

Apoptosis in normal oral tissues and odontogenesis

Ruchita Bali, Akhilesh Chandra¹, Renuka Verma²

Departments of Oral and Maxillofacial Pathology, Shree Bankey Bihari Dental College and Research Centre, Masuri, Ghaziabad, ¹Faculty of Dental Sciences, Institute of Medical Sciences, Banaras Hindu University, Varanasi, ²Carrier Institute of Dental Sciences and Hospital, Lucknow, Uttar Pradesh, India

Address for correspondence:

Dr. Akhilesh Chandra,
2/29, Rashmi Khand,
Sharda Nagar, Lucknow - 226 002,
Uttar Pradesh, India.
E-mail: drakhilesh_1979@yahoo.com

ABSTRACT

Programmed cell death or apoptosis is considered a vital component of various processes including normal cell turnover, proper development and functioning of the immune system, hormone-dependent atrophy, embryonic development, and chemical-induced cell death. Inappropriate apoptosis (either too little or too much) is a factor in many human conditions including neurodegenerative diseases, ischemic damage, autoimmune disorders, and many types of cancers. The process of apoptosis is generally characterized by distinct morphological characteristics and energy-dependent biochemical mechanisms. An understanding of its role in the pathophysiology of oral tissues is pertinent to the development of novel therapeutic approaches. The developing tooth passes through the various morphologic stages and apoptosis is observed selectively in certain locations. This review focuses on the current knowledge of apoptosis emphasizing its role in normal oral tissues and odontogenesis.

Key words

Apoptosis, necrosis, odontogenesis

INTRODUCTION

Apoptosis, controlled cell death, is the main mechanism by which cells are physiologically removed and thus plays a significant role in regulating tissues during embryogenesis and in normal homeostasis. In multicellular organisms, cells are continuously shed and replaced. It is estimated that 1×10^{11} cells die per day, equivalent to the turnover of an adult's total body weight every 18-24 months.^[1]

A dysfunctional apoptotic system can lead to either excessive removal or prolonged survival of cells. Therefore, dysregulation of apoptosis is involved in the pathogenesis of a variety of diseases such as cancers, viral infections, and immunological disorders.^[1]

Apoptosis word is of Greek origin, having the meaning "falling off or dropping off", in analogy to leaves falling off trees or petals dropping off flowers.^[2] The initial insight into the genetic basis of apoptosis or programmed cell

death (PCD), was gained from ingenious studies of the roundworm *Caenorhabditis elegans*.^[3]

HISTORICAL ASPECTS

In the year 1884, Weigert and Cohnheim described the microscopic appearance of cell death in necrotic tissue as coagulation necrosis. In 1885, Flemming described the process of chromatolysis in which the nuclei of mammalian ovarian follicles broke up and ultimately disappeared in spontaneous cell death. In the early 1970s, Kerr described the electron microscopic appearance of single-cell death in the livers of and called it "shrinkage necrosis."^[4,5] In a landmark paper in 1972, Kerr *et al.* described the characteristic sequential changes occurring in cell structure during the death process in healthy tissues, normal development, tumor regression, atrophy, and involution.^[6]

MECHANISM OF APOPTOSIS

PCD occurs following the induction of an intracellular genetically regulated cell death program.^[7] A number of physiological and pathological stimuli including lack of nutrients, activation of cell surface death receptors, chemicals, ionizing radiation, and direct physical injury can activate the apoptotic program [Figure 1].^[8] These stimuli activate different pathways leading to apoptosis, but often converge on one common pathway involving the activation of caspases. Caspases are a group of enzymes

Access this article online

Quick Response Code:



Website:
www.ejgd.org

DOI:
10.4103/2278-9626.115974

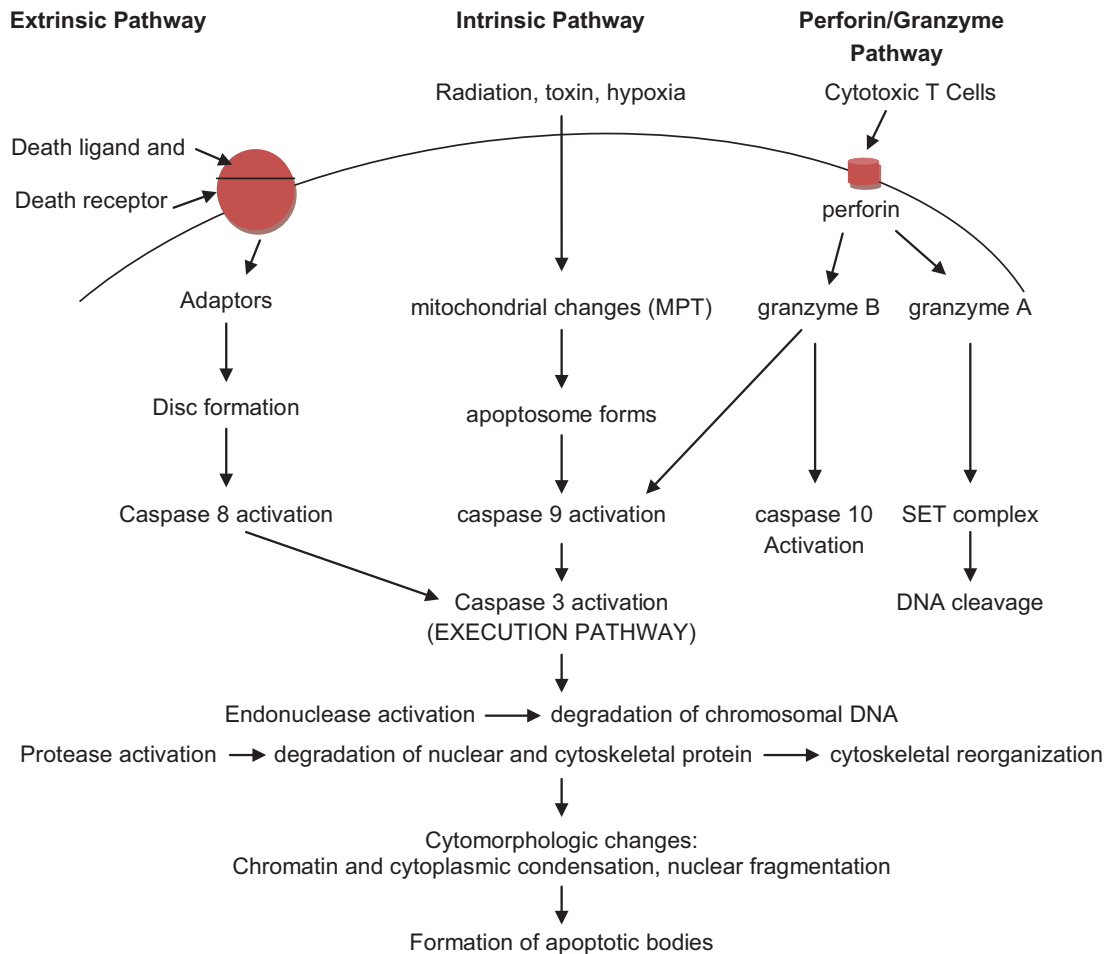


Figure 1: Schematic representation of apoptotic events showing two main pathways of apoptosis (extrinsic and intrinsic) as well as a perforin/granzyme pathway

that are involved in the regulation of apoptosis resulting in the classical apoptotic features.^[6]

Although caspases are important in the apoptotic pathways, recent studies indicate that caspases are not required for all forms of cell death and activation of caspases does not always lead to cell death but may be involved in cell differentiation.^[9] The first caspase-independent apoptosis effector to be identified was apoptosis-inducing factor, which translocates from the mitochondria to the nucleus where it interacts with Deoxyribonucleic acid (DNA).^[10]

Two distinct pathways leading to activation of caspases [Figure 1] have been identified. The extrinsic pathway is initiated by activation of transmembrane death receptors.^[11] The intrinsic pathway is activated by cellular stress and generally involves the release of mitochondrial proteins such as cytochrome-C. Certain molecules such as BH3 interacting domain agonist can amplify apoptosis by coupling the death receptor pathway to the intrinsic pathway.^[12]

Apoptosis in response to DNA damage may be induced in p53-dependent or independent pathways. Early DNA

damage sensing in the nucleus involves the ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and RAD3 related (ATR) protein kinases.^[13]

The p53-dependent signaling pathway induces transcriptional activation of proapoptotic genes such as Bcl-2 associated X (BAX) and [Fas]. Whereas, the p53-independent pathway involves transcriptional activation of p73 and procaspases through the transcription factor E2F-1 and activation of caspase-2.^[13]

Cell death by surface receptors

Cell surface death receptors of the tumor necrosis factor-receptor (TNFR) family, such as TNFR-1 and Fas Cluster of differentiation 95 (CD95) can transduce apoptotic signals upon engaging their respective ligands or specific antibodies. Death receptors of the TNFR superfamily are expressed in a wide variety of tissues including normal oral epithelium and oral carcinoma.^[14,15]

Upon stimulation by Fas ligand (FASL) or TNF- α , these death receptors trimerise and their cytoplasmic death domains engage cytoplasmic adapter proteins. The adapter protein for FAS is FAS associated death

domain (FADD) and that for TNFR1 is TNFR associated death domain (TRADD). FADD and TRADD then recruit and active caspase-8, which may further activate other caspases leading to apoptosis.^[10]

Cell death by granzyme B

Granzymes are a family of proteases that cleave a number of protein substrates, which in turn induce apoptotic cell death.^[16] Granzyme B is the only granzyme that shares substrate specificity with caspases, cleaving its substrate specifically after an aspartate residue.^[17]

Cytotoxic T-lymphocytes can kill target cells by release of cytotoxic granules, comprising lethal proteins such as perforin and granzymes [Figure 1]. A wide range of substrates including a number of caspases and apoptosis-related proteins are cleaved by granzyme B. Recent reports indicate that mitochondria play a key role in granzyme B-induced cytotoxicity.^[16,18]

APOPTOSIS IN NORMAL ORAL TISSUE

During embryogenesis, specific selected cells are destined to die by apoptosis. In developmental biology, the term PCD is often used to describe this form of cell death as cells are programmed to die after performing a particular function at a specific time. A delicate balance between cell death and cell survival is observed during the formation of oral epithelium and epithelial-mesenchymal interaction play an essential role in determining that which cells are to be shed and which ones are to survive.^[19]

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.^[1]

The Bcl-2 (B-cell lymphoma-2) family of proteins appears to be involved in regulating terminal differentiation of keratinocytes. The antiapoptotic Bcl-2 and Bcl-XL (B-cell lymphoma- extra large) proteins are preferentially expressed in the basal and lower spinous layers, whereas the proapoptotic protein BAX is expressed in the more differentiated suprabasal cell layers.^[20,21]

Epithelial cells also require contact with each other for survival signals. Detachment of an epithelial cell from its neighbors triggers a form of spontaneous apoptosis termed "anoikis." Anoikis is involved in a wide range of tissue-homeostatic, developmental and oncogenic processes.^[22]

APOPTOSIS IN ODONTOGENESIS

Apoptosis is apparently not a random event, which only controls tissue size of the tooth germ. Instead, apoptosis clearly correlates with changes in morphogenesis and with the removal of specific cells. In the tooth, apoptosis is mostly detected in epithelial cells. During early development, cell death was associated with epithelial budding morphogenesis and in advanced teeth, apoptosis was detected in several epithelial cell types, most of which will disappear by the time of tooth eruption.^[23]

In early bud stage, apoptotic cells are found in the budding epithelium in particular in the cells facing the oral cavity in rodent studies.^[24] When the tooth germ prolongs along its central axis at the late bud stage, the apoptotic cells become concentrated at the tip of the tooth bud. However, in the bud stage no apoptotic cells are seen in the mesenchyme.^[24,25]

In the cap stage, the clusters of apoptotic cells are localized within the enamel knot. As development continues the enamel knot does not show any evidence of loss of cell mass suggesting a rapid replacement by proliferating cells surrounding the enamel knot. With the disappearance of the primary knot, apoptosis is no longer observed in this area but is detected in the gubernaculum (epithelium joining the enamel organ to the buccal epithelium). At the cap stage, a few apoptotic cells are detectable in the condensed mesenchyme, but these show no restricted pattern.^[26]

During bell stage, apoptosis is evident in secondary enamel knots, stratum inter-medium cells adjacent to the enamel knots and adjacent mesenchyme. All teeth pass through the same developmental stages and consist of the same tissues.^[24,26]

Role of apoptosis in tooth development

Multiple roles for apoptosis in odontogenesis have been suggested. Apoptosis may: (a) Play a role in the disruption of dental lamina, (b) 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, (c) Play a role in deciding the final position and size of the tooth in the jaws, (d) Prevent tooth appositions in edentulous areas by preventing epithelial overgrowth between the teeth, (e) Play a role in deciding the final number of teeth, (f) Role in morphogenic mechanism in shaping the final crown tooth morphogenesis.^[24]

CONCLUSION

The study of apoptotic cell death is very important due to its implications in an organism's life from conception to death and its central role in certain diseases. By

understanding the spatially and temporally restricted distribution patterns of apoptotic cells, the multiple roles for apoptosis in dental development can be assessed.

Apoptosis also has roles in oral as well as dental diseases and dismorphology, but whether these are from primary defects in apoptotic pathways or due to secondary consequence is yet to be clarified. For apoptosis to be the target of therapeutic intervention in an effective and safe manner it is necessary to conduct research to determine the conditions in which apoptosis can be selectively regulated.

REFERENCES

- Loro L, Vintermyr OK, Johannessen AC. Apoptosis in normal and diseased oral tissues. *Oral Dis* 2005;11:274-87.
- Luvia ST, Vargas FD. Apoptosis: The phenomenon and its determination. *Téc Pecu Méx* 2003;41:49-62.
- Wang X. The expanding role of mitochondria in apoptosis. *Genes Dev* 2001;15:2922-33.
- Kam PC, Ferch NI. Apoptosis: Mechanisms and clinical implications. *Anaesthesia* 2000;55:1081-93.
- Curtin J, Cotter J. Historical perspective (apoptosis). *Essays Biochem* 2003;39:1-10.
- Kerr JF, Wyllie AH, Currie AR. Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 1972;26:239-57.
- Horvitz HR. Genetic control of programmed cell death in the nematode *Caenorhabditis elegans*. *Cancer Res* 1999;59:1701s-6.
- Elmore S. Apoptosis: A review of programmed cell death. *Toxicol Pathol* 2007;35:495-516.
- Abraham MC, Shaham S. Death without caspases, caspases without death. *Trends Cell Biol* 2004;14:184-93.
- Susin SA, Lorenzo HK, Zamzami N, Marzo I, Snow BE, Brothers GM, *et al.* Molecular characterization of mitochondrial apoptosis-inducing factor. *Nature* 1999;397:441-6.
- Debatin KM, Krammer PH. Death receptors in chemotherapy and cancer. *Oncogene* 2004;23:2950-66.
- Green DR, Kroemer G. The pathophysiology of mitochondrial cell death. *Science* 2004;305:626-9.
- Norbury CJ, Zhivotovsky B. DNA damage-induced apoptosis. *Oncogene* 2004;23:2797-808.
- Chen Q, Samaranayake LP, Zhen X, Luo G, Nie M, Li B. Up-regulation of Fas ligand and down-regulation of Fas expression in oral carcinogenesis. *Oral Oncol* 1999;35:548-53.
- Fukuda M, Hamao A, Tanaka A, Kitada M, Suzuki S, Kusama K, *et al.* Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/APO2L) and its receptors expression in human squamous cell carcinoma of the oral cavity. *Oncol Rep* 2003;10:1113-9.
- Roberts DL, Goping IS, Bleackley RC. Mitochondria at the heart of the cytotoxic attack. *Biochem Biophys Res Commun* 2003;304:513-8.
- Harris JL, Peterson EP, Hudig D, Thornberry NA, Craik CS. Definition and redesign of the extended substrate specificity of granzyme B. *J Biol Chem* 1998;273:27364-73.
- Goping IS, Barry M, Liston P, Sawchuk T, Constantinescu G, Michalak KM, *et al.* Granzyme B-induced apoptosis requires both direct caspase activation and relief of caspase inhibition. *Immunity* 2003;18:355-65.
- Thesleff I, Sharpe P. Signalling networks regulating dental development. *Mech Dev* 1997;67:111-23.
- Maruoka Y, Harada H, Mitsuyasu T, Seta Y, Kurokawa H, Kajiyama M, *et al.* Keratinocytes become terminally differentiated in a process involving programmed cell death. *Biochem Biophys Res Commun* 1997;238:886-90.
- Loro LL, Vintermyr OK, Liavaag PG, Jonsson R, Johannessen AC. Oral squamous cell carcinoma is associated with decreased bcl-2/bax expression ratio and increased apoptosis. *Hum Pathol* 1999;30:1097-105.
- Frisch SM, Screaton RA. Anoikis mechanisms. *Curr Opin Cell Biol* 2001;13:555-62.
- Vahtokari A, Aberg T, Thesleff I. Apoptosis in the developing tooth: Association with an embryonic signaling center and suppression by EGF and FGF-4. *Development* 1996;122:121-9.
- Matalova E, Tucker AS, Sharpe PT. Death in the life of a tooth. *J Dent Res* 2004;83:11-6.
- Nair BJ. Apoptosis in odontogenesis: A brief review. *Oral Maxillofac Pathol J* 2010;1:1225-7.
- Stock DW, Weiss KM, Zhao Z. Patterning of the mammalian dentition in development and evolution. *Bioessays* 1997;19:481-90.

How to cite this article: Bali R, Chandra A, Verma R. Apoptosis in normal oral tissues and odontogenesis. *Eur J Gen Dent* 2013;2:195-8.

Source of Support: Nil, **Conflict of Interest:** None declared.