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Modulation of host cell apoptotic pathways by intracellular pathogens

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Nearly all steps of the host cell apoptotic cascade can be subverted by intracellular microorganisms. Some pathogens modulate early steps and interfere with sensing of extracellular signals, cellular stress or signal transduction; others target Bcl-2 proteins, caspases, or inhibitor of apoptosis proteins (IAPs). In many cases the exact molecular mechanisms leading to interference with the host cell apoptotic cascade are still unknown. However, there are some examples where bacterial factors that modulate host cell death have been identified. In this review we will summarize recent findings on how intracellular pathogens or their secreted proteins alter the intrinsic and/or extrinsic host cell apoptotic pathways.

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Introduction

The evolution of the human species is characterized by its co-evolution with bacteria. While some bacteria (the microbiota) play key roles in our development, sustenance and well-being, others (pathogens) represent a threat to our health. Consequently, the human body has developed an arsenal of defense mechanisms to prevent infection with pathogens, whereas pathogens themselves have evolved numerous ways to disarm the human defense line. The ensuing battlefield is vast and includes cytoskeleton rearrangement, vesicular trafficking, signal transduction and cell death. Cell death is important for the host to eliminate infected cells and to activate the immune system. However, uncontrolled cell death may also lead to tissue damage, which might promote bacterial dissemination. Thus, the major cell death pathways (apoptosis, pyroptosis and necroptosis) are tightly regulated. Pathogens, in turn, have evolved multiple mechanisms to modulate these cell death pathways.

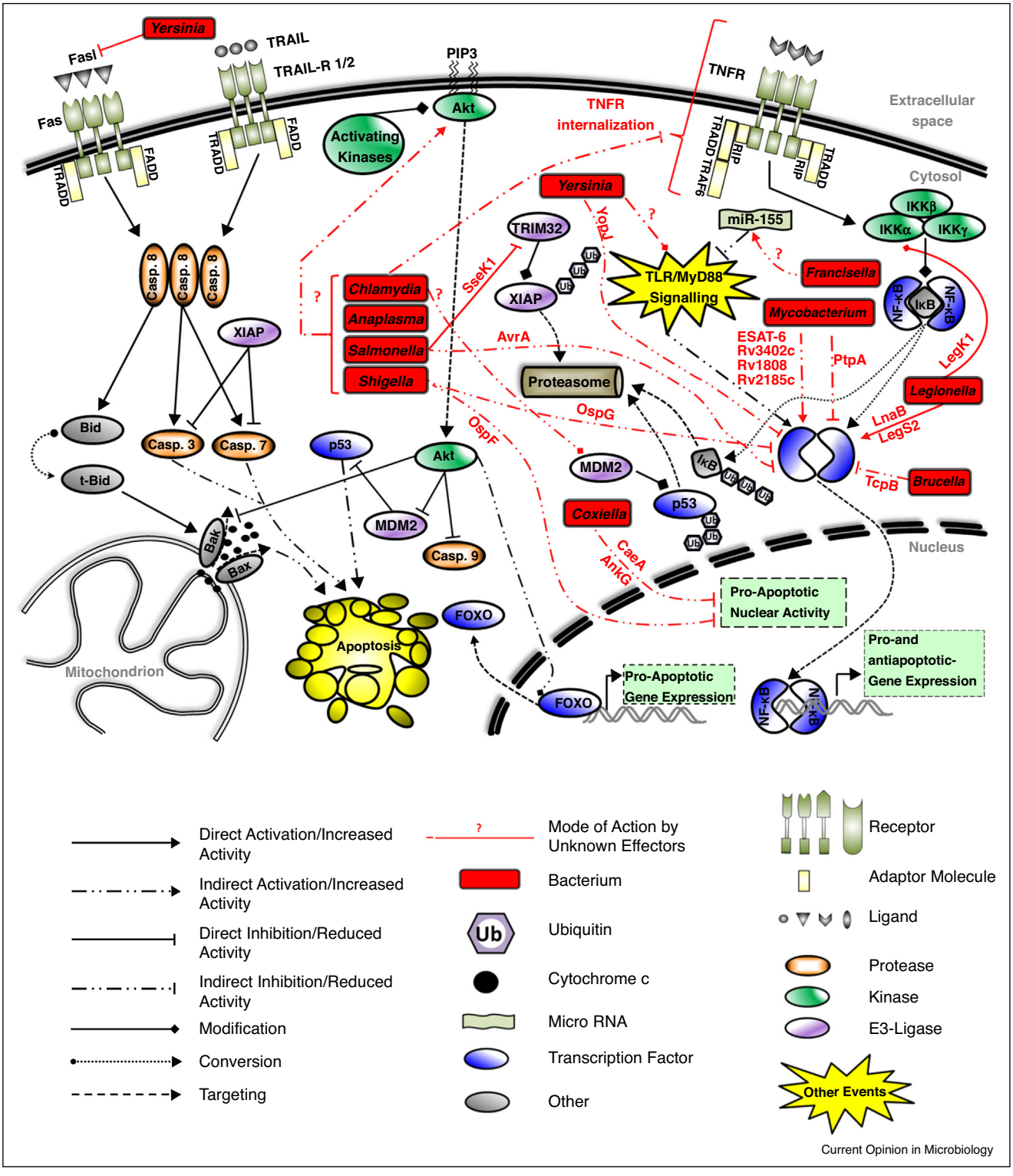
Two main pathways lead to apoptosis: the extrinsic and the intrinsic pathway.

The extrinsic cell death pathway (Figure 1) involves binding of extracellular stimuli to cognate death receptors (DR). These are a subset of the TNFR superfamily and include TNFR1, Fas, and TRAIL-R1/2. Binding of a ligand to its corresponding DR results in formation of a signalosome. In most cases this leads to the activation of caspase 8. Activated caspase 8 mediates apoptosis either directly by activating the effector caspases 3 and 7, or indirectly through proteolysis of the BH3-only family member Bid, generating truncated BID (t-Bid). T-Bid translocates to the mitochondria and activates mitochondrial (intrinsic) apoptosis [1]. Alternatively, the formation of the signalosome might lead to an inflammatory response or to necroptosis [2].

The intrinsic cell death pathway (Figure 2) is initiated in a cell-autonomous manner. Cellular stress, such as DNA damage or ER stress, can lead to apoptosis [1]. This involves activation of the pro-apoptotic molecules Bax and Bak and is regulated by the Bcl-2 protein family [3], which comprises both anti-apoptotic (Bcl-2-like proteins) and pro-apoptotic (BH3-only proteins) regulators. The ratio of positive to negative apoptosis regulators expressed in a cell plays a critical role for the activation status of Bax and Bak. Once activated, Bax and Bak oligomerize and permeabilize the mitochondrial membrane, resulting in the release of cytochrome c and the activation of caspase 9 through the apoptosome [4]. Activated caspase 9 then leads to activation of caspase 3 and 7. These key downstream effector caspases can process at least 1000 proteins [5], triggering cellular changes that result in apoptosis.

Some intracellular pathogens induce host cell apoptosis and thereby prevent being killed by the antimicrobial

Figure 1



Modulation of the extrinsic apoptotic pathway by intracellular pathogens.
Activation of the TNFR superfamily members of death receptors Fas, TRAILR or TNFR is mediated through binding of extracellular FasL, TRAIL or TNFα. Activated Fas and TRAIL-R recruits the initiator caspase 8 through adaptor molecules FADD and TRADD. Caspase 8 activates itself by autoproteolysis and subsequently proteolytically activates effector caspases 3 and 7. Further processing of downstream effectors by caspases 3 and 7 induces apoptosis, if not being directly inhibited by the E3-Ligase XIAP. XIAP itself is subject to ubiquitination by the E3-ligase TRIM32, followed by proteasomal degradation. A link to intrinsic apoptosis is mediated by caspase 8, which can alternatively cleave Bid into a truncated,