Apoptosis in immune-mediated diseases

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ABSTRACT

Apoptosis plays a significant role in both the physiological and pathological process. A dysfunctional apoptotic system can lead to either excessive removal or prolonged survival of cells. Therefore, dysregulation is involved in the pathogenesis of a variety of immunological diseases. The present review aims to provide an overview regarding role of apoptosis in immune-mediated disease.

KEY WORDS: Apoptosis, erythema multiforme, immune mediation, lichen planus, Systemic lupus erythematosis

The word apoptosis is originated from the ancient Greek mean "Falling off or dropping off" of petals from flowers or leaves from a tree.[1] It was first coined by Kerr *et al*. Wyllie and Curie in 1972 described apoptosis as a morphological and biochemical process leading to controlled cellular self-destruction.[2]

In apoptosis signaling cascade, there are four major factors involved in triggering and influencing the process. These includes caspases, Bcl-2 family proteins, tumor necrosis factor receptor (TNF-R) superfamily and adaptor molecules (protein).[3]

Caspases are a family of cysteine proteases that are main executors of the apoptotic process. Caspases are classified into initiator caspases 2, 8, 9, 10, effector caspases 3, 6 and inflammatory caspases 1, 4, 5, 11, 12, 13 and 14.[4] There are three pathways to activate caspases.[5] These are intrinsic or mitochondrial pathway, extrinsic pathway or the pathway dependent on the death receptors and recently known less understood intrinsic endoplasmic reticulum pathway. Intrinsic and extrinsic pathway ultimately leads to the common pathway or the execution pathway of apoptosis. Intrinsic pathway is regulated by Bcl-2 family membrane of proteins that directly regulate the release of cytochrome c into the cytoplasm. Extrinsic pathway is mediated by the activation of so-called "death receptors," which are cell surface receptors that transmit apoptotic signals after ligation with specific ligands. The best-known death receptors are TNF-R1 related protein called Fas and their ligands, TNF and Fas ligand (FasL) respectively.[1,2] Adaptor molecules are the connection between cell death initiator (caspases) and the cell death regulator (death receptors) and Bcl-2 family members. Ex.TNF-R1-associated death domain protein (TRADD) and receptor interacting protein.[3] Thus, apoptosis plays an efficient role of cell death program requiring modifications. A dysregulated apoptotic system can lead persistence of survival signals. Alternatively apoptosis can cause detachment of epithelial cells from neighboring cells resulting in excessive removal This apoptosis is induced by loss of adhesion of cells known as Anoikis.[1] The role apoptosis in immune mediated diseases such as oral lichen planus (OLP), erythema multiforme (EM), lupus erythematosus, pemphigus vulgaris, epidermolysis bullosa, oral graft versus host disease (GVHD) and Sjogren's syndrome are discussed.

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Apoptosis and Oral Lichen Planus

Oral lichen planus is an autoimmune chronic disease that affects the tongue and oral mucosa with papule lesions or rashes.[6] The pathogenesis of OLP is unclear,[7,8] but apoptosis has been evaluated in epidermal cells, indicating a role in epithelial destruction.[9] Histological degeneration of basal keratinocytes form colloid bodies and suggest that they are apoptotic keratinocytes.[1]

Mechanism involved for keratinocyte apoptosis

- T-cell secreted TNF-alpha binding the TNF-alpha R1 receptor on keratinocyte receptor
- T-cell surface CD95 L (FasL) binding to CD95 (Fas) on the keratinocyte receptor
- T-cell secreted granzyme B entering the keratinocyte in perforin induced membrane pores.

All these mechanisms may activate the keratinocyte caspase cascade resulting in keratinocyte apoptosis. The reduced or absent rate of apoptotic inflammatory cells has been thought to the development of OLP.[10]

Apoptosis and erythema multiforme

Erythema multiforme is a distinct skin disorder characterized by with or without mucous membrane involvement and eventually involvement of both. This includes a wide range of clinical patterns. EM minor, major, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis.[11] Histopathology of EM/SJS/toxic epidermal necrolysis (TEN) mononuclear clear cell infiltration into the epidermis and/or mucous membrane. Epidermis and dermis were more intense in the SJS/TEN group than the EM minor/major groups. Pathogenesis of keratinocyte apoptosis was triggered by drug-specific cytotoxic T lymphocyte (CTL), regulated proteins like p53 and Bcl-2 family proteins and Fas activation and FasL system. Epidermal cell has been found that perforin and granzyme B mediates apoptosis.[12]

Apoptosis and lupus erythematosis

Systemic lupus erythematosis is a multifactorial autoimmune disease. Influenced by genes and behavior of circulating lymphocytes and/or impaired clearance of apoptotic bodies may increase the quantity of nuclear antigens presented to T lymphocytes. The dysfunction due to the direct consequence of alterations in proteins/genes such as Fas, Bcl-2 and clq.[13]

Apoptosis and pemphigus vulgaris

Pemphigus vulgaris is a group of autoimmune blistering disorder characterized by loss of keratinocyte cell adhesion that leads to clinical blister formation.[14] Proapoptotic effect of pemphigus inhibited partially by induction of anti-Fas-L blocking antibodies. Sera on cultured keratinocytes and other mechanism may contribute to induction of apoptosis.[15] Activated caspase-3 immunohistochemistry recommended for the detection and qualification of apoptosis in the tissue section (January 17, 2003 Journal of Oral Pathology).

Apoptosis and epidermolysis bullosa

Hereditary vesiculo bullous lesion characterized by blistering of the skin and oral mucosa due to basal keratinocyte fragility.[16] Susceptible to apoptosis by activation of caspases 3 and 8 in this keratinocyte cellular model. Suggesting that the susceptibility of keratinocytes to caspase 8 mediated apoptosis is increased in mutated k-14 because of the impairment of the cytoprotective mechanism mediated by k-14 TRADD interaction.[17]

Apoptosis and the oral graft versus host diseases

It is an unexpected complication of bone marrow transplantation and characterized by an immune mediated attack by donor immune cells against various recipient host cells and tissues. Graft versus host disease (GVJD) occurs at minor histocompatibility loci programmed cell death as a major constituent in the pathogenesis of GVHD. The oral lesions of GVHD are clinically and histologically lichenoid in nature. Apoptosis not only plays a major role and contribute to a wide spectrum of both inflammatory and neoplastic disorders.[18] CTLs mediated by apoptotic pathway in GVHD. Through a proteolytic cleavage cascade, caspases and several intracellular proteases participate in apoptotic death signal.[19,20] Phosphorylation pathways based on regulation of signal transduction cascades.[21] Experimental study confirms the pathway even in the absence of immune cells, suggesting an additional mechanism for the induction of target cell injury.

Apoptosis and Sjogrens syndrome

Sjogrens syndrome is one of several autoimmune disorder mainly affects the exocrine glands and characterized by lymphocytic infiltration of salivary gland and lacrimal glands resulting in dryness of mouth and eyes.[22] Cytokines play an important role in the regulation of immunity and dysregulation of Sjogren's syndrome (cytokines in Sjogren's syndrome 2009 November 15 (8) NIH public access).

Role of apoptosis in relation to Sjogren's syndrome

- Defective apoptosis could lead to lymphoid cell accumulation and chronic inflammation in exocrine glands
- Increased apoptosis of epithelial cells might explain the loss of secreting epithelium, and
- Orderly destruction of cellular components might induce autoantibody production.[23]

The alpha fodrin binds to ankyrin, which contains a cell death domain. Highly suggestive of a role for calpain and caspase mediated cleavage of alpha fodrin in the functional activation of autoreactive T-cells in Sjogren's syndrome and Fas/Fas L – mediated apoptosis have a role in the development of autoimmune tissue destruction.[22]

Conclusion

Apoptosis has a major implication in health and diseases. Homeostasis is maintained between Mitosis and cell death by apoptosis. Understanding apoptotic signaling mechanisms help in understanding a wide variety of diseases. Moreover, there extensive association of apoptosis in the pathogenesis of various oral diseases and knowledge about it at different levels is essential from the therapeutic point of view.

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