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Role of apoptosis in pathogenesis of oral lesions: Molecular approach

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Abstract

Research in histology, genetics, and molecular biology indicate that virtually all animal cells are armed with the genetic machinery to die. Under normal physiological circumstances, damaged cells are removed through a genetically programmed type of cell death. The aberrations in the regulation of genetically programmed cell death have been found to cause disease and deformity. Cell death, the ultimate result of cell injury, is one of the most crucial events in pathology, affecting every cell type and being the major consequence of ischemia (lack of blood flow), infection, toxins and immune reactions. Cell death is critical during normal embryogenesis, lymphoid tissue development and normally induced involution and is the aim of cancer radiotherapy and chemotherapy. This article discusses role of apoptosis in pathologies of potentially malignant, malignant, autoimmune and reactive lesions of oral cavity.

Keywords: apoptotic bodies, BCL-2, caspases, MDM2 gene, necrosis, PMDs

1. Introduction

The term programmed cell death was introduced in 1964, proposing that cell death during development is not of accidental nature but follows a sequence of controlled steps leading to locally and temporally defined self-destruction^[1]. During necrosis, the cellular contents are released uncontrolled into the cell's environment which results in damage of surrounding cells and a strong inflammatory response in the corresponding tissue^[2, 3]. Apoptosis, by contrast, is a process in which cells play an active role in their own death. Light microscopic identification of apoptosis usually involves single cells or occasionally small groups of cells. The apoptotic cell shrinks and separates from its neighbors and is surrounded by a halo like clear space. The nuclear chromatin breaks up into irregular crescentic, beaded or nodular masses; small basophilic apoptotic bodies may be identified. The complete absence of normal cellular detail is due to protein denaturation and nuclear dissolution. Ultra structurally necrotic cell initially swells because cell membrane volume control is lost; the cell then lyses, organelles disintegrate, and with nuclear dissolution, there is random DNA degradation^[4]. The cytoplasmic contents of lysed necrotic cells excite an inflammatory reaction. Ultra structurally, apoptosis has a characteristic morphology: initially there is loss of cell junctions and specialized membrane structures, such as microvilli, with the formation of contorted surface protuberances (or) blebs. Condensation beneath the nuclear membrane is irregular, crescentic or bead like, highly osmiophilic chromatin, which corresponds to cleavage of DNA into large fragments. The cell then breaks up into resistant, membrane bound fragments called apoptotic bodies^[5].

Genetic basis of Apoptosis

Important genes involved in cell cycle regulation are: c-myc, c-fos, c-jun, p53, kinases and phosphatases^[6]. The major determinants of the "apoptotic phenotype" in lymphocytes are the levels of expression of Bcl-2, Bcl-x L, Fas and Fas ligand (FasL)^[7-10]. Both apoptotic signaling pathways converge at the level of the specific proteases-the caspases. There are 14 mammalian caspases which are synthesized as pro-enzymes, which usually undergo proteolysis and activation by other caspases in a cascade^[11-13]. Peptide caspase inhibitors can inhibit

downstream caspase activation and subsequently apoptosis. In intrinsic or mitochondrial pathway, internal damage to the cell (e.g., from reactive oxygen species) causes protein, Bax, to migrate to the surface of the mitochondrion where it inhibits the protective effect of Bcl-2 and inserts itself into the outer mitochondrial membrane punching holes in it and causing cytochrome c to leak out [14, 15]. This binds to the protein Apaf-1 ("apoptotic protease activating factor-1") utilising the energy provided by ATP, thus forming apoptosomes. Caspases are activated, thus causing phagocytosis of the cell. and degradation of chromosomal DNA.

In Extrinsic or death receptor pathway, Fas and TNF receptors with their receptor domains are exposed at the surface of the cell. The binding of the complementary death activator (FasL and TNF respectively) transmits a signal to the cytoplasm that leads to activation of caspase 8, which causes phagocytosis of the cell. In AIF pathway, apoptosis-inducing factor (AIF) is released from intermembranous spaces of mitochondria, binds to DNA, and then triggers the destruction of the DNA and cell death.

Apoptosis in physiological processes of human body

Apoptosis is useful for normal physiological conditions, as in formation of the fingers and toes of the fetus, sloughing off of the inner lining of the endometrium at the start of menstruation, formation of the proper connections (synapses) between neurons in the brain.¹⁸ The majority of the developing lymphocytes die either during genetic rearrangement events in the formation of the antigen receptor, during negative selection or in the periphery, thereby tightly controlling the pool of highly efficient and functional cells and at the same time keeping lymphocyte numbers relatively constant [Rathmell, 2002]. Programmed cell death is needed to destroy cells that represent a threat to the integrity of the organism. The process of apoptosis is controlled by a diverse range of cell signals, which may originate either extracellularly (extrinsic inducers) or intracellularly (intrinsic inducers). Extracellular signals may include toxins, hormones, growth factors, nitric oxide or cytokines, and therefore must either cross the plasma membrane or transduce to effect a response. These signals may positively or negatively induce apoptosis. The binding and subsequent initiation of apoptosis by a molecule is termed positive, whereas the active repression of apoptosis by a molecule is termed negative.

Apoptosis in pathological conditions

In multicellular organisms, homeostasis is maintained through a balance between cell proliferation and cell death. Abnormal regulation of apoptosis has been implicated in the onset and progression of many diseases. Many disorders can be classified based on whether they are associated with too much or too little apoptosis.¹⁷ During their pathogenesis, however, most apoptotic disorders feature too much apoptosis of one type of cell and too little elimination of another kind of cell.

Leukoplakia & Lichen planus: The leukoplakia lesions showed positive keratinocyte staining for P53, P21, MDM2 and BCL-2, and these positive cells are distributed in the basal and prickle cell layers. In contrast oral lichen planus lesions shows keratinocytes positive for P53, P21, MDM2 and BCL-2, that were distributed predominantly in the basal strata of the mucosa.¹⁹ There was a prominent expression of FaSR/ FaSL in oral lichen planus, with a rather uniform distribution throughout the inflammatory cell infiltrate. This expression of

Fas proteins was more abundant in the basal cell area compared to the suprabasal cell layer. Quantitative assessment of apoptosis in oral lichen planus done by Balvinder K. *et al*, concluded that apoptotic cell was detected approximately per millimeter of basal layer, with cell death increasing with lymphocytic infiltration. Epithelial cell proliferation did not correlate with apoptosis, BCL-2 expression was weak (or) absent in basal cells, and Bax was localized to upper prickle cells. The topographical distribution of keratinocytes expressing proteins involved in apoptotic signal transduction pathways varies among different lesions. The percentage of supra basal keratinocytes expressing BCL-2 and MDM2 in leukoplakia lesions were higher than those in Oral lichen planus. Topographical distribution of two oncoproteins, BCL-2 and MDM2 in leukoplakia indicates that leukoplakia has more potential for malignant transformation than oral lichen planus.

Role of Apoptosis in Oral malignancies

Experimental studies, known that tumor cell apoptosis is regulated by numerous oncogenes and tumor suppressor genes. Apoptotic index (AI) is defined as the percentage of apoptotic cells bodies in the total number of tumor cells [16]. According to Arends *et al*, tumors can have low AIs intermediate AIs, or high AIs. Tumors of a particular type had an AI that was restricted within narrow range. There is an increase in apoptosis from intra epithelial neoplasia to carcinomas in which the AI correlates with Gleason grade. Normal human melanocytes and melanocytes in benign nevi express BCL-2 and this correlates with minimal apoptosis. BCL-2 expression is reduced as these tumor acquire a more malignant phenotype. In tumors undergoing metastases, Bcl-2 levels have been found to be largely inactive [6].

The carcinogenic transformation is postulated to result from alterations of apoptotic signal transduction proteins in epithelial cells A recent hypothesis implicates malfunction in apoptotic signaling events as the cause of malignant changes in a variety of cell types. (Thompson C.B. 1995). This hypothesis is supported by the findings that several proteins identified in apoptotic signaling pathways regulate cell growth and cell division. Such apoptotic signaling proteins include tumor suppressive protein P53, and cyclin dependent kinase (CDK) inhibitor P21 and onco proteins MDM2 and BCL-2.[6] MDM2 onco-protein, originally cloned from a spontaneously transformed BALB/c mouse cell line, is a known inhibitor of P53 mediated transcriptional activation. The MDM2 genes possess P53 response elements, and inhibit P53 dependent cell cycle arrest and apoptosis. Similarly increased expression of BCL-2 has been reported in nasopharyngeal and other carcinomas.

Recent advances and role in treatment

Insight into the mechanisms of apoptosis leads to a surge in research into novel therapies for degenerative, neoplastic, and autoimmune disorders. Gene therapies hold good potential in future. Injectable molecules are targeted at the upstream modulators of apoptosis (eg. Growth factors (or) soluble FaSL), which will help in controlling undesirable apoptotic changes. For apoptotic based therapy to be feasible, therapeutic molecules must be delivered to and active only in specific target cells. Considering the complexity of apoptosis signaling combinational therapies that target multiple cell death molecules for activation or inactivation may offer the best hope of therapeutically modulating apoptosis

Conclusion

Understanding the physiological process of apoptosis at the molecular level not only affords insights into diseases pathogenesis but also opens new avenues for developing diagnostic, prognostic and therapeutic tools. Understanding the molecular apoptotic pathway will allow the development of non-pharmaceutical therapies in future.

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