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REVIEW ARTICLE

Apoptosis in normal and diseased oral tissues

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Apoptotic cell death plays an important role in maintenance of the normal physiological state and in the pathogenesis of diseases in the body. Over the last three decades the molecular mechanisms of apoptosis have been unravelled leading to development of novel therapeutic approaches. This paper aims to present current knowledge of the role of apoptosis in normal oral tissues and in the development of oral diseases.
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Introduction

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 (Israels and Israels, 1999). Apoptosis is the main mechanism by which cells are physiologically removed and thus plays an important role in regulating tissues during embryogenesis and in normal homeostasis. 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. This review focuses on current knowledge on apoptosis in normal oral tissues and its role in the pathogenesis of a variety of diseases in the oral cavity. An understanding of the role of cell death in the pathophysiology of oral tissues is pertinent to the development of novel therapeutic approaches.

Cell death may take place by apoptosis or by non-apoptotic forms such as necrosis. The differences between various forms of cell death are not clear-cut. There exist forms of cell death that display intermediate features between classical apoptosis and necrosis. The mode of cell death and its morphological features is dependent on a number of factors including cell type, inducing factor and signalling pathway (Ziegler and Groscurth, 2004). Cell death by necrosis occurs following pathological injury caused by factors such as infection, ischaemia or hypoxia. Necrosis is characterized by cell swelling and rupture, leading to the release of the cell's toxic contents, which induce an inflammatory response. Apoptosis, on the other hand, is characterized by cell shrinkage, blebbing of the plasma membrane and nuclear condensation and fragmentation (Figure 1). Apoptotic cells eventually fragment into small membrane bound bodies (apoptotic bodies), which are phagocytosed by macrophages, or neighbouring cells without inducing an inflammatory response (Kerr *et al*, 1972). Phagocytic cells recognize 'eat me' signals sent out by dying cells (Fadok *et al*, 2001; Moreira and Barcinski, 2004). The entire apoptotic process is insidious and explains why little was known about apoptosis until relative recently.

During embryogenesis-specific, selected cells are destined to die by apoptosis. In developmental biology the term programmed cell death (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. PCD occurs in the oral epithelium where basal keratinocytes continuously proliferate mature and differentiate to flattened squames, which are then shed-off from epithelial surfaces. This process is often referred to as terminal differentiation.

Epithelial cells require contact with each other for survival signals. Detachment of an epithelial cell from its neighbours triggers a form of spontaneous apoptosis termed 'anoikis' (Frisch and Screaton, 2001; Grossmann, 2002). Anoikis is involved in a wide range of tissue-homeostatic, developmental and oncogenic processes. Loss of cell–cell contact deprives epithelial cells of necessary integrin- and cadherin-mediated survival signals (Evan and Vousden, 2001). It has become clear that the integrin-$\alpha 6\beta 4$, a major component of hemidesmosomes, is able to transduce signals from the extracellular matrix to the interior of the cell, which critically modulate the organization of the cytoskeleton, proliferation, apoptosis and differentiation (Borradori and Sonnenberg, 1999). Maintenance of cell–cell contact is

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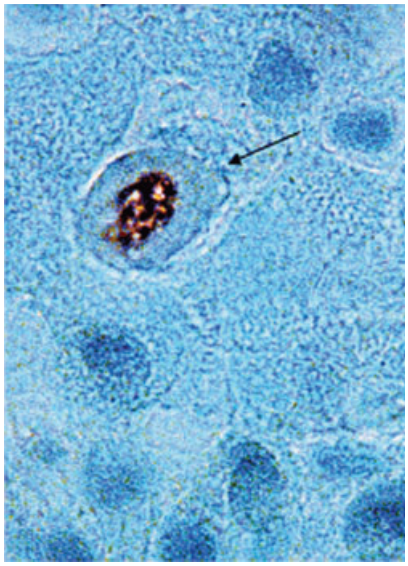

Figure 1 An early apoptotic cell in oral squamous cell carcinoma. The terminal transferase deoxyuridin triphosphate (UTP) nick-end labelling (TUNEL)-positive cell (arrow) shows the shrinking and DNA condensation characteristic of apoptotic cells (original magnification ×1000, oil emulsion)

therefore important for preservation of normal epithelial structure and function.

The characteristic morphological features of apoptosis and its underlying biochemical mechanisms permit its detection by a number of methods possible. The widely used terminal transferase deoxyuridin triphosphate (UTP) nick-end labelling (TUNEL) method detects DNA breaks in apoptotic cells (Figures 1 and 2a). However, the TUNEL method also detects non-apoptosis-induced DNA damage, such as DNA breaks in accidentally damaged cells or in necrotic cells. These limitations dictate that a number of standardization experiments and controls be conducted for each tissue prior to assessment of apoptotic cell death by the TUNEL method (reviewed in Potten, 2001; Loro *et al*, 2003). Other methods used for assessing cell death include light microscopy on a standard haematoxylin and eosin stained slide (Figure 2b), electron microscopy and immunocytochemical techniques based on antibodies raised against cleavage products of apoptosis (reviewed in Loro *et al*, 2003).

Apoptotic pathways

Programmed cell death occurs following the induction of an intracellular genetically regulated cell death programme (Horvitz, 1999). 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 programme (Figure 3). 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 that are involved in the regulation of apoptosis resulting in the classical apoptotic features (Kerr *et al*, 1972). 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 (reviewed in Abraham and Shaham, 2004). The first caspase-independent apoptosis effector to be identified was apoptosis-inducing factor (AIF; Susin *et al*, 1999), which translocates from the mitochondria to the nucleus where it interacts with DNA (Daugas *et al*, 2000). Two distinct pathways leading to activation of caspases (Figures 3 and 4) have been identified. The extrinsic pathway is initiated by activation of transmembrane death receptors (reviewed in Debatin and Krammer, 2004). The intrinsic pathway

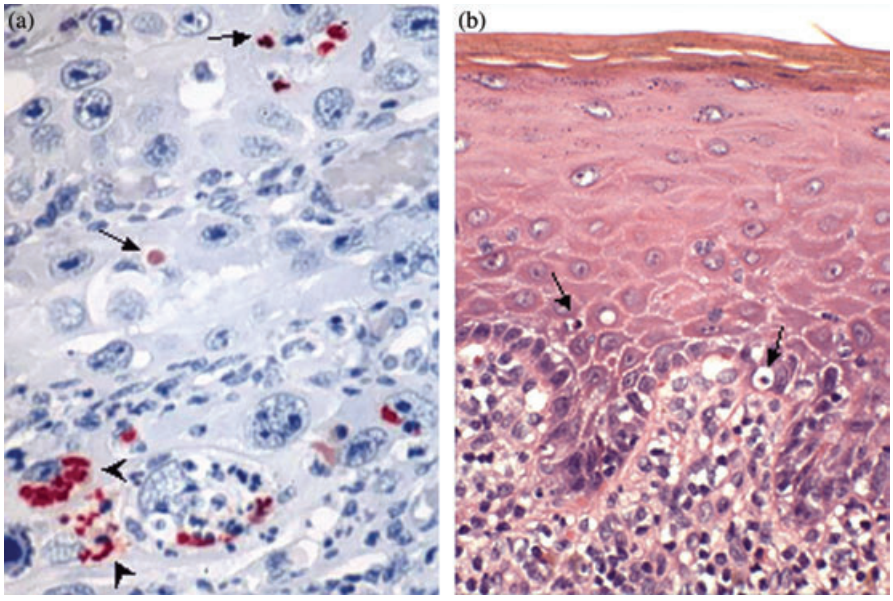

Figure 2 Demonstration of apoptotic cell death by the terminal transferase deoxyuridin triphosphate (UTP) nick-end labelling (TUNEL) method and by light microscopy in tissue sections. TUNEL-positive apoptotic cells were detected as single cells in a section of oral squamous cell carcinoma (**a**, arrows). Aggregates of necrotic cells in microabscesses were also TUNEL reactive (**a**, arrowheads). (**b**) Late apoptotic cells (Civatte/colloid bodies; arrows) observed in a haematoxylin and eosin-stained tissue section of oral lichen planus (**a** and **b**, original magnification ×400)

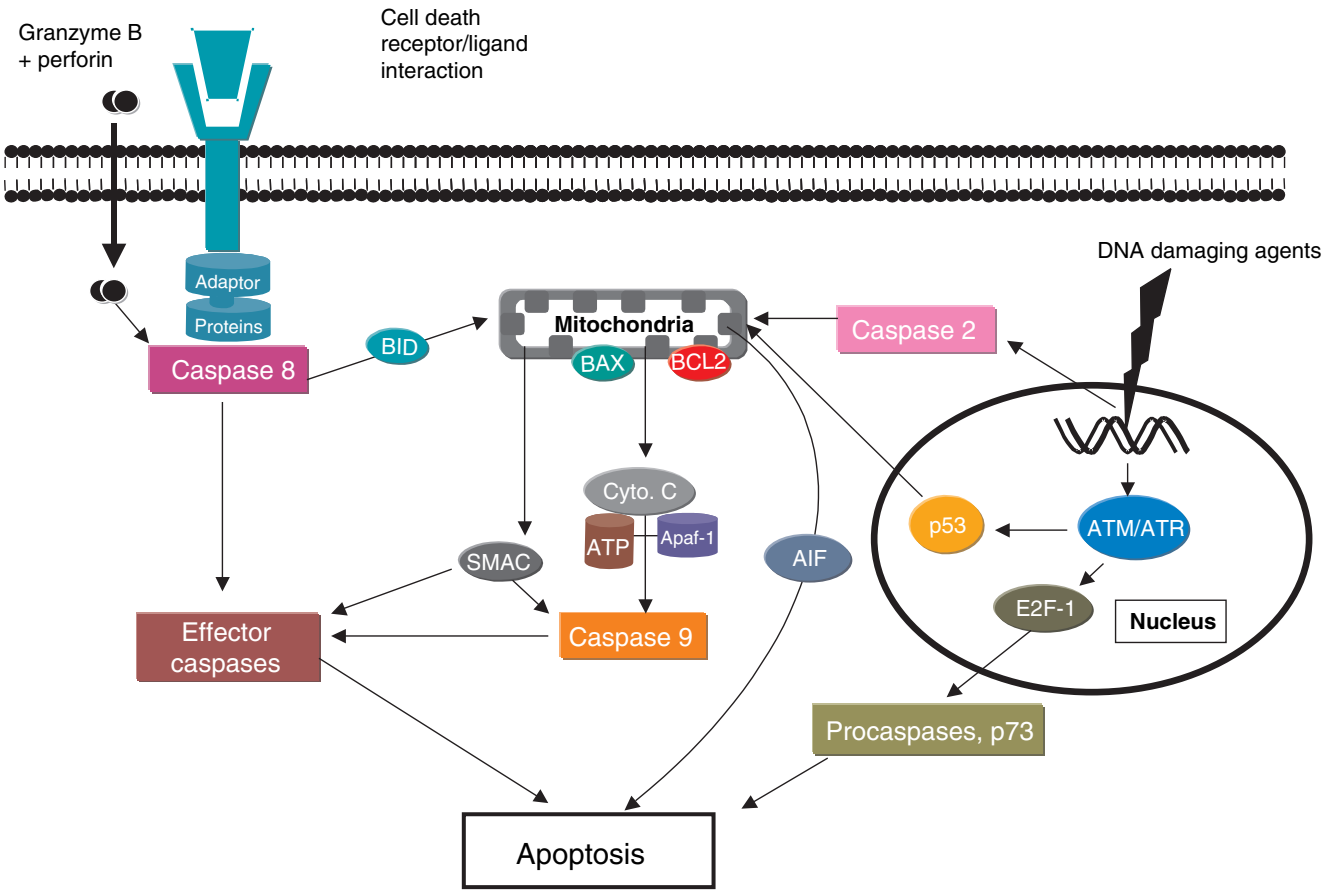

Figure 3 An overview of apoptosis signalling pathways. Apoptosis may be triggered by a variety of stimuli such as activation of cell surface death receptors or release of granzyme B and activation of the mitochondria by cellular stresses. Apoptotic stimuli trigger a cascade leading to induction of apoptosis

is activated by cellular stress and generally involves the release of mitochondrial proteins such as cytochrome *c* (reviewed in Green and Kroemer, 2004). Certain molecules such as BH3 interacting domain agonist (BID) can amplify apoptosis by coupling the death receptor pathway to the intrinsic pathway (Figure 3).

Apoptosis in response to DNA damage may be induced in p53-dependent or -independent pathways (Figure 3). Early DNA damage sensing in the nucleus involves the Ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and RAD3 related (ATR) protein kinases (reviewed in Norbury and Zhivotovsky, 2004). The p53-dependent signalling pathway induces transcriptional activation of proapoptotic genes such as *BAX* and *FAS*. Whereas, the p53-independent pathway involves transcriptional activation of *p73* and procaspases via the transcription factor E2F-1 and activation of caspase-2 (Norbury and Zhivotovsky, 2004).

Cell death by surface receptors

Cell surface death receptors of the tumour necrosis factor-receptor (TNFR) family, such as TNFR1 and Fas (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 (Chen *et al*, 1999; Loro *et al*, 1999a; Fukuda *et al*, 2003). Upon stimulation by FasL or TNF-α, these death receptors trimerise and their cytoplasmic death domains engage cytoplasmic adapter proteins (reviewed in Debatin and Krammer, 2004). 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 (Figure 3).

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 (reviewed in Roberts *et al*, 2003). Granzyme B is the only granzyme that shares substrate specificity with caspases, cleaving its substrate specifically after an aspartate residue (Harris *et al*, 1998). Cytotoxic T lymphocytes can kill target cells by release of cytotoxic granules, comprising lethal proteins such as perforin and granzymes. A wide range of substrates including a number of caspases and apoptosis-related proteins are cleaved by granzyme B (reviewed in

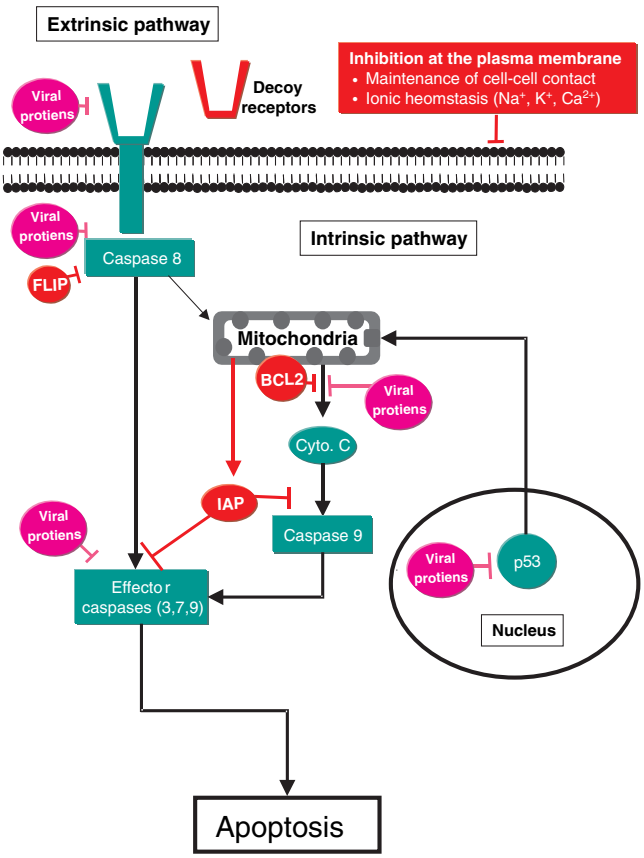

Figure 4 An overview of inhibition of apoptosis by cellular and viral proteins. Every living cell in multicellular organisms has an in-built apoptotic programme, which is kept in check by a number of mechanisms including maintenance of cell-to-cell contact, plasma and mitochondrial membrane integrity and homeostasis, and by inhibitors of apoptosis molecules such as BCL-2. In disease states such as cancer and viral infections cells develop mechanisms of evasion of apoptotic cell death, which include release of decoy receptors and production of molecules by virus

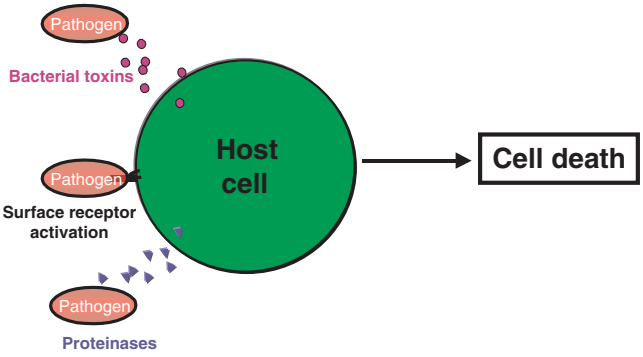

Figure 5 A summary of mechanisms by which oral pathogens induce cell death in host cells. Oral pathogens induce tissue damage by release of bacterial toxins, proteinases and interaction of bacterial surface molecules with host cells

Roberts *et al*, 2003). Recent reports indicate that mitochondria play a key role in granzyme B-induced cytotoxicity (Goping *et al*, 2003; Roberts *et al*, 2003).

Prevention and evasion of apoptosis

Each living cell has the ability to undergo cell death. It is therefore crucial for the survival of a cell that the apoptotic programme is kept under strict control to avoid unnecessary death. Cells contain a number of molecules that prevent the inappropriate activation of the apoptotic programme. These molecules can inhibit apoptosis at critical points such as at the plasma membrane, the mitochondria and the caspases (Figure 4). Cancer cells and viruses exploit these control points to their own advantage. At the level of the cell membrane apoptosis is prevented by factors such as maintenance of intercellular contacts, ionic homeostasis (Bortner and Cidlowski, 2004) and decoy receptors (Debatin and Krammer, 2004). At the mitochondrial level the antiapoptotic members of BCL-2 family block mitochondrial events that trigger apoptosis (Sharpe *et al*, 2004). In the cytosol molecules such as inhibitor of apoptosis protein (IAP), survivin (Ambrosini *et al*, 1997), ubiquitin (Zhang *et al*, 2004) and viral products (Polster *et al*, 2004) are involved in suppressing apoptosis (Figure 3).

Apoptosis in normal oral tissues

During oral embryogenesis the regulation of the delicate balance between cell death and cell survival and the epithelial–mesenchymal interaction play an essential role in determining which cells are to be shed and which ones are to survive (Thesleff and Sharpe, 1997; Hogan, 1999). Molecules involved in regulating the development of oral soft and hard tissues include fibroblast growth factor (Hoffman *et al*, 2002; Miletich and Sharpe, 2003), bone morphogenic proteins (BMP), sonice hedgehog (Shh), wingless type-1 (WNT-1) and TNF family (Chai *et al*, 2003; Miletich and Sharpe, 2003). The lining of 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 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. The antiapoptotic BCL-2 and $BCLX_L$ 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 (Maruoka *et al*, 1997; Loro *et al*, 1999b). Also, the differential expression of antiapoptotic and proapoptotic proteins of the BCL-2 family corresponds to expression of the keratinocyte differentiation markers cytokeratin and involucrin (Maruoka *et al*, 1997). *In vitro* studies have shown that terminal differentiation is associated with decreased expression of p53, p21 and increased levels of transforming growth factor-β and phospholipase C-γ1 (Min *et al*, 1999; Oh *et al*, 2003).

Apoptosis in oral diseases

Reactive lesions

Cells in multicellular organisms are inflicted with a variety of challenges to which they react by regeneration, hyperplasia, dysplasia, hypertrophy, atrophy or metaplasia depending on the nature of the challenge. These modes of cellular adaptability involve modulation of the balance between cell proliferation and cell death. The mouth is the inlet to the gastrointestinal tract and is thus exposed to a wide range of ingested substances, some of which may induce physical, chemical or microbial irritation. Some individuals may react adversely to some of these substances by developing epithelial lesions. Triclosan, an active ingredient in dentifrices used in the prevention of plaque formation and treatment of gingivitis, can induce cell death in human gingival epithelial cells (Zuckerbraun *et al*, 1998). Physical irritation from ill-fitting dentures to the oral mucosa may lead to ulceration or production of an exuberant fibrous reparative connective tissue. Also, removable dentures may contain bioactive substances that can have toxic effects on the mucosa. Poly(methyl methacrylate) resins, used as base material for removable dentures, have been shown to induce both apoptotic and necrotic cell death in human monoblastoid cells and in murine fibroblasts (Cimpan *et al*, 2000a,b).

Besides chemical and physical irritation, hormonal changes may influence normal oral mucosa. Pyogenic granuloma in pregnancy, a reactive oral lesion associated with hormonal changes during pregnancy, is characterized by complete or partial regression after childbirth. A recent study showed that regression of pyogenic granuloma after parturition is associated with increased apoptosis and lack of vascular endothelial growth factor (Yuan and Lin, 2004).

Other substances that may affect normal oral mucosa include tobacco products, which modulate the turnover of epithelial and mesenchymal tissues. Smokeless tobacco is increasingly being used in some parts of the world including the Indian subcontinent, the Sudan, parts of Scandinavia and the USA (Idris *et al*, 1998; Warnakulasuriya, 2004). Use of smokeless tobacco is associated with white lesions in the oral mucosa, whereas smoking causes hypermelanocytosis and melanosis (Sarswathi *et al*, 2003). Tobacco induced changes at the cellular level may be observed in apparently normal oral mucosa of smokers after chronic exposure and include DNA anueploidy, oxidative stress, enhanced cell proliferation and increased apoptosis (Bagchi *et al*, 2001; Schwartz *et al*, 2003). The effects of tobacco on oral mucosa are strongly associated with the development of oral cancer and will be more specifically addressed in the section on apoptosis and oral tumorigenesis (see below).

Apoptosis and oral ulcers

Ulceration of oral epithelium is a common occurrence and may be caused by factors such as trauma, chemicals, infections, immunological disorders or neoplasms. Non-steroidal anti-inflammatory drugs such as aspirin (acetylsalicylic acid) are widely used for treatment of headaches and a range of pains including toothache. Aspirin is known to impair mucosal defences and tissue repair. Reports in the literature indicate that aspirin delays healing of oral mucosal ulcers by amplification of apoptosis (Slomiany and Slomiany, 2001a,b) and inhibition of cell proliferation (Law *et al*, 2000). Besides the effects of systematically administered aspirin topical application can also induce ulceration of oral mucosa, commonly referred to as 'aspirin burn'. Chronic alcohol ingestion is another factor that may cause delayed wound healing. A study on animals has indicated that chronic alcohol consumption triggers proinflammatory cytokine production and apoptosis causing a delay in mucosal repair responses (Slomiany *et al*, 2000).

Recurrent aphthous ulceration (RAU) is a common inflammatory condition of the oral mucosa with a poorly understood pathogenesis. RAU occurs predominantly in non-keratinizing oral mucosa and is consistently seen in Behćet's syndrome. Apoptotic degeneration of the prickle cell layer was demonstrated microscopically in RAU lesions (Honma *et al*, 1985). More recently, lymphocytes obtained from patients with Behćet's syndrome were relatively resistant to Fas-induced apoptosis, suggesting that a defect in the Fas pathway may be involved in this condition (Yang *et al*, 2002).

Erythema multiforme (EM) 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 (Ayangco and Rogers, 2003). 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 (Table 1; Chrysomali *et al*, 1997). In Stevens-Johnson syndrome and toxic epidermal necrolysis, two conditions with severe blistering and ulceration of epithelial surfaces, serum levels of FasL were increased but not in ordinary EM-type drug-induced lesions (Abe *et al*, 2003). Moreover, serum from patients with Stevens-Johnson syndrome was able to induce cell death in cultured keratinocytes (Abe *et al*, 2003). These studies show that Fas signalling is involved in the pathogenesis of Stevens-Johnson syndrome but not in EM pointing to differences in the molecular basis of the systemic and localized forms of EM.

Systemic lupus erythematosus and discoid lupus erythematosus are autoimmune diseases, which may both manifest in the mouth as erythematous or ulcerative lesions with white striae radiating from the margins. Microscopically, the lesions show keratosis, basal cell loss, and subepithelial and perivascular lymphocytic infiltration. Destruction of basal keratinocytes results in formation of Civatte (apoptotic) bodies (Reibel and Schiodt, 1986). Mutations in the *Fas* gene have been associated with defective apoptosis in systemic lupus erythematosus (Vaishnaw *et al*, 1999). A number of studies in the literature indicate that increased apoptosis or abnormal clearance of apoptotic material can contribute to autoimmune diseases (reviewed in Kaplan, 2004).

Table 1 A summary of apoptotic findings in oral ulcerative and vesiculobullous diseases

Disease	*Features*	*Molecular findings*	*References*
Behćet's disease/ aphthous ulceration	Ulceration due to prickle cell layer apoptosis	Resistance of lymphocytes to FAS-induced apoptosis	Honma *et al* (1985), Yang *et al* (2002)
Erythema multiforme	Ulceration due to basal and parabasal keratinocyte apoptosis	↓p53, BAX; ↑BCL-X	Chrysomali *et al* (1997)
Lupus erythematosus	Autoimmune destruction of basal keratinocytes	FAS mutations	Vaishnaw *et al* (1999)
Oral lichen planus	Basal keratinocyte apoptosis and interface lymphocytic infiltrate	↑p53, TNF-α, FAS, FasL, MMP-9, granzyme-B and caspase-3; ↓BCL-2	Dekker *et al* (1997), Bloor *et al* (1999), Sugerman *et al* (2000), Neppelberg *et al* (2001), Tobon-Arroyave *et al* (2004)
Pemphigus vulgaris	Bullae and ulceration due to keratinocyte acantholysis (anoikis)	↑p53, FAS, FasL, sFasL, BAX; ↓BCL-2	Puviani *et al* (2003), Wang *et al* (2004)
Epidermolysis bullosa	Bullae due to keratinocyte apoptosis	Mutant keratin-5, -14 and integrin-β4, TNF signalling	Bonifas *et al* (1991), Jonkman *et al* (2002), Yoneda *et al* (2004)

TNF, tumour necrosis factor; MMP, matrix metalloproteinase, ↑ increased, ↓ decreased expression.

Apoptosis and oral lichen planus

Oral lichen planus (OLP) is characterized histologically by a dense band-like infiltration of lymphocytes subepithelially and destruction of the basal keratinocyte cell layer. The aetiology of OLP remains unclear. However, a psychoneuroimmune hypothesis has been proposed (Prolo *et al*, 2002). Apoptotic keratinocytes (Civatte/colloid bodies) in OLP are routinely observed by light microscopy as shrunken cells with condensed nuclei and eosinophilic cytoplasm (Figure 2b). Apoptotic cells in OLP have also been demonstrated by the TUNEL method (Neppelberg *et al*, 2001; Karatsaidis *et al*, 2004) and by electron microscopy (Tobon-Arroyave *et al*, 2004). It is thought that activated T cells are responsible for induction of keratinocyte apoptosis in OLP. In a recent study the majority of cells detected by the TUNEL method in OLP were lymphocytes (Karatsaidis *et al*, 2004). However, the mechanism by which lymphocytes and keratinocytes die in OLP is not yet clear. The frequently observed cell death among lymphocytes may be partly accounted for by the relatively short lifespan of lymphocytes. Also, local factors at the epithelial–connective tissue interface are supposed to have a specific role in lymphocyte apoptosis in OLP. So far, some factors have been implicated in induction of apoptosis in lichen planus including p53 (Dekker *et al*, 1997), the BCL-2 family proteins (Dekker *et al*, 1997; Bloor *et al*, 1999), TNF-α, the Fas/FasL pathway, granzyme B-perforin system, proteases of the matrix metalloproteinase-9 type (MMP-9; Sugerman *et al*, 2000) and caspase-3 (Tobon-Arroyave *et al*, 2004; Table 1). Data from our laboratory indicate that the OLP is associated with loss of CD40 and CD40L in basal keratinocytes (E. Neppleberg, L. L. Loro, A. C. Johannessen, unpublished observation). It is still unknown what molecules are involved in the interaction between basal keratinocytes and lymphocytes, and if the molecular mechanisms underlying cell death in lymphocytes are the same as those responsible for cell death in keratinocytes.

Apoptosis and vesiculobullous diseases

Vesiculobullous diseases are characterized by loss of cell contact between keratinocytes or between basal keratinocytes and the basement membrane leading to cell death by anoikis. The resultant vesicles may eventually rupture to form ulcers. A decade ago, it was suggested that Fas/FasL signalling might play an important role in the pathogenesis of diseases-like pemphigus vulgaris, bullous pemphigoid and EM (Sayama *et al*, 1994). A recent study confirmed these earlier findings and showed that the sera of patients with pemphigus vulgaris contain soluble FasL, which is able to induce keratinocyte cell death in culture (Puviani *et al*, 2003). Also, other genes such as *BCL-2*, *BAX* and *TP53* have been found to be altered in pemphigus vulgaris (Puviani *et al*, 2003; Wang *et al*, 2004; Table 1).

Epidermolysis bullosa, a hereditary vesiculobullous disease characterized by blistering of the skin and oral mucosa because of basal keratinocyte apoptosis, is caused by mutations in the genes encoding keratin-5 and -14 (Bonifas *et al*, 1991). A recent study on an *in vitro* epidermolysis bullosa model showed that the mutant keratin-5 and -14 proteins form aggregates, which induce cell death by stimulation of TNFR1 signalling (Yoneda *et al*, 2004). Other molecular defects in epidermolysis bullosa include integrin-α6β4, a major component of hemidesmosomes involved in proliferation, apoptosis and differentiation (Borradori and Sonnenberg, 1999). In epidermolysis bullosa, deletion of the cytoplasmic domain of integrin-β4 results in impaired hemidesmosomes thus predisposing basal keratinocytes to apoptosis (Jonkman *et al*, 2002). Normal keratinocytes are protected from apoptosis via integrin signalling in a BCL-2-dependent manner (Tiberio *et al*, 2002).

Apoptosis and oral viral infections

A variety of viruses are present in the oral cavity, many of which are involved in the pathogenesis of some oral

diseases. Viruses such as herpes simplex virus (HSV), varicella zoster virus (VZV) and coxsackie viruses may cause vesiculobullous diseases. Others such as human pallomaviruses (HPV) and Epstein–Barr virus (EBV) are involved in the development of benign oral lesions such as squamous cell papilloma, condyloma, verruca and focal epithelial hyperplasia. There is evidence in the literature indicating a relationship between HPV and oral squamous cell carcinoma (Syrjanen, 2003), and between AIDS and oral hairy leukoplakia (OHL) and Kaposi's sarcoma (KS; Teo, 2002).

Viruses exert their effects on tissues by modulating the balance between cell death and cell proliferation. They can induce apoptosis in infected host cells by production of an array of viral products (reviewed in Roulston *et al*, 1999; Table 2). Induction of apoptosis in infected cells permits escape of viruses, hence facilitating viral spread. Host cells respond to viral infection by initiating the suicide programme through inflammatory responses (Roulston *et al*, 1999). However, viruses have evolved mechanisms to overcome host defences (Figure 4), which include: blockage of apoptosis by viral BCL-2 (vBCL-2) homologues (reviewed in Polster *et al*, 2004), utilization of the phosphatidylinositol 3-kinase-Akt signalling pathway (reviewed in Cooray, 2004) or suppression of inducers of apoptosis such as p53 (reviewed in Roulston *et al*, 1999).

In vitro and animal studies have shown that HSV induces apoptosis in activated T cells (Raftery *et al*, 1999) and dendritic cells (Muller *et al*, 2004). HSV-induced apoptosis of dendritic cells could be reduced by blocking cell death receptors but not by the antiviral drug acyclovir (Muller *et al*, 2004). This may explain why acyclovir has limited effectiveness in the treatment of herpetic infections. Infection by VZV causes varicella (chickenpox) in sero-negative individuals and herpes zoster (shingles) in previously infected persons. VZV characteristically progresses along sensory nerves and remains quiescent in sensory ganglia during latency. In a recent study, it was shown that VZV-infected neurones were resistant to apoptosis compared with infected fibroblasts, suggesting that inhibition of apoptosis in neurones may play an important role in establishment of the latency stage by promoting survival of neurones (Hood *et al*, 2003). An earlier study had shown that VZV-infected dendritic cells were resistant to apoptosis and were able to transmit the infection to T lymphocytes, suggesting a mechanism for transmission of VZV infection from mucosal surfaces to regional lymph nodes (Abendroth *et al*, 2001). The mechanisms by which HSV and VZV induce apoptosis are not clearly understood.

Infection with Coxsackie viruses or enterovirus 71 (EV71) leads to viraemia and lesions in the oral mucosa and cutaneous surfaces of the hands and feet (Hand-foot-and-mouth disease). The vesicles, which rupture quickly to become ulcers, occur as a result of keratinocyte apoptosis induced by viral products. Expression of the 2A protease of EV71 was able to induce apoptotic cell death in several cell lines (Kuo *et al*, 2002).

The HIV infection causes apoptosis of infected lymphocytes and increased spontaneous apoptosis of uninfected lymphocytes leading to massive CD4+ T-cell depletion in AIDS patients (Dianzani *et al*, 2003). Lymphocyte apoptosis in AIDS is induced by viral components such as gp120, tat, nef and cell surface death receptors (reviewed in Dianzani *et al*, 2003). The immunodeficient state that may develop consequent to HIV infection results in the development of otherwise rare conditions such as OHL, KS (Dianzani *et al*, 2003) and oral lymphomas (Regezi *et al*, 1998). OHL is characterized by massive EBV viral replication and excessive epithelial keratinization on the surface of the tongue. EBV produces viral proteins, which induce hyperproliferation of infected cells, and resists apoptosis by production a viral homologue of BCL-2 (Webster-Cyriaque *et al*, 2000). A strong association between KS, AIDS and human herpesvirus-8 (HHV-8)/Kaposi's sarcoma-associated herpesvirus (KSHV) has been reported (Schalling *et al*, 1995). HHV-8/KSHV modulates a number of cellular events such as immune evasion, cell proliferation and inhibition of apoptosis by encoding a number of protein including viral interleukin-6 (vIL-6)

Table 2 Common oral viral infections, causative virus, viral products and their effects on cell survival

Disease	*Viral cause*	*Viral product*	*Effect of viral product*	*Reference*
Herpes simplex infections	Herpes simplex virus type 1 and 2	?[a]	Proapoptotic	Tropea *et al* (1995)
Varicella (chicken pox), Zoster (shingles)	Varicella zoster virus	?[a]	Proapoptotic	Sadzot-Delvaux *et al* (1995)
Hand-foot-and-mouth disease	Coxsakie viruses	?[a]	Proapoptotic	Roivainen *et al* (2000)
	Enterovirus 71	Proteases (2A and 3C)		Kuo *et al* (2002), Li *et al* (2002)
Oral hairy leukoplakia	Epstein–Barr virus	BHRF1	Antiapoptotic	Dawson *et al* (1995)
		LMP1	Cell survival	Webster-Cyriaque *et al* (2000)
Kaposi's sarcoma	Human herpesvirus-8	vBCL-2	Antiapoptotic	Sarid *et al* (1997)
	Kaposi's sarcoma-associated herpes virus	vFLIP		Dittmer *et al* (1998)

[a]No viral products have been identified from HSV, VZV or coxsakie viruses, which are responsible for induction of apoptosis.
vBCL-2, viral BCL-2; HSV, herpes simplex virus; VZV, varicella zoster virus.

and vBCL-2 (reviewed in Cathomas, 2003; Moore and Chang, 2003).

The ability of viruses to both induce and evade apoptosis plays an important role in the pathogenesis of viral diseases. The understanding of these mechanisms is important for the elucidation of the molecular basis of viral diseases and for the development of vaccines and effective inhibitors directed against viral proteins.

Apoptosis and periodontal disease

Periodontal disease is characterized by destruction of the periodontium leading to loss of tooth support and if untreated to tooth loss. Periodontal disease develops when an imbalance between host defences and endogenous or exogenous microbial agents ensues. In subjects with gingivitis or periodontitis the cell death/proliferation ratio was found to be highest in the most apical part of the gingival sulcus (Jarnbring *et al*, 2002). Periodontal pathogens cause tissue destruction by a number of mechanisms including production of cell death-inducing factors such as leukotoxins, lipoproteins and lipopolysaccharides (LPS), and by induction of inflammatory cells to secrete tissue destructive cytokines and lysosomal enzymes (Figure 5).

Actinobacillus actinomycetemcomitans was shown to induce apoptosis of leucocytes by secretion of leukotoxin in a pathway involving casapase-1 (Kelk *et al*, 2003). Besides inducing cell death, leukotoxin is known to cause rapid degranulation of polymorphonuclear leucocytes (PMNL; Johansson *et al*, 2000; Claesson *et al*, 2002) leading to tissue destruction. An aggressive form of periodontal disease seen in Africa has been related to excess production of leukotoxin as a result of mutation in the leukotoxin gene (Brogan *et al*, 1994).

Porphyromonas gingivalis causes chronic adult periodontitis by evasion of host immune response and induction of tissue damage by surface molecules and secretion of proteinases (reviewed in Nakayama, 2003). Bacterial LPS are known to prolong the lifespan of neutrophils *in vitro* and to cause tissue damage (Murray and Wilton, 2003). LPS produced by *P. gingivalis* and lipoproteins produced by *Bacteroides forsythus* have been shown to induce apoptotic signalling in fibroblasts and keratinocytes (Alikhani *et al*, 2003; Hasebe *et al*, 2004). Furthermore, data from an *in vivo* study indicates that LPS can induce expression of many apoptotic genes and down-regulation of several antiapoptosis genes (Alikhani *et al*, 2003).

Apoptosis and oral tumorigenesis

Cancer cells have attained the ability to evade activation of their inherent apoptotic programme and to escape apoptosis induced by the immune system (Hanahan and Weinberg, 2000). In multicellular organisms, normal cells have a number of potent apoptotic mechanisms for elimination of cells damaged by a variety of stresses such as hypoxia, lack of nutrients, DNA damage and anticancer therapy. It is therefore essential for cells to overcome cell death induced by these stimuli for cancer to develop (Hoeijmakers, 2001). Tumour cells may evade apoptosis by inactivation of apoptosis-inducing genes or by enhancement of the activity of antiapoptosis genes. The role of apoptosis in oral carcinogenesis has been covered by a number of reviews (Kamer *et al*, 1999; Polverini and Nor, 1999; Loro *et al*, 2003; Nikitakis *et al*, 2004).

The *TP53* gene is important for induction of cell cycle arrest and apoptosis. The p53 protein appears to exert its effects at multiple stages of cancer progression, implying that there is a strong selection for tumour cells to inactive *TP53* (Evan and Vousden, 2001; Woods and Vousden, 2001). The importance of p53 inactivation during tumorigenesis is shown by the frequency with which it is mutated in human cancers. Besides *TP53* a number of apoptosis-inducing proteins, such as BAX and BAD, may be inactivated in tumours. BAX was shown to be down-regulated in oral carcinoma cells (Papa *et al*, 2003) and in snuff (toombak)-associated oral carcinomas (Loro *et al*, 2000). A recent report showed that nicotine enhances cell survival by inactivation of BAD (Jin *et al*, 2004).

Tumours also increase the expression of proteins that inhibit apoptosis. $BCLX_L$, an antiapoptosis protein was found to be overexpressed in oral cancer cells (Masuda *et al*, 2002) and could confer resistance to multiple chemotherapeutic agents in several squamous cell carcinoma cell lines (Noutomi *et al*, 2002). The role played by BCL-2 in tumorigenesis has been demonstrated in several tumours (reviewed in Liu *et al*, 2003). However, in oral carcinogenesis its role is less clear. Reports in the literature on BCL-2 expression and its prognostic significance in oral carcinomas remain controversial (reviewed in Loro *et al*, 2003). It is intriguing that some reports indicate a loss of BCL-2 in basal cells of premalignant and malignant oral epithelia (Loro *et al*, 1999b, 2002; Teni *et al*, 2002). Data from our laboratory indicate that loss of BCL-2 mRNA and protein in these lesions is not associated with mutations in the *BCL-2* gene suggesting that aberrant BCL-2 expression in dysplastic and neoplastic epithelia may be under transcriptional regulation (L. L. Loro *et al*, in press). Both BCL-2 and $BCLX_L$ possess antiapoptotic and antiproliferative properties (Greider *et al*, 2002) and have been shown to inhibit tumour progression in animal (Furth *et al*, 1999; Murphy *et al*, 1999) and human cancers (Sinicrope *et al*, 1995; Silvestrini *et al*, 1996). These findings seem paradoxical because *BCL-2* was originally cloned as an activated oncogene in follicular lymphomas because of a breakpoint translocation (Tsujimoto *et al*, 1985). It appears that differential modulation of the antiapoptosis and antiproliferation functions of BCL-2 can result in either enhanced oncogenic or tumour suppressive activities (Janumyan *et al*, 2003). The implications of the dual effects of BCL-2 in oral tissues still remain obscure.

Many solid and haematological malignancies are known to evade apoptosis by overexpression of IAP. Survivin, a member of the IAP family is undetected in most normal adult tissues, but is interestingly overexpressed in human tumours (reviewed in Altieri,

2003). Survivin is not expressed in normal oral epithelium but is detected in premalignant oral lesions, oral squamous cell carcinoma (Lo Muzio *et al*, 2003a,b; Tanaka *et al*, 2003) and ameloblastomas (Kumamoto and Ooya, 2004). Furthermore, survivin expression was associated with a more aggressive and invasive phenotype of oral cancer (Lo Muzio *et al*, 2003b). A number of molecular mechanisms by which survivin regulates cell death and cell division have been identified (reviewed in Altieri, 2004). The selective expression of survivin in neoplastic tissues and its role in inhibition of cell death provides a novel therapeutic target for cancer treatment.

Most of the work on apoptosis and oral tumours has largely been on malignant neoplasms particularly, oral squamous cell carcinomas. There are a limited number of studies on apoptosis and benign oral neoplasms. In ameloblastomas BCL-2 was predominantly expressed in the periphery of tumour islands (Mitsuyasu *et al*, 1997; Sandra *et al*, 2001), whereas the proapoptotic proteins BAX and BAK were preferentially expressed in the central stellate reticulum zones, where apoptotic cell death was most pronounced (Sandra *et al*, 2001). Other studies have suggest a role of p53, Fas, FasL and heat shock proteins (HSP) in modulating apoptosis during tumorigenesis of ameloblastomas (Kumamoto, 1997; Kumamoto *et al*, 2001, 2002). In benign odontogenic tumours such as odontogenic myxoma and oral granular cell tumour it has been proposed that survival of tumour cells may be attributed to suppression of apoptosis by antiapoptosis proteins of the BCL-2 family (Bast *et al*, 2003; Chrysomali *et al*, 2003). In salivary gland tumours a differential expression of BCL-2, c-erbB-2 and p53 compared with normal salivary tissue is thought to contribute to resistance to apoptosis and tumour progression (Nagler *et al*, 2003).

Apoptosis and 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. Factors such as inflammation or trauma stimulate epithelial rests to proliferate sealing off the inflamed or traumatized region from the surrounding healthy tissues. Debris from dead cells in periapical lesions contributes to the formation and expansion of cysts by increasing osmotic pressure within the lumen of newly formed cyst (Takahashi *et al*, 1999). Cyst expansion appears to also involve IL-1α, which is expressed in the lining epithelia and cysts cavities of jaw cysts (Kubota *et al*, 2000).

The role played by apoptosis in the pathogenesis of cysts in the jaws has not been extensively investigated. Apoptosis in periapical cysts appears to involve the proapoptosis proteins of BAX, Fas and FasL (Ungureanu *et al*, 2000). A recent study indicated that p53, BAX, BCL-2 and caspase-3 were involved in the pathophysiology of radicular cysts (Suzuki *et al*, 2005). HSP27, an inhibitor of cell death, was found overexpressed in epithelial cell rests, islands of epithelium and epithelial lining of microcysts suggesting that HSP27 may be involved in increased resistance of epithelial cells to cell death (Leonardi *et al*, 2001).

Keratocysts in nevoid basal cell carcinoma (Gorlin's) syndrome and a subset of sporadic keratocysts are associated with inactivation of the Patched (*PTCH*) gene, which results in evasion of apoptosis and abnormal cell growth (Barreto *et al*, 2000). *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 (Levanat *et al*, 2000). Moreover, a number of known tumour suppresser genes, such as p16, p53 and cyclin D1 are inactivated in odontogenic keratocytes (Lo Muzio *et al*, 1999; Agaram *et al*, 2004) thus supporting a neoplastic rather than developmental pathogenesis of keratocysts.

Several studies have shown that keratocysts have a higher proliferative rate compared with radicular or dentigerous cysts (reviewed in Shear, 2002), a fact that may explain why the lumen of keratocysts are filled with desquamated apoptosed keratinocytes. The desquamated keratinocytes in turn increase the protein content of the cyst lumen raising the osmotic pressure and thus contributing to an increase in cyst size. Apoptotic cells in the epithelium of odontogenic cysts may undergo intracellular dystrophic calcification to form Rushton's hyaline bodies (Pesce and Ferloni, 2002). The high proliferative rate and apoptotic activity in keratinocytes in a confined area may contribute to the aggressiveness of keratocysts.

Apoptosis and Sjögren's syndrome

Sjögren's syndrome is a chronic autoimmune disease characterized by loss of epithelial glandular cells of salivary and lacrimal glands and their replacement with a focal lymphocytic infiltrate. Studies on Sjögren's syndrome have proposed apoptosis as the mechanism underlying the damage of salivary and lacrimal gland tissues resulting in impaired secretory function (reviewed in Jonsson *et al*, 2003; Manganelli and Fietta, 2003). Fas signalling has been proposed as an important mechanism of salivary gland apoptosis in Sjögren's syndrome (Ichikawa *et al*, 1995; Shibata *et al*, 2002; Bolstad *et al*, 2003). However, another study showed that despite high levels of Fas and FasL in salivary glands of Sjögren's syndrome subjects, TUNEL-positive cells were rarely detected in the lymphocytic infiltrate suggesting that these lymphocytes may be resistant to Fas-induced cell death (Ohlsson *et al*, 2001). The level of detection of apoptotic cells in salivary glands may be dependent on the stage in the development of the disease with its detection likely to be very low in severely atrophic glands. Other suggested mechanisms of apoptosis in acinar and ductal epithelial cells in salivary and lacrimal glands include: cell death induced by cytotoxic T cells through the perforin/granzyme B system (Darmon *et al*, 1996; Atkinson *et al*, 1998), the BCL-2 family proteins (Masago *et al*, 2001; Badillo-Almaraz *et al*,

2003) and cytokines such as CD40 (Ohlsson *et al*, 2002), TNF-α and interferon-γ (Kamachi *et al*, 2002). It is clear that apoptosis regulatory molecules are involved in the pathogenesis of Sjögren's syndrome. However, it still remains unknown which of these molecules is/are crucial or how they influence each other during the development of Sjögren's syndrome.

Conclusion

Apoptosis has emerged over the last three decades as an important biological process involved in normal physiology and in the pathogenesis of a variety of diseases. This review is an attempt to sum up current knowledge on the role of apoptosis in oral diseases. The understanding of the molecular basis of apoptotic cell death has lead to the development of therapeutic strategies in the treatment of a number of diseases including cancer, immunological disorders and autoimmune diseases. There is still a lot that is unknown about the molecular mechanisms underlying disease in the oral cavity. It is unclear why KS has a strong predilection for the hard palate or why aphthous ulceration predominantly affects non-keratinizing oral epithelium. So far, little has been done to understanding the role of apoptosis in benign oral tumorigenesis.

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