Review

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Programmed necrosis in microbial pathogenesis

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Programmed cell death is an important facet of host–pathogen interactions. Although apoptosis has long been implicated as the major form of programmed cell death in host defense, the past decade has seen the emergence of other forms of regulated death, including programmed necrosis. While the molecular mechanisms of programmed necrosis continue to be unveiled, an increasing number of viral and bacterial pathogens induce this form of death in host cells, with important consequences for infection, control, and pathogenesis. Moreover, pathogen strategies to manipulate or utilize this pathway are now being discovered. In this review, we focus on a variety of viral and bacterial pathogens where a role for programmed necrosis is starting to be appreciated. In particular, we focus on the mechanistic details of how the host or the pathogen might appropriate this pathway for its own benefit.

Controlled cell death pathways

Programmed cell death (PCD) plays a significant role in the development, immune homeostasis, and host defense of multicellular organisms. For nearly 30 years, PCD has been synonymous with apoptosis, and apoptosis remains the most well studied of the PCD pathways. This controlled form of 'suicide' is an important arm of innate host defense that serves to limit pathogens, and allows the immune system to quickly and effectively dispose of dead and dying cells.

In addition to apoptosis, it is becoming clear that other modes of cell death are carefully controlled by eukaryotic cells [1–3] (Box 1). Necrosis has been traditionally regarded as accidental and uncontrolled cell death. However, in the past several years, this view has been challenged by clear evidence that some forms of necrotic death are genetically programmed. Similar to apoptosis, necrosis can also be initiated in response to various extrinsic and intrinsic signals and carried out through specific signaling cascades resulting in death. Such necrotic cell death is commonly referred to as programmed necrosis, regulated necrosis, or 'necroptosis'.

Programmed necrosis can be initiated by death ligands, Toll-like receptor (TLR; see Glossary) ligands, or microbial

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Glossary

Adapter proteins involved in signal transduction

Apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC): adapter protein that functions to bridge procaspase-1 and other proteins within the inflammasomes, leading to procaspase-1 cleavage and activation.

TIR domain-containing adapter-inducing interferon-β (TRIF): adapter protein that functions downstream of TLRs 3 and 4 to mediate downstream signals resulting in immune responses.

Interferon (IFN) response

Interferon regulatory factor 3 (IRF3): member of the interferon regulatory factor (IRF) family of transcription factors. Activated in response to viral nucleic acids by phosphorylation. Important for the transcription of IFNαβ and IFNβ, as well as other genes important in antiviral responses.

Janus kinase (JAK): family of intracellular, nonreceptor tyrosine kinases that mediate signal transduction initiated from IFNs. Activated by autophosphorylation and subsequently phosphorylates and activates specific STAT proteins.

Mitochondrial antiviral signaling protein (MAVS): adapter protein that transmits signals from the cytosolic RNA sensor, RIG-1, resulting in activation of IRF3 and transcription of IFNα and IFNβ genes.

Signal transducers and activation of transcription (STAT): family of transcription factors that are activated by JAKs. Upon activation, homo- or heterodimerize and translocate to the nucleus to transcriptionally activate many IFN-stimulated genes.

Stimulator of interferon genes (STING): adapter protein involved in host response to cytosolic pathogen-derived or self-DNA. Acts by activating transcription factors IRF3 and STAT6.

Molecules involved in cell death pathways

Cellular FLICE-like inhibitory protein (cFLIP): potent negative regulator of caspase-8 present as long ($cFLIP_L$) and short (cFLIPs) isoforms. $cFLIP_L$ inhibits both apoptosis and programmed necrosis, whereas cFLIPs inhibits apoptosis but sensitizes cells towards programmed necrosis.

Cellular inhibitor of apoptosis protein (cIAP): family of ubiquitin E3 ligases important for regulation of apoptosis and programmed necrosis. Loss of cIAPs sensitizes cells towards programmed necrosis by facilitating the spontaneous assembly of an RIP1RIP3 containing signaling complex, termed the 'ripoptosome'.

Fas-associated death domain (FADD): adapter protein that functions downstream of some death receptors (e.g., Fas and TNF) to mediate downstream signals through the formation of a death-associated signaling complex (DISC). Loss of FADD potentiates RIP1–RIP3 programmed necrosis.

Mixed lineage kinase domain-like (MLKL): direct target of RIP3 kinase activity and important for mediating programmed necrosis downstream of RIP3.

Phosphoglycerate mutase family member 5 (PGAM5): a mitochondria-associated phosphatase that is activated by MLKL in certain conditions of programmed necrosis. Dephosphorylates Drp1 that leads to mitochondrial fission.

Reactive oxygen species (ROS): oxygen containing byproducts of metabolism, including oxygen anions and peroxides. Important second messengers and play roles in signal transduction leading to inflammation and cell death.

Pattern recognition receptors (PRRs)

Nucleotide oligomerization domain (Nod)-like receptor (NLR): intracellular PRRs that initiate immune response to injury, toxins, or microbial infection. Activation of some NLRs can result in the assembly of 'inflammasomes' that activate caspase-1.

Toll-like receptor (TLR): membrane-associated PRRs that are involved in recognizing a variety of pathogen-associated molecular patterns (PAMPs) and initiating downstream signal cascades resulting in host responses during infection.

Box 1. Forms of programmed cell death

Apoptosis: characterized by cell shrinkage, nuclear condensation, chromosomal fragmentation, membrane blebbing, and eventual breakdown into apoptotic bodies that are detected and disposed of by phagocytes. Requires the activation and activity of cysteine proteases known as caspases. Induced by external stimuli, such as death receptor ligation or pattern recognition receptor (PRR) activation, or by internal stimuli that influence mitochondrial integrity. Caspases exist as latent zymogens in the cell. 'Initiator' caspases, such as caspases-8 and -9, are activated in response to signals, which then activate 'executioner' caspases, caspases-7 and -3, that target cellular substrates leading to apoptotic death.

Programmed necrosis: characterized by organelle damage, cell swelling, and rupture of the plasma membrane, leading to the release of cytoplasmic contents. Associated with inflammation. Some forms of programmed necrosis are mediated by the RIP3 kinase. See text for details.

Pyroptosis: caspase-1-dependent, nonapoptotic cell death. Characterized by loss of plasma membrane integrity, release of cytoplasmic contents, and tightly associated with the maturation and secretion of inflammatory cytokines, including interleukin (IL)-1β and IL-18. Caspase-1 is activated by the assembly of the 'inflammasome', comprising activated cytosolic pathogen-sensing NLRs [nucleotide oligomerization domain (Nod)-like receptors] that recruit caspase-1 directly or through the adaptor ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) [86,87].

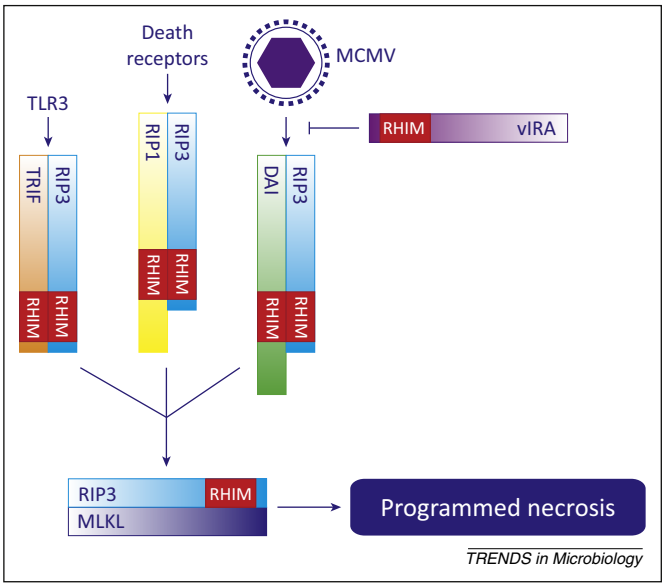

Figure 1. Central role of RHIM domains in programmed necrotic signaling. Extrinsic signals from death receptors, TLRs, or viruses require RHIM containing adapters to activate programmed necrosis. RIP3 associates with either RIP1 (TNFR1), TRIF (TLR3) or DAI (MCMV) through homotypic interactions of the RHIM domain. This subsequently activates MLKL that then conveys the signal downstream. vIRA protein of MCMV inhibits RIP3–DAI-mediated signaling during infection through its RHIM domain by binding and sequestering RIP3 to prevent complex formation. Abbreviations: RHIM, RIP homotypic interaction motif; TLR, Toll-like receptor; RIP, receptor-interacting protein; TNFR1, tumor necrosis factor receptor 1; TRIF, TIR domain-containing adapter-inducing interferon-β; MCMV, murine cytomegalovirus; MLKL, mixed lineage kinase domain-like; vIRA, viral inhibitor of RIP activation.

infection. The most well-studied signaling pathway that is induced by death ligands is tumor necrosis factor (TNF). Paradoxically, it has been known for over 15 years that TNF can induce apoptosis in some instances and necrosis in others [4]. Unlike apoptosis, programmed necrosis is independent of caspase activity, and inhibition or lack of caspase-8 can sensitize cells to programmed necrosis [5]. Indeed, many additional proteins involved in regulation of apoptosis, including Fas-associated death domain (FADD), cellular inhibitor of apoptosis proteins (cIAPs), and cellular FLICE-like inhibitory proteins (cFLIPs), are implicated in regulation of programmed necrosis [2]. Signaling from TNF receptors activates the receptor-interacting protein (RIP) kinases 1 and 3, which then play central roles in mediating downstream signals. Several 'extrinsic' necrotic signals from TNF, TLR3 activation, and certain virus infections converge on RIP3 [6] (Figure 1). Several recent reviews have focused on the signaling cascade from TNF resulting in activation of the RIP1–RIP3 complex termed the 'necrosome' [2,7]. Activation of RIP1 and RIP3 involve auto- or cross-phosphorylation and dimerization through a motif called a RIP homotypic interaction motif (RHIM). Recently, it has been demonstrated that RIP1 is dispensable for some extrinsic signals (Figure 1); however, RIP3 plays an essential role in all, thus forming the crucial convergence point for execution of necrosis. Activated RIP3 then phosphorylates and activates downstream targets, ultimately leading to programmed necrosis. One common downstream substrate that is activated in all cases of RIP3-dependent necrosis is the pseudokinase mixed lineage kinase domain-like (MLKL) [8–10]. MLKL therefore probably comprises an essential step in necrosis progression, although events downstream of MLKL are just beginning to be elucidated. Recent studies suggest activation results in oligomerization and plasma membrane association of MLKL, which promotes calcium and/or sodium influx, and ultimately leads to membrane lysis [11,12]. However, in some cell types, MLKL activates PGAM5, resulting in mitochondrial fission, reactive oxygen species (ROS), and necrosis [13]. It has been demonstrated that RIP3-dependent programmed necrosis does not require mitochondria or ROS production in mouse fibroblast and endothelial cell lines [14], suggesting that, similar to RIP1, the requirement for mitochondria and ROS in programmed necrosis might be specific to certain agonists, cell types, or conditions. Thus, the minimal requirement for execution of RIP3-dependent programmed necrosis remains an important unanswered question.

Pyroptosis is another important form of nonapoptotic programmed cell death (Box 1). Initially described as the caspase-1-dependent apoptosis of macrophages during *Salmonella enterica* serovar Typhimuriumn (*S*. Typhimurium) infection [15], further investigations revealed significant morphological and biochemical differences between apoptosis and pyroptosis [1,16]. Although dependent upon the activity of caspases, pyroptosis results in loss of plasma membrane integrity and is associated with release of inflammatory cytokines. Owing to these features, pyroptosis has multiple potent proinflammatory effects that influence infection and immunity.

Necrosis and infection

Cellular suicide initiated by infected cells constitutes an effective mechanism to contain pathogen replication and spread. At the same time it facilitates the uptake and clearance of infected cells by phagocytes of the immune

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