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Cytotoxic lymphocytes originated granular serine proteases: An update of their functionalities

Jamshaid Ahmad
University of Peshawar, Pakistan

Cytotoxic Lymphocytes (CL) eliminate virus infected and tumor cells by initiating target cell apoptosis through two pathways: Ligation of cell surface death receptors and the granule exocytosis pathway. The granule exocytosis pathway involves secretion of cytotoxic granules containing perforin and granzymes into target cells, thereby initiating apoptotic pathways. Perforin is a pore forming protein that utilizes a poorly understood mechanism to efficiently deliver granzymes, a family of serine proteases synthesized by CL, into the target cell cytoplasm. In humans, there are five granzyme genes (GzmA, GzmB, GzmH, GzmK, GzmM) located at three different chromosomal loci. Based on their specificities theses serine proteases can be grouped into tryptases (GzmA and GzmK), aspases (GzmB) and chymases (GzmM and GzmH). These different granzymes perform intra and extracellular functions. Three intracellular roles, dependent on perforin-mediated delivery into target cells, have been described: Cytotoxicity, accessory functions and cytokine signaling. Extracellular functions, independent of perforin have been reported for some granzymes and involve cleavage of extracellular matrix; possibly to facilitate immune cells migration. Although less data is available for these proteases, however the over-expression of these genes in certain disease conditions like autoimmune diseases has made it a subject of interest for designing potential inhibitors to stop their activity, as when they are synthesized in excess, becomes lethal to normal cells in a human body. This study also highlights the significance of these proteases and their possible involvement in various disease conditions.

jamshaidbiotech@yahoo.com