



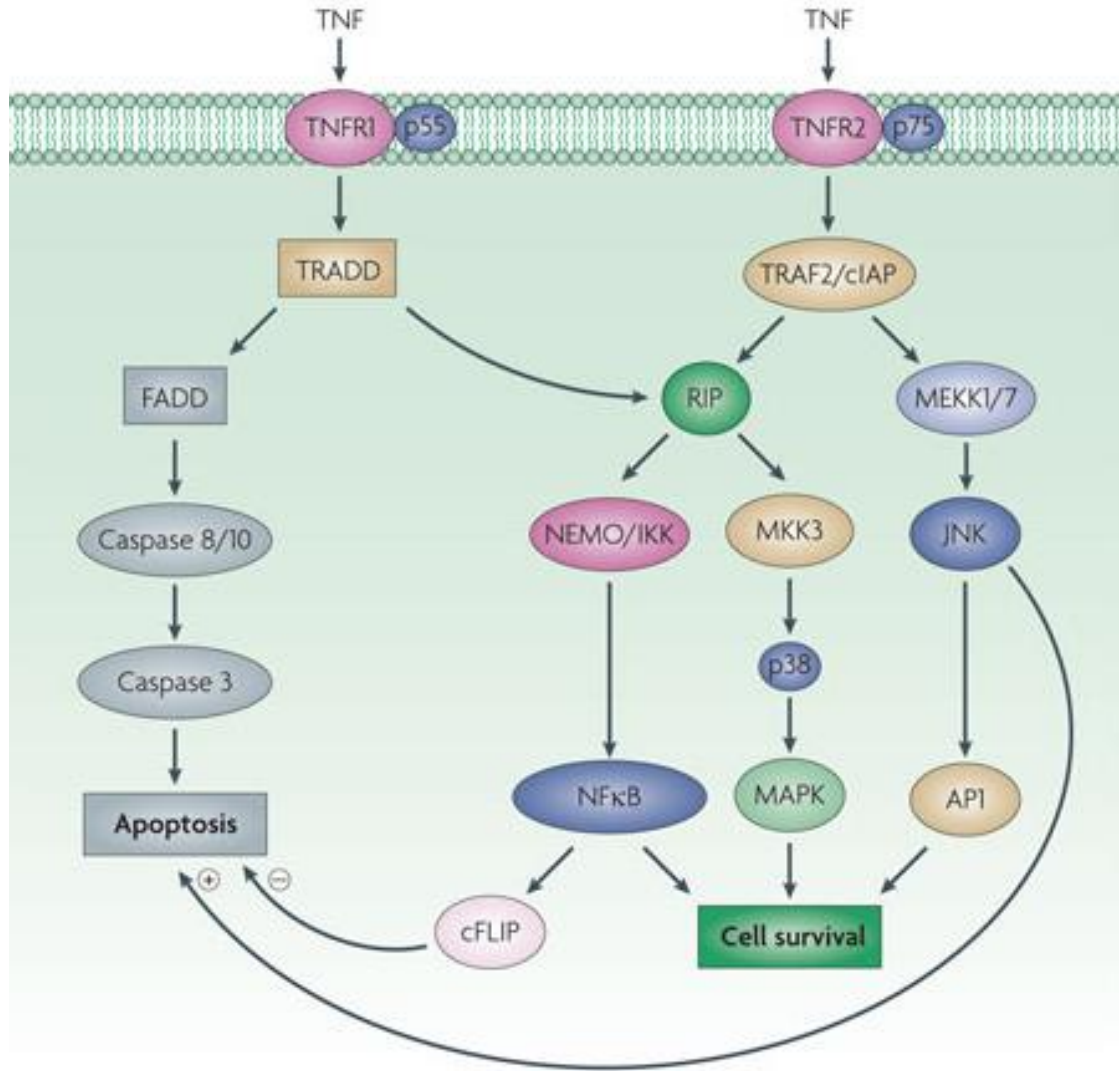
APOPTOSIS: EXTERNAL AND INTERNAL STIMULI



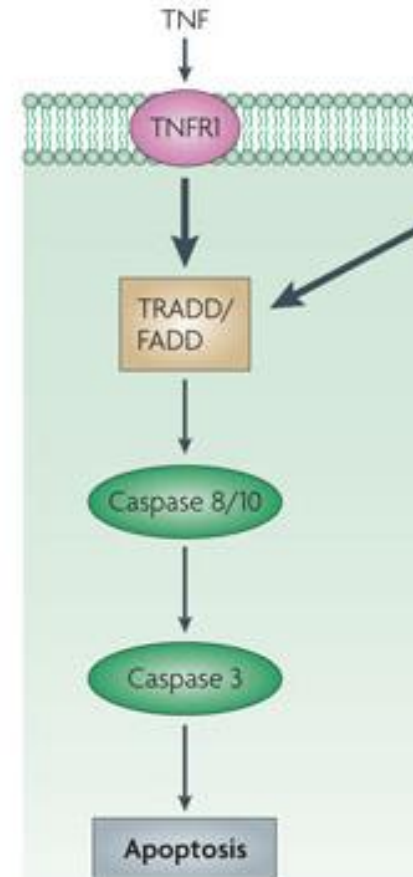
EXTERNAL STIMULI: TNF PATHWAY

- TNF-alpha is a cytokine produced mainly by activated macrophages, and is the major extrinsic mediator of apoptosis. Most cells in the human body have two receptors for TNF-alpha: TNFR1 and TNFR2.
- The binding of TNF-alpha to TNFR1 has been shown to initiate the pathway that leads to caspase activation via the intermediate membrane proteins TNF receptor-associated death domain (TRADD) and Fas-associated death domain protein (FADD).
- cIAP1/2 can inhibit TNF- α signaling by binding to TRAF2. FLIP inhibits the activation of caspase-8. Binding of this receptor can also indirectly lead to the activation of transcription factors involved in cell survival and inflammatory responses.
- However, signalling through TNFR1 might also induce apoptosis in a caspase-independent manner. The link between TNF-alpha and apoptosis shows why an abnormal production of TNF-alpha plays a fundamental role in several human diseases, especially in autoimmune diseases.

a Normal T cells



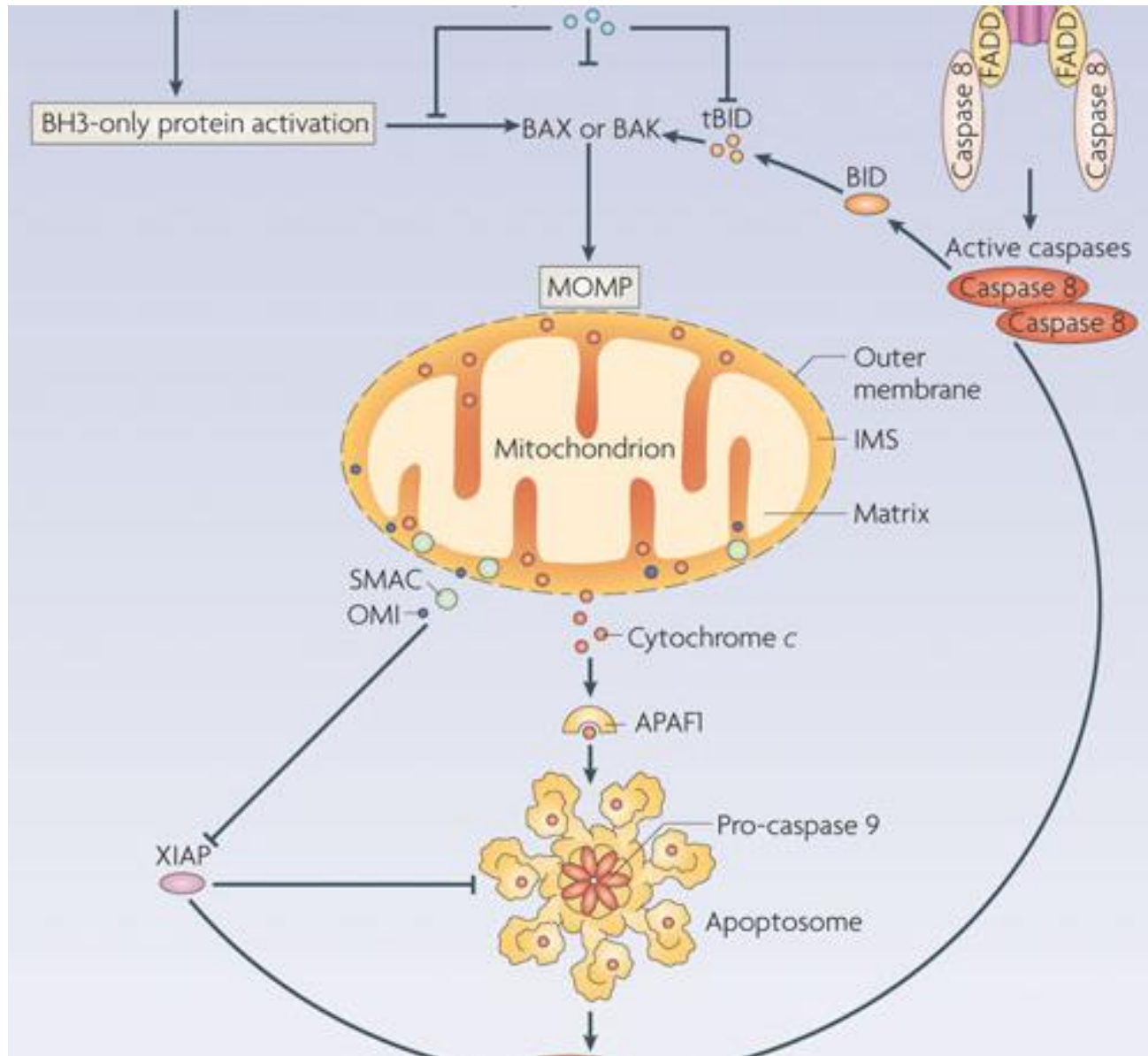
b Abnormal (autoimmune) T cells



TNF PATHWAY

INTERNAL STIMULI PATHWAY

- Intrinsic apoptotic stimuli, such as DNA damage or endoplasmic reticulum (ER) stress, activate B cell lymphoma 2 (BCL-2) homology 3 (BH3)-only proteins leading to BCL-2-associated X protein (BAX) and BCL-2 antagonist or killer (BAK) activation and mitochondrial outer membrane permeabilization (MOMP).
- Anti-apoptotic BCL-2 proteins prevent MOMP by binding BH3-only proteins and activated BAX or BAK. Following MOMP, release of various proteins from the mitochondrial intermembrane space (IMS) promotes caspase activation and apoptosis.
- Cytochrome c binds apoptotic protease-activating factor 1 (APAF1), inducing its oligomerization and thereby forming a structure termed the apoptosome that recruits and activates an initiator caspase, caspase 9. Caspase 9 cleaves and activates executioner caspases, caspase 3 and caspase 7, leading to apoptosis.
- Mitochondrial release of second mitochondria-derived activator of caspase (SMAC; also known as DIABLO) and OMI (also known as HTRA2) neutralizes the caspase inhibitory function of X-linked inhibitor of apoptosis protein (XIAP).



INTERNAL STIMULI PATHWAY