

Review Article

Apoptosis in Oral Health and Disease: a Brief ReviewDr. Shwetha Nambiar¹, Dr. Veda Hegde²

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Abstract: Apoptosis is a well defined mode of cell death which plays an important role in the development, regulation, and maintenance of the cell count in all multicellular organisms. It is responsible for the cell-death events that occur right from the formation of the early embryo and the sculpting and moulding of organs in adult life. Apoptosis has role in both health and diseases with defective apoptotic mechanisms leading to wide range of pathologies including oral diseases. This review focuses on the role and significance of apoptosis in various physiologic as well as pathologic processes affecting the oral cavity.

Keywords: Apoptosis, autoimmune, Bcl-2, Fas, Fas L, dentinogenesis, keratinocyte

INTRODUCTION

The word apoptosis is derived from the Greek word for 'dropping off' or 'falling off' of petals from flowers or leaves from trees. In 1972, Kerr FR et al coined the term apoptosis, to describe, 'programmed cell death' a process of cell death involved in cellular development and aging [1].

Apoptosis is a form of 'co-ordinated and internally programmed cell death' having a role in a variety of physiologic and pathologic conditions. It is a complex, tightly regulated and active cellular process whereby individual cells undergo self destruction in a manner that neither injures the neighbouring cells nor elicit any inflammatory reaction unlike necrosis [1].

Apoptotic cell death plays a significant role in maintenance of the normal physiological state, as well as responsible for disease process of the body. A dysfunctional apoptotic system is implicated in pathogenesis of a variety of diseases including oral pathologies [2].

The present review emphasizes the role and significance of apoptosis in various oral diseases.

IN HEALTH

The development and maintenance of multicellular biological systems depends on a complicated interplay between the cells forming the organism, it sometimes even seems to involve a selfless

behaviour of individual cells in favour of the organism as a whole. During development many cells are produced in excess which eventually undergo programmed cell death and thereby contribute to metamorphosis of many organs and tissues [3].

Cells of an adult organism constantly undergo physiological cell death which must balance the proliferation in order to maintain homeostasis in terms of constant cell numbers [4, 5]. Apoptotic processes are of widespread biological significance, being involved in development, differentiation, proliferation/homoeostasis, regulation and function of all systems and in the removal of defective or harmful cells [5].

In adulthood, about 10 billion cells die every day simply to keep balance with the number of new cells arising from the body's stem cell populations. This normal homeostasis is not just a passive process but regulated through apoptosis. The same mechanisms serve to "mop up" damaged cells. With ageing, apoptotic responses to DNA damage may be less tightly controlled and exaggerated, contributing to degenerative disease [6].

APOPTOSIS OCCURRING IN ORAL CAVITY

During tooth development, controlled proliferation, differentiation and elimination of particular cell populations are considered to determine the final tooth shape, size and position in the jaw. Apoptosis occurs during all stages of tooth

development: early stages of morphogenesis, dentinogenesis, amelogenesis and during eruption. The restricted temporo-spatial patterns of apoptotic cells suggest multiple roles for apoptosis in dental development. For example, central cells of the invaginating dental epithelium undergoing apoptosis suggest involvement of the programmed cell death in budding morphogenesis [7].

Apoptosis in the budding morphogenesis of dental epithelium

Apoptosis in the most superficial layer of the dental epithelium (early and middle bud stages) may support proliferation of underlying basal mucosal cells. The restricted apoptotic areas in the mucosal layer seem to be a factor for determining the position of the tooth germ. Apoptosis occurring in the dental lamina seems to prevent the mesial and vertical overgrowth of the tooth germ and thus to maintain the exact position of the tooth germ in the jaw. The reduction of the dental lamina and rudimentary tooth germs, which disappear during odontogenesis, occurs via apoptosis [8].

The localization of apoptotic cells of the enamel knots reflects a significant role of apoptosis in the regulation of tooth form. Enamel knots are morphologically distinct transient thickening of the enamel epithelium which has important signaling centres regulating tooth morphogenesis. The primary enamel knot appears during transition from bud to cap stage and it determines and regulates the formation of tooth cusps. Secondary enamel knots are associated with the formation of additional cusps during bell stage. Apoptosis is seen in both primary and secondary enamel knots. Thus apoptosis may be the mechanism whereby the enamel knot cells are removed after fulfilling their tasks in initiating cusp formation. Several signal molecules are expressed in the enamel knot including FGF-4, BMP-2,4,7, Shh etc [9].

Apoptosis in maintaining the final size and position of tooth

Disruption of the dental lamina results in loss of connection between tooth germ and oral epithelium during bell stage. So during bell stage apoptosis is located in the dental lamina and the adjacent outer enamel epithelial cells. The apoptosis in the dental lamina prevents mesial and vertical overgrowth of the tooth germ and is important in governing final size and position of tooth in the jaw [10].

Apoptosis in maintainance of normal oral tissues

During embryogenesis, specific selected cells are destined to die by apoptosis. During the formation of oral epithelium, epithelial-mesenchymal interaction play an essential role in determining which cells are to be shed and which ones are to survive. The lining of the oral mucosa is covered by a dynamic epithelium that is constantly renewed by proliferating basal cells. Basal keratinocytes differentiate and migrate through

epithelial layers to the surface where they are shed off as keratin squames. In this way, keratinocytes are programmed to divide, differentiate, and die by the process referred to as terminal differentiation. Therefore, for maintenance of epithelial structure and function, cell proliferation, terminal differentiation, and spontaneous apoptosis have to be strictly regulated. The Bcl-2 family of proteins appears to be involved in regulating terminal differentiation of keratinocytes.¹⁰ The antiapoptotic Bcl-2 and Bcl-XL proteins are preferentially expressed in the basal and lower spinous layers, whereas the proapoptotic protein Bax is expressed in the more superficial cell layers. Epithelial cells also require contact with each other for survival signals. Detachment of an epithelial cell from its neighbours triggers a form of spontaneous apoptosis termed “anoikis.” Anoikis is involved in a wide range of tissue homeostasis and development [11, 12].

Role of apoptosis in tooth development

Multiple roles for apoptosis in odontogenesis have been suggested. Apoptosis may:

- Play a role in the disruption of dental lamina
- Occur in the central cells of the invaginating epithelium during the early and middle bud stage, which may support the proliferation of underlying basal, mucosal cells
- Play a role in deciding the final position and size of the tooth in the jaws
- Prevent tooth appositions in edentulous areas by preventing epithelial overgrowth between the teeth
- Play a role in deciding the final number of teeth,
- Role in morphogenic mechanism in shaping the final crown tooth morphogenesis [12].

Apoptosis in amelogenesis

Early amelogenesis consists of a sequence of cell-to-cell and matrix-to-cell interactions. The ameloblasts undergo a remarkable transition from protein secretory cells to cells active in enamel matrix maturation. This transition is accompanied by apoptosis of approximately 25% of the ameloblasts. An additional 25% of ameloblasts undergo apoptosis when maturation of enamel matrix takes place with removal of water and protein from the increasingly mineralized matrix [8].

The ratio of Bax to Bcl-2 determines the susceptibility of cells to programmed death following an apoptotic stimulus. The intense localization of Bcl-2 and light staining for Bax in the pre-ameloblasts suggest that apoptosis is inhibited in the proliferating pre-ameloblasts. In the late secretory and transition ameloblasts, and adjacent stratum intermedium, evidence of apoptosis of the ameloblasts can be observed. Bax and Bcl-2 were co-localized in the proximal ends of late secretory, transition and early maturation-stage ameloblasts, but immunoreactivity for

Bax markedly increased in the proximal ends of late secretory and transition ameloblasts, while the Bcl-2 staining appeared to be lighter. This suggests that Bax antagonizes Bcl-2 function, limiting the ability of Bcl-2 to prolong cell survival. In the early maturation stage, Bax staining is less than Bcl-2. Apoptosis occurs in reduced ameloblasts during tooth eruption. Naturally occurring cell death aids in tissue remodeling and eliminates supernumerary cell populations [13].

Apoptosis in dentinogenesis

At the advancing stage of dentinogenesis, odontoblasts become crowded as the pulp space is reduced. It is seen as pseudostratified layer and an apoptotic elimination of an important percentage of odontoblasts occur. Secondary dentin deposition associated with odontoblast reorganization as a single layer results in a hyperbolic decrease in odontoblast number, which seems to result from massive apoptosis [8].

During dentinogenesis, apoptosis is found in odontoblasts, sub-odontoblastic regions, central pulp fibroblasts, and perivascular endothelial cells. It has been found that Bcl-2 affects cellular adhesion, proliferation, and differentiation besides its role as an anti-apoptotic factor [14].

Apoptosis in bone remodelling

In the postnatal and adult skeleton, apoptosis is integral to physiological bone turnover, repair, and regeneration. The balance of osteoblast proliferation, differentiation, and apoptosis determines the size of the osteoblast population at any given time. Apoptosis may occur through one of many death receptors in the tumor necrosis factor (TNF) receptor superfamily. TNF-alpha has been linked to osteoblast apoptosis in vitro. Osteoblast survival and death, RANKL and OPG have been implicated as regulators of cell survival. Apoptosis may be proliferation-dependent or proliferation-independent. Proliferation is associated with apoptosis through the actions of tumor suppressor genes such as p53, which controls key stages of the cell cycle to ensure that cells in which DNA becomes significantly flawed are eliminated through cell death [15].

In humans, increased osteocyte apoptosis has been correlated with sites of rapid bone turnover, during bone formation and fracture healing. Osteoblasts undergo an orderly developmental progression that ultimately ends in apoptosis [16].

Apoptosis in the fusion of palatal shelves

The processes of apoptosis and epithelial-mesenchymal transformation have been identified as two major mechanisms by which secondary palatal shelves achieve fusion. TUNEL staining showed that the number of apoptotic cells in the palatal shelves increased as the inter shelf distance increased,

becoming marked in shelves that did not achieve fusion. The amount of epithelial-mesenchymal transformation, however, decreased with increasing inter shelf distance. Epithelial-mesenchymal transformation and apoptosis to palatal shelf development and fusion can be altered by physical proximity. Therefore, one mechanism behind clefting in utero may result from an imbalance in epithelial-mesenchymal transformation and apoptosis as observed in vitro where palatal shelves are challenged to fuse by physical separation [17].

APOPTOSIS AND DISEASE

Disease in which apoptosis is involved is divided into two groups:

- Those in which there is an increase in cell survival (Diseases with the inhibition of apoptosis)
- Those in which there is an increase in cell death (Diseases associated with excess of apoptosis) [4]

Apoptosis in autoimmune diseases

Oral Lichen Planus (OLP):

Lichen planus is a disease of the skin and/or oral mucous membrane and is a disease of the stratified squamous epithelia. One of the histopathological features of lichen planus shows orthokeratotic hyperkeratosis with basal cell degeneration. Apoptotic cell death may be a contributory cause of basal cell degeneration. Within the epithelium the apoptotic cells were confined to the basal cell layer, and more apoptotic cells were seen in areas with basal cell degeneration and atrophic epithelium. The following mechanisms are proposed for keratinocyte apoptosis:

- T-cell-secreted TNF- α binding to TNF- α R1 receptor on keratinocyte surface,
- T-cell surface CD95L (Fas ligand) binding to CD95(Fas) on the keratinocyte surface,
- T-cell-secreted granzyme B entering the keratinocyte via perforin induced membrane pores.

All these mechanisms activate caspase cascade resulting in keratinocyte apoptosis. Expression of cell proliferation proteins like PCNA and apoptotic proteins like Bcl-2 and Bax were found to be altered in OLP as seen in epithelial dysplasia suggesting their potential for malignant transformation [18, 19].

Erythema Multiforme (EM):

This may present as ulcers in the oral cavity particularly on the lower lip and usually occurs following a cytotoxic attack on keratinocytes induced by viruses or drugs. Keratinocyte cell death in EM was found to be associated with altered expression of p53 and proteins of the BCL-2 family but not the Fas/FasL system.

In Stevens-Johnson syndrome, and toxic epidermal necrolysis, two conditions with severe blistering and ulceration of epithelial surfaces, serum levels of FasL were increased resulting in disease manifestation [20].

Pemphigus Vulgaris (PV)

Pemphigus Vulgaris (PV) is a potentially lethal mucocutaneous blistering disease characterized by cell-cell detachment (acantholysis) within the stratified epithelium comprised by keratinocytes and associated with IgG autoantibodies binding to several self-antigens expressed on the keratinocyte plasma membrane, including desmosomal cadherins and acetylcholine receptors. Induction of apoptosis by pemphigus IgG may be (i) part of the mechanism by which sera and IgG induce acantholysis or (ii) a consequence of loss of adhesion (anoikis) and a result of acantholysis.

The major auto-antibodies in pemphigus target Dsg-1 (PF and PV) and Dsg-3 (PV). (desmoglein 1 and 3). The conventional concept is that PV IgG binds to Dsgs resulting in steric hindrance, interference with desmosomal cadherin trans-interactions and loss of intercellular adhesion resulting in acantholysis[21,22].

Sjogren's Syndrome

Apoptosis of the acinar and ductal epithelial cells of the salivary and lacrimal glands has been proposed as a possible mechanism responsible for the impairment of secretory function. Apoptotic cell death may be induced by either cytotoxic T cells through the release of proteases, such as perforin and granzyme B, or the interaction of Fas ligand (FasL/CD95L), expressed by T lymphocytes, with Fas (Apo-1/CD95) on epithelial cells. The increased rate of apoptosis of epithelial cells may result from either the imbalance between the down-regulated apoptosis-inhibitor Bcl-2 and the up-regulated apoptosis-inducer Bax, or the autocrine and/or paracrine Fas/FasL interaction [23].

Lupus Erythematosus (LE)

It is the prototypic autoimmune disorder with a broad spectrum of clinical presentations encompassing almost all organs and tissues.

Patients with LE demonstrate defective clearance of apoptotic cells, during which cells shrink and change morphology by engulfing self-antigens, forming membrane-bound blebs that are exposed on the cell surface. With defective clearance of apoptotic blebs, cells undergo secondary necrosis, releasing nuclear auto-antigens. This process triggers the production of inflammatory cytokines and interferon-alpha (IFN α), promoting auto-antibody production [24].

The interaction of Fas and Fas ligand (FasL) transduces an active signal for cellular apoptosis. Defective Fas mediated apoptosis results in massive lymphoproliferation by a mutation in the FasL gene

leading to a non-functional FasL molecule in patients with SLE, resulting in disease manifestation [24, 25].

Epidermolysis Bullosa

It is a vesiculo-bullous hereditary disease that has blistering of the skin and oral mucosa due to basal keratinocyte fragility. The cells are susceptible to apoptosis by activation of caspases 3 and 8. TNF- α release and the subsequent activation of the TNF- α receptor by an autocrine/paracrine pathway causes cell death and disease manifestation [26].

Apoptosis in oral viral infections

Various types of viruses like herpes simplex virus (HSV), human papilloma viruses (HPV), and human immunodeficiency virus (HIV) have been involved in the pathogenesis of different oral lesions. Several viral gene products affect apoptosis by interacting directly with components of the highly conserved biochemical pathway which regulates cell death. On one hand it appears that viruses block apoptosis to prevent premature death of the host cell and so maximize virus progeny from a lytic infection or facilitate a persistent infection. On the other hand it appears that a growing number of viruses actively promote apoptosis, evading host inflammatory responses [27].

Herpes Simplex Virus (HSV) infections:

HSV infection prevents apoptotic cell death and has a role in the development of herpetic disease. HSV-1 induced apoptosis of immature dendritic cells is associated with downregulation of the cellular FLICE-inhibitory protein (c-FLIP) and enhancing apoptosis via expression of both Fas and Fas ligand on the surface of neonatal neutrophils [27].

Human Papilloma Virus (HPV) infections:

High risk HPV oncoproteins E6, E7, and E5 can modulate host mediated apoptosis by inhibiting death receptor signaling and thus regulate the survival of infected cells. HPV E6 proteins inhibit apoptosis in both p53-dependent and p53-independent manners. HPV-18 E6 inhibits Bak induced apoptosis in differentiating keratinocytes, in which replicates [27].

Human Immunodeficiency Virus (HIV) infections

Apoptosis has a role in pathogenesis of human immunodeficiency virus (HIV) infection. Although multiple mechanisms contribute to the gradual T cell decline that occurs in HIV-infected patients, programmed cell death of uninfected bystander T lymphocytes, including CD4+ and CD8+ T cells, is an important event leading to immunodeficiency. Several mechanisms have been proposed to explain these results:

- Direct role of HIV-specific proteins
- Activation-induced cell death (AICD)
- Direct infection of T lymphocytes

- (iv)Autologous cell-mediated killing of uninfected T cells
- Dysregulation of cytokine/chemokine production [28].

Apoptosis in jaw cysts

Cyst formation, like the development of neoplasms, involves a dysregulation of the balance between cell proliferation and cell death. Induced proliferation of epithelial cell rests (rests of Serres or Malassez) in the jaw region plays an important role in the pathogenesis of odontogenic cysts [29].

Odontogenic keratocyst (OKC):

OKCs are associated with inactivation of the Patched (PTCH) gene, which results in evasion of apoptosis and abnormal cell growth PTCH seems to have tumour suppressive activity and appears to be inactivated in developmental cysts of the jaw (dentigerous cyst and dermoid cyst) but not in inflammatory cysts. A number of known tumour suppresser genes, such as p16, p53 and cyclin D1 are inactivated in odontogenic keratocytes [29].

Several studies have shown that keratocysts have a higher proliferative rate compared with radicular or dentigerous cysts, a fact that may explain why the lumen of keratocysts are filled with desquamated apoptosed keratinocytes. Apoptotic cells in the epithelium of odontogenic cysts may undergo intracellular dystrophic calcification to form Rushton's hyaline bodies [30].

Dentigerous cyst

Bcl-2 positivity was significantly higher in atrophic epithelium of dentigerous cysts suggesting that apoptosis is involved in its cyst formation and maintaining the regular thickness of the lining epithelium in this cyst[31].

Radicular Cyst

Radicular cysts represent a periapical inflammatory disease evoked by infected and necrotic dental pulp. Epithelium of radicular and residual cysts showed expression of apoptosis related factors like ssDNA, p53, Bax, Bcl-2, caspase-3, Fas, Fas-L, and Ki-67 antigen suggesting their role in the biologic behavior of the periapical inflammatory lesions [30, 31].

Apoptosis in inflammatory diseases

Recurrent Aphthous Ulceration (RAU)

It is a common inflammatory condition of the oral mucosa. RAU occurs predominantly in non-keratinizing oral mucosa and is consistently seen in Behcet's syndrome. Apoptotic degeneration of the prickle cell layer was demonstrated microscopically in RAU lesions. More recently, lymphocytes obtained from patients with Behcet's syndrome were relatively resistant to Fas-induced apoptosis, suggesting that a

defect in the Fas pathway may be involved in this condition [32].

Periodontal diseases

Periodontal disease is an acute or chronic inflammatory condition which causes destruction of tooth-supporting tissue leading to mobility and tooth loss. Increased Caspase-3, Fas, FasL, p53, and chromatin condensation are noted in the inflammatory infiltrates of periodontitis patients. Monocytes are the most lysis-sensitive leukocytes for *A. actinomycetemcomitans* leukotoxin, which depends on caspase 1-activation. *P. gingivalis* can induce significant apoptosis in primary human gingival epithelial cells. Increased fibroblast proliferation and a simultaneous decrease in apoptosis contribute to gingival overgrowth.

Apoptosis in precancer and cancer

Actinic Cheilitis

Actinic Cheilitis (AC) is a condition that causes damage to the lips through exposure to sunlight and has the potential to undergo malignant transformation into squamous cell carcinoma. Overexpression of p53 and Bcl-2 expression was seen suggesting that DNA-damaged cells by UV radiation in AC are eliminated by apoptosis which also play a significant role in malignant transformation in AC [33].

Oral Leukoplakia

Greater expression of oncoproteins MDM2 and Bcl-2 were seen in leukoplakia with altered keratinocyte maturation. Abundance of p27 expression in oral leukoplakia may be associated with inhibition of cell proliferation leading to apoptosis of premalignant tumor cells thus preventing tumor progression. Increased mitotic, apoptotic, and Ki-67 index indicate unfavourable prognosis of leukoplakia [34].

Oral Squamous Cell Carcinoma

Oral Squamous Cell Carcinoma (OSCC) may be caused by enhanced proliferation of neoplastic cells, diminished cell turnover, or a combination of both processes. There are two major ways that could downregulate cancer cell apoptosis:

- Mutation of somatic and nonsomatic cells and/or loss of expression of proapoptotic molecules
- overexpression of apoptosis inhibitory molecules

Mutations within caspase family proteases are common in malignancies. Caspase-7 proved to be an independent prognostic marker and predictor of locoregional recurrence in patients of OSCC. In OSCC, compared with oral epithelium, there is a decreased Bcl-2 expression, a lowered Bcl-2/Bax ratio, and increased apoptosis. Expression of Bax correlates with histological tumor grading as well as predicting the prognosis of OSCC.

Fas is expressed in low quantities whereas FasL expression correlates negatively with degree of differentiation and apoptosis in OSCC. Thus, apoptosis have got a significant bearing in initiation, progression, and prognosis of OSCC [35].

Table-1: Apoptosis in oral health

1. Budding morphogenesis of dental epithelium
2. Maintaining the final size and position of tooth
3. Maintainance of normal oral tissues
4. Role of apoptosis in tooth development in amelogenesis in dentinogenesis
5. Role in bone remodelling

Table-2: Apoptosis in oral diseases

1. Apoptosis in autoimmune diseases Oral Lichen Planus Erythema Multiforme Pemphigus Vulgaris Sjogren's Syndrome Lupus Erythematoses Epidermolysis Bullosa
2. Apoptosis in oral viral infections Herpes Simplex Virus infections Human Papilloma Virus infections Human Immunodeficiency Virus infections
3. Apoptosis in jaw cysts Odontogenic Keratocyst Dentigerous cyst Radicular cyst
4. Apoptosis in inflammatory diseases Recurrent Aphthous Ulcerations Periodontal diseases
5. Apoptosis in precancer and cancer Actinic Chelitis Oral Leukoplakia Oral Squamous Cell Carcinoma

CONCLUSION

It is important to understand the mechanism of apoptosis and it's influences in both health and disease. This review is an attempt to provide an update on the importance of apoptosis in oral health and disease.

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