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Review

The Commonalities in Bacterial Effector Inhibition of Apoptosis

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Antiapoptotic pathways of the host cell play integral roles in bacterial pathogenesis, with inhibition of those pathways resulting in halted disease pathology. Certain pathogens have developed elegant mechanisms to modulate the fate of the host cell, many of which target novel pathways that are poorly understood in the context of the cell biology. Bacterial pathogenesis research not only promotes the understanding of the role of antiapoptotic pathways in bacterial infection, but has a broader context in understanding the epitome of human disease, that is, developing the understanding of tumorigenic or inflammatory pathways. Here we review host antiapoptotic signalling pathways manipulated by translocated bacterial effectors that propagate the disease state, drawing common parallels and showing the novel differences.

Apoptosis and Bacterial Pathogenesis

Bacterial infection of human epithelial cells activates multiple host signalling pathways which stimulate host immunity and impose cellular stresses. Prolonged activation of these pathways often results in programmed cell death, also termed apoptosis [1,2]. Apoptosis is a highly regulated, innate immune response that occurs canonically by two different pathways: extrinsic and intrinsic. In the context of infection, apoptosis eliminates pathogens at the point of infection without emitting systemic alarms [3–9]. Apoptosis is controlled and progressed by the activation of cysteine-dependent aspartate-specific proteases (caspases), which cleave signal transduction, cytoskeletal and nuclear proteins to induce cell death. It should be noted that a caspase-independent pathway exists, mediated by apoptosis-inducing factors, but this is outside the scope of this review. Apoptotic signalling pathways are supported by other signalling pathways, such as the nuclear factor-kappa B cells (NF-κB) pathway. NF-κB is a collective term to describe a family of closely related transcription factors that are involved in inflammation, the immune and stress response, and can increase/decrease the transcription of pro- or antiapoptotic proteins depending upon the type and duration of apoptotic stimuli.

For some pathogens, the timely induction of apoptosis enables dissemination, evasion of immune cells, and nutrient access. As part of an effective infection strategy, bacterial pathogens have evolved mechanisms to manipulate apoptosis by expressing or translocating effector proteins to control host signalling pathways. The mechanisms used to manipulate apoptotic pathways vary greatly among pathogens and host cell types. However, in recent years commonalities have emerged that show that translocated bacterial effectors target specific points in apoptotic and apoptotic-related pathways. This review focuses on why translocated bacterial effectors share common targets and modes of action (Table 1) covering the extrinsic (Figure 1), intrinsic (Figure 1), generalist antiapoptotic, and the NF-κB-dependent pro-survival pathway (Figure 1) to promote cell survival.

Trends

Emerging data have shown commonalities in the targeting of specific host apoptotic pathways by translocated bacterial effectors, including common modes of action.

Bacterial effectors manipulate BCL-2 family members, regulating cell survival for bacterial survival and dissemination.

Deletion or loss-of-function in antiapoptotic bacterial effectors has considerable impact on pathogenesis, often significantly stunting the disease state.

A number of bacterial effectors target novel cellular pathways that are poorly understood in the context of the cell biology. As such, they provide valuable insight into not only pathogenesis but also in developing our understanding of apoptotic signaling pathways.

Targeting antiapoptotic bacterial effectors represents a potential therapeutic target for the treatment of disease.

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Table 1. Overview of the Antiapoptotic Bacterial Effectors Discussed[a]

Bacterium	Effector name	Target	Targeted Pathway	Enzymatic Activity	Identified Mode of Action on Apoptosis	Similar Homologue	Refs
Extrinsic Apoptosis							
Escherichia coli	NleB1	DD-containing proteins: FADD/TRADD/TNFR1/RIPK1	Extrinsic/transcription	N-linked glycosyl transferase	(i) Blocks DISC formation to inhibit caspase-8 activation (ii) Modulates GADPH to activity to block NF-κB activation and prevent proapoptotic protein transcription	SseK	[18,19]
Escherichia coli	NleB2	DD-containing proteins: TRADD	Extrinsic	N-linked glycosyl transferase	Blocks DISC formation to inhibit caspase-8 activation	NleB1	[18]
Salmonella enterica (multiple serovars)	SseK 1/2/3	TRADD (identified for SseK1)	Extrinsic	N-linked glycosyl transferase	Inhibits NF-κB signalling	NleB1	[20,21]
Intrinsic Apoptosis							
Helicobacter pylori	CagA	GRB2/c-MET/ZO-1/CRK	Intrinsic	None identified	(i) Upregulates antiapoptotic protein Mcl-1 (ii) Activates PI3K, MAPK, and NF-κB to induces post-translational modification of c-IAPs, Bcl-xL, and BAD		[24]
Chlamydia trachomatis	CPAF	BH-3 only proteins	Intrinsic/transcription	Serine protease	(i) Degradation of proapoptotic BCL-2 family members BIM, PUMA, and BAD (ii) Degrades PARP-1 to regulate apoptotic response (iii) Cleaves transcription factors RFX5, USF1, and p65/RelA to modulate apoptotic gene expression		[29–31] [65,66]
Legionella pneumophila	SidF	BNIP3, Bcl-Rambo	Intrinsic	None identified	Inhibits formation of the permeability transition pore in mitochondria		[33]
Anaplasma phagocytophilum	Ats-1	BAX	Intrinsic	None identified	Uptaken into the mitochondria and processed by the host for insertion into the mitochondrial membrane thereby blocking BAX insertion and MOMP		[35]