteins of this family exhibit contentious functions. Investigations are still unable to find out precisely whether they suppress cell death or induce it. Theories suggested regarding the pertinent contribution of Bcl2 (B-cell lymphocyte/leukaemia-2) family cannot confer much clear understanding of its mechanisms. About 15 Bcl-2-like genes, which have been identified to date, program this group of proteins [31]. This family of proteins incorporates both the apoptosis inhibitory, Bcl-2 and Bcl-xl and other apoptosis promoting proteins like Bax (Bcl-2 associated protein x) and Bik (Bcl-2 interacting killer) [32]. Besides, antiapoptotic associates of this family are capable of restraining both apoptotic as well as necrotic deaths [33]. To sum up, supplementary studies are required to realize the valid contribution of Bcl-2 family to cell death. One of the reasons for this comment could be the discovery of another Bcl-2 protein molecule, BNIP3 (Bcl-2/Adenovirus E1B 19-kDa interacting Protein), a potential supporter of necrotic cell death [34].

### Ions and lipids

Active distraction of ion homeostasis also takes part in cell death. Significant rises in cytosolic  $[Ca^{2+}]$ ,  $[Na^+]$  and  $[Mg^{2+}]$  account for cell swelling and eventually death by necrosis. Then again, cells with high  $[H^+]$  and low  $[K^+]$ , along with normal  $[Na^+]$  and normal to moderate  $[Ca^{2+}]$  increases undergo death by apoptosis. Therefore, the levels of these ions centrally govern signaling action followed by cell death [35]. Very importantly, calcium ions appear to play the most prevailing role as mediators in cell degeneration because deletion of  $Ca^{2+}$  from medium (by chelators EGTA or BAPTA) protects cells from necrotic death instigated by starvation and anoxia [11].

In addition, necrotic cell death induced by lipids and similar products is also noteworthy. This can be exemplified by oxidized

low-density lipoproteins (ox-LDL) induced necrosis, oxidized sterols induced necrosis in fibroblasts but apoptosis in endothelial and smooth muscle cells [36].

### Protein kinases

The enzyme, protein kinase is considered to be a triggering element in cellular collapse. For instance, protein kinase JNK (c-Jun N-terminal protein kinase) of MAPK (mitogen activated protein kinase) family (also called stress-activated protein kinase, SAPK) is the main protein kinase implicated in stress-induced apoptosis. Data illustrate that this enzyme also takes part in necrotic mechanism of cell death [11]. Additionally, the death-associated protein kinase (DAPK) family DAPK and its linked kinase, death associated related protein kinase-1 (DRP-1) are known as  $Ca^{2+}$ /calmodulin-regulated kinases, which play a role as conclusive effectors of cell death through caspase dependent apoptotic pathway in association with an assortment of stimuli like interferon- $\gamma$ , TNF $\alpha$ , and TGF $\beta$  (transforming growth factor  $\beta$ ) [37]. Accordingly, it can be articulated that the effectiveness of these kinases in cell death arrangement is inevitable.

### Mechanisms of Host Cell Death Induced by Bacterial Infections

The vigorous interaction between eukaryotes (host cells) and prokaryotes (bacteria) is a very complex ideology of medical science in view of the involvement of diverse effectors, mediators and toxins leading to an extensive array of pathways. Therefore, it is sort of challenge to localize all facets of this very obvious natural phenomenon. However, in this review, feasible efforts will be made to explain assorted modes of cell fatality while encountering bacterial pathogens. In order to comprehend how cellular breakdown or malfunction is triggered by bacteria, possible effects of hostile factors of these pathogens need to be detailed. Many pathogenic bacteria are equipped with a wide range of virulence determinants, which interact with vital components of the host leading to cell death. These determinants may also barricade the regulation of transcription factors, which are recruited in monitoring cell survival [1]. Diverse bacterial exotoxins have the ability to bring about direct lysis of cells and ultimately help with microbial spread through tissues by causing momentous damage to the extracellular matrix or the plasma membrane of eukaryotic cells. Perhaps, these toxins result in this cellular injury by dint of enzymatic hydrolysis or pore development. In view of proven information, bacterial hyaluronidases, collagenases, and phospholipases are capable of decaying cellular membrane or matrices [38]. Cell death pathways with respect to the impact of different toxins can be typified by certain bacteria for a reasonable perception.

### Pore Formers vs Host Cells

A wide range of bacteria produces pore-forming toxins that interfere with the cell cycle regulation. For instance, these toxins upset the selective mobilization of ions across the plasma membrane by introducing a transmembrane pore. Both gram-positive and gram negative bacteria produce pore-forming toxins, such as the RTX (repeats in toxin) toxins produced by certain gram-negative bacteria, streptolysin O by *Streptococcus pyogenes*, and the *Staphylococcus aureus*  $\alpha$ -toxin [38].

### *Staphylococcus aureus*

*Staphylococcus aureus* is the causative agent of a variety of diseases, such as skin lesions, food poisoning, toxic shock syndrome, endocarditis, and osteomyelitis [39]. Alphatoxin has been recognized as the most important haemolysin of this bacterium that provokes cell death

through the classical apoptotic pathway [40]. Alpha toxin forms pores in a number of eukaryotic cell membranes and activates programmed cell death in T-lymphocytes. At low doses, the toxin connects to specific cell surface receptors. Then it produces miniature pores resulting in the ease of the release of monovalent ions. Finally, these events facilitate DNA fragmentation and cell death. More importantly, alpha-toxin non-specifically absorbs to the lipid bilayer at high doses inducing the formation of larger pores that happen to be  $\text{Ca}^{2+}$  permissive resulting in substantial necrosis without DNA fragmentation [7]. Other studies express that  $\alpha$ -toxin undergoes a set of precise steps during access to host cells in order to damage cell membranes. It selectively carries out three sequential events. First, toxin protomers possibly bind to target membranes by high-affinity receptors or through non-specific assimilation to phosphatidylcholine or cholesterol like substances on the lipid bilayer. Then membrane-bound protomers, oligomerize to generate a heptamer complex capable of forming a pore. In the end, the heptamer goes through a succession of conformational changes that trigger the formation of the stem domain of the toxin, which is then inserted into the membrane. The  $\alpha$ -toxin pore facilitates the influx and efflux of small molecules and ions leading to characteristic swelling and death of nucleated cells and osmotic lysis of erythrocytes [38].

### *Escherichia coli*

Another RTX toxin, which is produced by *Escherichia coli*, is called alpha-haemolysin (HlyA) infection with this pathogen accounts for diseases like severe bloody diarrhoea, abdominal cramps, and haemolytic uremic syndrome particularly in children. HlyA mediates cell death via LFA-1 (lymphocyte function-associated antigen 1) in human immune cells [6]. Attempts have been made to understand the possible interaction between *E. coli* and host cells. As an outcome, host cells have shown certain morphological changes that confirm the role of alpha-haemolysin in the cell death pathway. For instance, cytoskeleton rearrangement is found in erythrocytes exposed to *E. coli* HlyA that eventually brings about the formation of teardrop-shaped protuberance from the surface. The production of cytokine is also disturbed by alpha-haemolysin [41]. This pore-forming toxin is primarily virulent in its acylated form. The species of the acylated form inserts as a monomer into the plasma membrane bilayer of target mammalian cells in order to create a transmembrane pore for the permeability of cations over anions [6].

### Infection with Protein Synthesis Inhibitors

An assortment of bacterial species is concerned with this group. These pathogens are responsible for the type of host cell death that is triggered by protein synthesis inhibition, and are capable of doing so by the secretion of specific bacterial proteins (toxins), which have intrinsic enzymatic activity. These proteins consist of an A-B conformation with the B subunit being able to mediate ligation with eukaryotic cells and the enzymatically operational A fragment translocated across the cell membrane to its cytosolic destination.

Some of the examples of these proteins are diphtheria toxin (Dtx) secreted from *Corynebacterium diphtheriae*, *Pseudomonas* exotoxin A, and the Shiga and Shiga-like toxins [42].

### *Corynebacterium diphtheriae*

This gram-positive rod is the predominant cause of diphtheria in humans and well identified as an extracellular pathogen. Infection takes upon interaction with host cells across plasma membrane [43]. Diphtheria toxin (DT) also described as A-B toxin binds to the DT receptor on the host cell surface through its B fragment. This binding

allows internalization of the toxin into acidic endocytic vesicles leading to the liberation of catalytic DT-A into the cytoplasm, where this subunit implements its cytotoxicity by ADP-ribosylating elongation factor 2 (EF-2). This mechanism, eventually, hinders protein synthesis in infected cells, thereby killing them. Experimental evidences further strengthen the notion of the cytotoxic effect of diphtheria toxin on host cells. In a previous study, transgenic mice expressing human pro-HB-EGF [heparin-binding EGF (epidermal growth factor)-like growth factor, recognized as DT receptor was infected with diphtheria toxin by intramuscular injection. This experiment brought about complete ablation of transgene-representing cardiomyocytes in mice and subsequent heart failure resulting from the autophagic cell death pathway [44]. However, it is also considerable that Dtx cannot plot the destiny of infected host cells by means of solely protein synthesis inhibition because certain observations have reported the absence of cellular apoptosis despite effective obstruction of this synthesis in cells. A host nuclear transport factor, cellular apoptosis susceptibility (CAS) protein, is suspected to be engaged by Dtx-mediated apoptosis in order to enhance the possibility of death of target cells [45]. To epitomize, on the basis of the explained protein synthesis inhibition route, the true mechanism of *Corynebacterium* (Dtx)-infected host cell death still remains vague in studies.

### *Shigella dysenteriae*

This pathogenic species is one of the major causes of dysenteric syndromes in humans with typical kidney and central nervous system manifestations. Toxins generated by this bacterium are Shiga and Shiga-like toxins (Slt) and verotoxin that have been experimentally proven to be efficient in *Shigella*-caused route of cell death by launching inhibition of protein synthesis. A subunit of Shiga toxin has capacity to cleave a single adenine residue from the 28S rRNA component of eukaryotic ribosomes by its N-glycosidase activity. Thus, ribosome function is disturbed ending in disruption of protein synthesis [46]. Past studies failed to detect the important accountability of Shiga toxin secreted from *Shigella dysenteriae* 1 in this mechanism [47]. Research in the last decade years, conversely, has developed knowledge about the apparent effect of this toxin on rectal mucosa infected with *S. dysenteriae* 1 and improved our understanding of its possible mechanism leading to cell death. Interestingly enough, both apoptosis and necrosis were observed in infected rectal tissues. A marked upregulation of Fas co-localized to cells was found to be associated with apoptosis, whereas necrosis mediated by perforin, a protein of natural killer cells, was mostly discernible in the surface epithelium. Also, *in vitro* studies with peripheral blood mononuclear cells have established that Shiga toxin induces a rapid Fas-assisted cell death with a decline in Bcl-2 expression. These consequences reveal that *S. dysenteriae* 1 adopts such a mechanistic strategy upon contact with host cells that results in initial Fas-associated apoptosis followed by elimination of *Shigella* antigen positive cells by perforin-activated cytotoxicity at a later phase [48].

### Execution by Type-III Protein Secretion Pathway

Type-III protein secretion is a novel pathway, which is now thought to be broadly functional in the interaction of pathogenic bacteria with host cells. It has been observed in diverse gram-negative bacteria, such as *Salmonella*, *Shigella*, *Yersinia*, and enteropathogenic *Escherichia coli* (EPEC) that are highly pathogenic to animals. This protein secretion system is also known as contact-dependent system. Certain distinctive features of this secretion pathway are the absence of a typical, cleavable, sec-dependent signal sequence in the secreted targets; the necessity of a huge amount of accessory proteins for the export process; and

the export of the target proteins through both the inner and surface membranes. Most importantly, this protein secretion system can be completely efficient provided that extracellular signals are activated [49]. Equally, Type-III secreted proteins are aimed at changing host cell signal transduction pathways upon interaction [50]. Mechanism of this critical pathway can be sensibly explained with respect to an assortment of certain pathogenic bacterial species causing infection to host cells.

### ***Salmonella typhimurium***

This species of *Salmonella* genus is basically responsible for gastroenteritis [22]. Virulence genes of this species are particularly positioned in *Salmonella* pathogenicity islands (SPI) of the chromosome. Among a small number of SPI described so far, SPI-1 and SPI-2 determine Type-III secretion systems (TTSS). This bacterium displaces bacterial effector proteins into the host cell cytosol upon infection via the SPI-1- encoded Type- III secretion system. Some of these proteins have the ability to bind to certain host enzymes like protein kinase. By this binding action, they can gain access to the epithelial cell cytosol, and, as an obvious phenomenon, they interfere with host cell signaling pathways while residing in the cell cytosol resulting in considerable changes in the host cell cytoskeleton, with consequent bacterial internalization and changes in host gene expression [51]. Studies have discovered that *Salmonella typhimurium* infection gives rise to cytoplasmic projections of the epithelial cells with characteristic disruption of the underlying cytoskeleton that facilitate the formation of ruffles mediating internalization of this pathogen into epithelial cells [19].

*Salmonella* infection also induces the production of inositol (isomeric alcohol) phospholipids in certain cell lines. Although it is unclear, these phospholipids may mediate calcium fluxes in the corresponding cells. In addition to these, this microorganism prompts the production of pro-inflammatory cytokines, principally IL-8, by inducing nuclear reactions eventually leading to cell disintegration [49]. It has been reported that *Salmonella* can induce apoptotic macrophage death by the activation of caspase-1 through binding of SPI-1 TTSS secreted protein SipB (sulphur-induced protein B) to it [52]. Here, it will be worth focusing that, though apoptosis has always been demonstrated as a programmed cell death that does not elicit inflammation, introduction of caspase-1 in this mechanism, of course, induces the release of active pro-inflammatory cytokine, IL-1 $\beta$  [19]. Hence, the theory regarding apoptosis is deemed to be quite sophisticated based on the observation of its diverse molecular mechanisms. Despite that research has revealed that *Salmonella* can affect abrupt dendritic cell death in a necrotic manner via SPI-1 TTSS pathway involving the so-called caspase-1 activation [53]. For this reason, *Salmonella*-infected cell death in many cases can be possibly marked as pyroptosis for a clearer elucidation.

### ***Yersinia enterocolitica***

This gram-negative pathogen is fairly recognized as a causative agent of gastrointestinal ailment, septicemia and adenitis. The Type-III secretion system of *Yersinia* is determined on the virulence plasmids of this organism [54]. The best studied secreted protein of this bacterium is the *Yersinia* protein tyrosine phosphatase (PTP) YopH (*Yersinia* outer protein H) (51-kDa), which is mandatory for *Yersinia* pathogenesis, and is translocated into eukaryotic cells by the Type-III pathway upon contact with the host cell [55]. This protein has the capacity to activate antiphagocytosis or antagonize internalisation after the infection of epithelial cells or macrophages with *Yersinia*. Among other proteins characterized so far, YopE seems to be very significant in terms of

antiphagocytic activity. It is largely accountable for cytotoxicity in host cells leading to drastic changes in cell morphology in collaboration with YopH. Investigations have reported that infection of epithelial cells or macrophages with *Yersinia* induces remarkable modifications in the microfilament structure of the host cell. For example, infection during progression reduces well-organized actin filaments to jumbled structures that become granular in appearance [56]. Manifestations related to cytotoxicity have been reported in host cells after infection with this pathogen. During this process, cells first undergo condensation, which is then followed by shrinkage in cellular structure. YopH can also inhibit the oxidative burst in macrophages, which is adjudicated by ligation of Fc receptors, by its tyrosine phosphatase action [49]. Another protein of this bacterium, YopP has been reported to be very effective being responsible for its contribution to apoptosis. It blocks the activation of transcription factor NF- $\kappa$ B (Nuclear Factor  $\kappa$ B) in macrophages by down-regulating the synthesis of antiapoptotic proteins, such as apoptosis inhibitors and Bcl-2 family members [57]. This phenomenon therefore, gives rise to the suppression of NF- $\kappa$ B-dependent antiapoptotic activities. Besides, YopP interferes with MAPK pathways by ligating and inhibiting MAPK kinase family members [26]. However, the conception of upstream participation of FADD and caspase-8 in host cell apoptosis in response to *Yersinia* infection is still somewhat divisive [58]. YopJ interferes with signaling pathways of host cells enhancing apoptosis [59] and the pathogen kills macrophages without inducing inflammatory responses [60]. YopK is another protein of *Yersinia* that helps the pathogen to evade pyroptosis [61].

### **Prospects and Constraints of a Cell Death**

Death, as an ultimate recourse adopted by host cells responding to bacterial infection, is becoming a progressively interesting issue in the coverage of current medical studies. The reason why a cell undergoes termination via a set of molecular mechanisms is still debatable to a large extent. Undoubtedly, this natural scenario serves a broad range of subtle purposes of both the pathogen and host cells. It is now assimilated that apoptosis plays a vital role in T cell biology. Non-functional T lymphocytes, during development, as well as extravagant population of effector T cells, during immune responses, are deleted by apoptosis directly or indirectly that leads to the improvement of host cell immunity in terms of T lymphocyte development [62]. The dysregulation of the apoptotic process is believed to be the precursor of autoimmunity, tumorigenesis and immunodeficiency. It is also said that the two well-known pathways of cell death, namely death receptor signaling and Bcl-2 coordination regulate T lymphocyte development and function [63]. Similarly, necrotic cell death helps with the eradication of disabled or unwanted cells, which could lead to physiological complications if not removed [11]. Nevertheless, cell death may also be the reason for grave afflictions of the host [64]. Massive amount of death will allow bacteria to further invade and gain access to target cells through tissues resulting in broad spectrum infections. For an instance, subversion of the autophagic pathway facilitates the pathogen with a suitable environment for huge reproduction inside the host cell tissue and supplies nutrients for its growth [28]. Thus, bacteria largely benefit if host cells fail to survive due to invasion and subsequent induction of toxicity. Perhaps, infection is an essential task in the life cycle of all pathogenic bacteria. It may be assumed that they are committed to infecting the host to serve the purpose of better metabolism and effective cell division, which are much likely to be possible due to collapse of eukaryotic cells that are the natural reservoir of diverse growth factors for this bug [65]. In contrast, it is actually challenging to understand the negative effects of cell death

on this microorganism. Certain types of cellular demise are most likely to limit or down regulate bacterial population in the host body. Autophagy or Type-II programmed cell death has been proven to be a specific mechanism in mammalian cells that is capable of degrading invasive bacteria [66].

Likewise, apoptosis appears to be significant in circumscribing bacterial infection. For example, in Shigella-generated apoptosis, infection may subside due to the induction of a particular inflammatory response, which possibly plays a successful role in localizing the infection [42].

## Conclusion

Although a large number of attempts have been made to successfully elicit appropriate knowledge of different pathways of cell death induced by pathogenic bacterial infection, many complex mechanisms of these pathways are still obscure. However, it is now clear that bacteria, in order to initiate effective cell degenerative process, depend mostly on host cell effectors and mediators, which form a signaling complex for the induction of programmed cell death. Past studies have discovered that a variety of host molecules, such as certain proteins of the Bcl2 family have capacity to suppress cellular collapse. Yet it is quite uncertain how bacteria adopt alternative approaches to retain the process of killing eukaryotic cells for their own benefit. Therefore, it could be a specific goal of cutting edge research. Also, because suppression of cell death is not always blissful for the host, sensible development of therapeutic agents for bacterial infection control is a challenge for the future.

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