Fas/Fas-L and its involvement in Autoimmune Diabetes

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Apoptosis

- Cysteine proteases a part of the caspase protein family are activated specifically in apoptosis
- Caspases – proteins that selectively cleave a restricted set of target proteins at one or few positions in the primary sequence; results in inactivation or activation of the target protein
- Caspases are synthesized as enzymatically inert zymogens that require proteolytic cleavage to be activated

Three general mechanisms of caspase activation

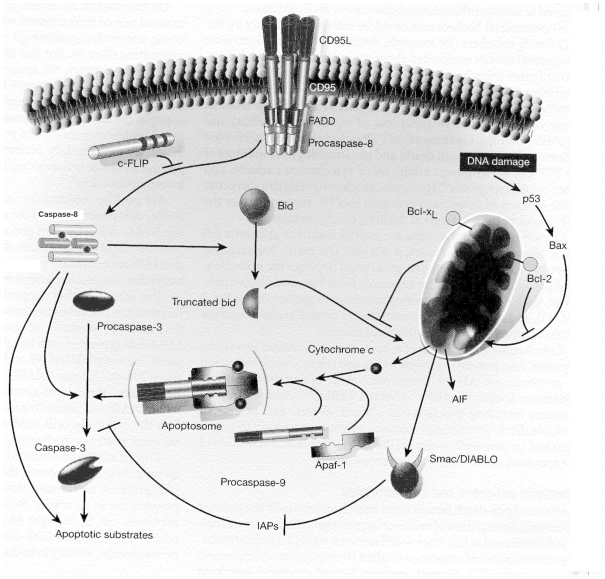
- Association with a regulatory subunit – association with a dedicated protein cofactor, Apaf-1 (caspase-9)
- Induced Proximity – upon ligand binding, death receptors, CD-95 aggregate and form membrane-bound signalling complexes which recruit several caspase molecules, under these crowded conditions, the intrinsic protease activity of the proteins mutually cleave and activate one another (caspase-8, they key initiator in the death receptor pathway)
- Processing by an upstream caspase – activation of the caspase by an already activated caspase molecule (caspase –3, -6, -7)

Death Receptor Pathway: Type I

- Triggered by members of the death-receptor superfamily (ex CD-95)
- Binding of CD-95 ligand to CD-95 induces a clustering of receptors and initiates the formation of death inducing signaling complex (DISC)
- Complex recruits multiple procaspase-8 molecules, via the Fas- associated death domain protein (FADD), resulting in caspase-8 activation through induced proximity

Death Receptor Pathway:Type II

- Very little DISC is formed, so the caspase cascade cannot be propagated directly but must be amplified via the mitochondria
- Caspase-8 cleaves Bid, which activates the mitochondria
- Activated mitochondria releases pro-apoptotic molecules such as cytochrome c and Smac/DIABLO which work with Apaf-1 to activate procaspase-9, which then activates downstream caspases which induce apoptosis



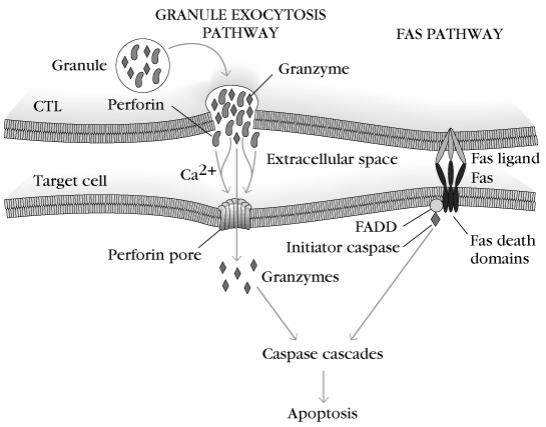
CTL – Cytotoxic T Lymphocytes Granule Exocytosis Pathway

- Contain perforin and granzyme molecules in granules that are exocytosed to extracellular space when in close proximity to target cell
- Perforin and granzyme enter target cell via perforin pores inducing caspase cascades that cause apoptosis

CTL – The FAS (CD-95) pathway

- Fas ligand exists as a transmembrane protein which connects with Fas on the target cell
- The ligation of the two trimeric Fas units results in the activation of the death receptor pathway resulting in apoptosis

Proposed model of target-cell apoptosis stimulated by CTLs



Applications of CD-95 in the Immune System

- CD-95L is expressed continuously in immune-privileged sites such as the testis and the eye, which may be used as tumor suppressors or altered to delay the rejection of transplants
- Viral gene products of HIV-infected cells penetrate non-infected cells in the immune system, especially CD+4 cells, rendering them hypersensitive to apoptosis via CD-95. This suggests that CD-95 may have a significant role in the T helper cell depletion of AIDS. This information could prove useful in the development of therapeutic strategies aimed at intervening with the loss of CD+4 cells in HIV positive individuals.