# Scarless healing: oral mucosa as a scientific model

**Cutaneous wound healing's usual endpoint is scar formation. In contrast to the skin, the oral mucosa heals in a scarless manner, despite undergoing the same stages of the healing process. While wound environment may play a part, studies have demonstrated that inherent differences in the phenotypic and genotypic characteristics of the resident fibroblast populations may have a role in mediating this differential healing. This article analyses the evidence surrounding scarless healing in the oral mucosa and discusses future areas of research and highlights the potential clinical implications of this fascinating phenomenon.**

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Normal cutaneous wound healing involves a complex but well-orchestrated series of events leading to the repair of injured tissues. Injury to the skin due to surgery, trauma or burns can result in varying degrees of scarring depending on the severity and anatomical location of the insult (Enoch et al, 2004a). In certain instances, the scarring can be excessive and unregulated resulting in hypertrophic and keloid scars (Enoch et al, 2006b). Contractures, a scar variant frequently a result of burns or scalds, often occur over flexural surfaces such as the neck or elbow and can result in severe, long-term functional problems.

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In contrast to scar formation mammals, embryos and early gestational foetuses in utero heal rapidly and in a scarless fashion (Shah et al, 1995). In non-foetal tissue anatomical areas such as the oral mucosa also exhibit this 'privileged' pattern of rapid and scarless healing (Szpaderska et al, 2003), despite wounds in the oral mucosa and the skin proceeding through the same stages in the healing process as other parts of the body (Sciubba et al, 1978; Walsh et al, 1996). Some critics may however argue that healing in the oral mucosa is not strictly 'scarless' as observed in the foetus since, unlike the foetus that heals by regeneration, non-foetal tissues heal by repair. Although this argument might be considered valid if the tissue is scrutinised by microscopic examination, unlike the skin, the oral mucosa do not clinically exhibit any form of scarring, subtle or overt, after injury. Excessive scarring such as hypertrophic scars and keloid scars have not been reported in the oral mucosa. Scalds to the oral mucosa do not result in contractures unlike scalding to the skin (Enoch et al, 2006a). In addition to healing in a scarless manner, oral mucosal wounds also heal rapidly which is comparable to foetal wounds (Sloan et al, 1991). This article will evaluate the scientific evidence and discuss the current and future research areas in this area and the potential clinical application of the findings.

## History of research into scarless healing

Early investigations into scarless healing were predominately conducted in foetal wounds. Initial investigations attributed the observed difference between foetal and non-foetal wound healing to the intrauterine environment — the sterile, warm amniotic fluid rich in hyaluronic acid and growth factors — and the relative hypoxemic state of foetal tissues in utero (Longaker et al, 1989; 1990). However, this was soon challenged when the capacity for scarless repair intrinsic to foetal tissue was demonstrated in an experiment where the researchers subcutaneously grafted human foetal skin (15–22 weeks gestation) onto the backs of athymic adult mice. After wounding the mice they identified that only the subcutaneously grafted foetal skin healed without scar formation (Lorenz et al, 1992). Likewise, Longaker et al (1994) observed that intrauterine environment alone was not sufficient to induce scarless repair. After transplanting adult sheep skin onto the backs of 60-day-old sheep foetuses incisional wounds were created in the transplanted adult skin and adjacent foetal skin 40 days later. When examined microscopically, only the foetal skin wounds healed without scarring.

The irrelevance of the sterile, fluid, embryonic environment to scar-free healing was conclusively demonstrated in an ontological investigation of wound healing and scarring in the pouch young

of the marsupial Monodelphis domestica (Armstrong and Ferguson, 1995; 1997). These early pouch young are regularly contaminated with maternal urine and faeces that contrasts with the sterile amniotic fluid environment of their placental counterparts. However, despite these striking differences, skin wounds on early pouch young of M. domestica heal perfectly with no scars (Armstrong and Ferguson, 1995; 1997). A number of unique properties of foetal skin repair have been identified that contribute to scarless healing in the foetus including reduced or lack of pro-inflammatory signals (Cowin et al, 1998), high synthetic capabilities to lay down collagen rapidly (Bullard et al, 2003), differential expression of transforming growth factor-β (TGF-β) isoforms (Shah et al, 1992; 1994), altered balance between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) (Lorenz et al, 2001), lower levels of decorin expression (decorin assists in TGF-β activity (Beanes et al, 2001) and altered gene expression profiles (Stelnicki et al, 1997; 1998).

Just as scarless healing in the foetus was previously attributed to the uterine environment, scarless healing in the oral mucosa was thought to be attributable to its moist environment and the presence of cytokines and growth factors in the saliva. Angelov et al (2004) using a murine model, hypothesised that secretory leukocyte protease inhibitor (SLPI; a cationic serine protease inhibitor with antimicrobial and anti-inflammatory properties) found in large quantities in the saliva may have a role in mediating scarless healing in the oral mucosa; a concept previously hypothesised and supported by in vitro studies (Sumi et al, 2000).

Although SLPI positively contributes to normal wound healing (Ashcroft et al, 2000) there is a paucity of credible scientific data at present for its role in mediating scarless healing. However, scarless healing as an inherent characteristic of the oral mucosa, rather than due to an extraneous interference or influence, has been illustrated by studies which reported that skin tissue transplanted into oral mucosal defects retain their normal anatomic and phenotypic characteristics, and thus heal with scar formation (Bussi et al, 1995). Likewise, although excessive scarring conditions such as keloid scars have rarely been observed in the oral mucosa, transplanted skin used to reconstruct a defect in the oral cavity has been shown to heal with intraoral keloid formation (Reilly et al, 1980), with the keloid arising from the wound in the skin rather than from the oral mucosa. In addition, histological examination of skin transposed into the oral cavity in reconstructive surgery has shown only the skin-mucosal interface to heal without a scar (effectively an oral mucosal type of healing) although the skin retained the ability to maintain keratinisation and other textural peculiarities (Bussi et al, 1995).

## Role of fibroblasts

Fibroblasts are ubiquitous cells that play a significant role in various stages of the healing process. Following injury, fibroblasts migrate into the wound, proliferate and produce the matrix proteins (fibronectin, hyaluronic acid, collagen and proteoglycans) and, in doing so, form granulation tissue (Enoch et al, 2008). They then reorganise the provisional extracellular matrix (ECM) and remodel the resulting scar (Thomas et al, 1995). They also interact with keratinocytes, releasing growth factors and cytokines that play a further role in modulating wound repair (Slavin, 1996; Smith et al, 1997). The composition of the ECM (and thus the final wound healing outcome) can be altered by the balance between the MMPs and TIMPs — enzymes produced by fibroblasts. In addition to wound healing, fibroblasts are implicated in the aetiology of many pathological conditions related to wound healing outcomes such as keloid and hypertrophic scars, Dupuytren's contracture, pulmonary fibrosis and retroperitoneal fibrosis.

## Role of myofibroblasts and fibrocytes

One of the best-characterised sub-types of fibroblasts is the myofibroblast, which plays an important role in scar formation. Myofibroblasts are characterised by the presence of stress fibres that contain α-smooth muscle actin and indented nuclei (Gabbiani et al, 1971; Eyden, 2003), and thus have structural properties between those of a fibroblast and a smooth muscle cell. Although their precise origin is a matter of debate, the consensus is that fibroblasts differentiate into myofibroblasts after migration into the wound under the influence of growth factors such as TGF-β1 (Dugina et al, 2001) and mechanical stress (Hinz et al, 2001). In addition to fibroblasts, some smooth muscle cells and pericytes are also thought to be capable of differentiating into myofibroblasts (Gabbiani, 1996). Myofibroblasts appear about three days after wounding and increase in number to a maximum level between day 10 and 21. Their main function is to contract the granulation tissue and deposit new ECM. Although they promote wound closure, myofibroblasts are also responsible for subsequent wound contracture and scarring. Therefore, a delicate balance of fibroblasts and myofibroblasts in the wound is essential for optimum wound healing (Desmoulière and Gabbiani, 1996).

Estes et al (1994) demonstrated a clear link between the appearance of myofibroblasts in the wound and scar formation in foetal sheep. They found that the transition from scarless tissue repair to healing with scar formation, which occurs during late gestation, is accompanied by an increased appearance and presence of myofibroblasts in the wound environment. The precise role of myofibroblasts in oral mucosal healing remains unclear although, unlike in the skin, there is little evidence to suggest that myofibroblasts play an important role in oral mucosal healing.

Fibroblasts present in the wound site are thought to be recruited from the surrounding connective tissue. However, Bucala et al, (1994) identified a population of circulating cells that specifically entered sites of tissue injury. This novel cell type, termed a fibrocyte, was characterised by its distinctive phenotypic characteristics (positive for collagens I and III, vimentin, CD34, CD86 and MHC II), its entry from blood into the wound space and its presence in connective tissue scars. Subsequently, fibrocytes were found

to be derived from the bone marrow and peripheral blood mononuclear cells and display fibroblast-like properties, synthesising ECM macromolecules and contributing to the myofibroblast population in the wounded skin (Mori et al, 2005). They are thought to potentially upregulate the inflammatory cytokines, have potent immunostimulatory properties and are found in increased numbers in hypertrophic scars, keloid scars and fibrotic lesions (Yang et al, 2005). Fibrocytes are thus implicated in the development of scars and excessive scarring conditions. Complementing this fact is the observation that fibrocytes have not been identified in tissues that exhibit scarless healing such as foetal wounds and oral mucosal wounds.

## Phenotypic characteristics of oral mucosal fibroblasts

In line with general fibroblast heterogeneity, it has been previously shown that oral mucosal fibroblasts exhibit a distinct cellular phenotype when compared with their counterparts in skin wounds. Compared with skin fibroblasts, oral mucosal fibroblasts have been shown to have an increased ability to migrate and repopulate within a wound (al-Khateb et al, 1997), and buccal mucosal fibroblasts have been shown to migrate into a collagen gel in vitro faster than their skin counterparts (Irvin et al, 1994). Likewise, differences have been reported between oral mucosal fibroblast's and skin fibroblast's ability to reorganise ECM, although different researchers have reported incongruous results. Stephens et al (1996; 2001a) demonstrated that oral mucosal fibroblasts have an increased ability to reorganise their surrounding ECM. Likewise, a recent study by Shannon et al (2006) demonstrated oral mucosal fibroblasts have a better ability to reorganise three-dimensional collagen lattices than patient-matched skin fibroblasts. However, Lee and Eun (1999) observed that skin fibroblasts reorganise the collagen lattices better than corresponding oral mucosal fibroblasts, although the period of observation in this study was shorter than in the experiments by others. Their results were in line with the findings of Tsai et al (1995) in a study that compared the contraction potency of fibroblasts from hypertrophic scars, normal skin and oral mucosal fibroblasts. They found that fibroblasts derived from hypertrophic scars possessed the greatest reorganisation potency and skin fibroblasts showed a greater ability to reorganise collagen lattice compared with oral mucosal fibroblasts. This variation in the ECM reorganisational ability of skin fibroblasts and oral mucosal fibroblasts has been associated with variations in the activity of MMP and TIMP profiles. Stephens et al (2001a) demonstrated that oral mucosal fibroblasts produced more MMP-2 and less TIMP-1 and TIMP-2 compared with patient-matched skin fibroblasts, suggesting that the balance between these two proteases played a role in the reorganisation ability of these cells within collagen lattices, and thus in the differential healing observed between oral mucosal and skin wounds in vivo.

## Role of growth factors in mediating scarless and scar-forming wounds

Since a large proportion of research undertaken to decipher the mechanics of scarless healing have been on foetal or embryonic wounds, most data currently available about the role of growth factors in scarless healing have been obtained from research on mammalian foetuses and embryos. Normal embryonic skin and embryonic wounds, due to rapid expansion of skin volume, contain high levels of morphogenetic factors involved in skin growth, remodelling and morphogenesis. As a consequence of altered inflammatory response and skin morphogenesis, the growth factor profile of a healing embryonic wound is qualitatively (the types of growth factor present), quantitatively (the amounts of such growth factors present) and temporally (the length of time the growth factors are present) different compared with an adult wound (Whitby and Ferguson, 1991; O'Kane and Ferguson, 1997; Shah et al. 2000). Although the functions of various growth factors have been evaluated, TBF-β and hepatocyte growth factor (HGF) have been shown to play important roles in mediating the differential pattern of healing. Oral mucosal fibroblasts, in comparison with skin fibroblasts, have been shown to produce more HGF (Stephens et al, 2001b; Shannon et al, 2006) and keratinocyte growth factor (Okazaki et al, 2002).

Other growth factors, such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF-2), also show subtle differences in temporal and spatial appearance in the healing foetal wound (Whitby and Ferguson, 1992). Adult wounds contain large quantities of PDGF, which is virtually absent in embryonic wounds (owing to the lack of platelet degranulation), whereas embryonic wounds contain higher levels of endogenous FGFs involved in skin morphogenesis (Whitby and Ferguson, 1991). Exogenous PDGF is shown to induce fibrosis in foetal rabbit wounds (Haynes et al, 1994) and FGF isoforms 2, 5, 7, 9 and 10 have differential expression in scarless wounds compared with wounds that scar. Dang et al (2003) observed an overall down-regulation of FGF expression during scarless healing in foetal rats.

## Discussion

From an evolutionary perspective, skin wounds represent not just a physical impediment due to blood loss or tissue damage, but threaten the very survival of the species from development of infection and sepsis due to invasion of micro-organisms or soil contaminants. The immediate imperative of the body is to close the wound and prevent establishment of infection. It achieves this objective by the means of a rapid and robust inflammatory response, with recruitment of neutrophils, macrophages and lymphocytes to the wound site. This is followed by fibroplasia, ECM synthesis and reorganisation, perhaps in a haphazard manner, in an attempt to reduce the size of the wound (with the help of myofibroblasts) as early as possible. Prevention of scar formation, it can be argued, is the least of the priorities of the body's defence mechanism. However, in the current evolutionary stage with cleaner wounds and advances in antiseptics, it could be postulated that a massive inflammatory overdrive resulting in a scar might not be an evolutionarily optimal endpoint. How does this evolutionary intention relate to the scarless healing observed in the oral mucosa? Similar to the skin,

the oral mucosa is also subjected to repeated trauma, although from different aetiologies such as mastication and the irritant effects of some foods. The oral cavity is also colonised and contaminated with more micro-organisms than the skin. Non-healing wounds in the oral cavity can prevent adequate intake of food, which can compromise the very survival of the species. Thus the oral mucosa has more impetus to heal more rapidly than the skin. Although this can be rationalised from an evolutionary viewpoint, why should the wounds heal in a scarless manner? The answer to this conundrum is in the fact that the oral mucosa is subjected to more trauma than the skin. Hence, as with skin, if all these wounds healed with scarring (and the associated hypertrophic scar, keloid scar, contractures and fibrosis), it would severely compromise the functionality of the oral cavity.

So has the oral mucosa evolved to heal in a scarless manner? If so, could the reason be the result of a reduced or an altered inflammatory response? Could it be due to a different gene transcriptional profile of the fibroblasts? (Enoch, 2004; Enoch et al, 2004b; 2005). Or could it be due to the presence of 'foetal-like' cells or progenitor stem cells in the wounds so that the fibroblasts can be constantly replenished to expedite healing in the oral mucosa?

The observation that the in vivo response of oral mucosa to repair defects without scar formation is more akin to regeneration (as seen in foetuses) rather than repair, supports a provocative but rational idea that the cell lineage of some, if not all, oral mucosal fibroblasts could have been derived from a resident, multi-potent cell population within the lamina propria of the oral mucosa. This leads to the novel hypothesis that a stem cell or a 'stem cell-like' population may be present within the oral mucosa, which contributes to their preferential healing. Further studies are needed to explore this line of investigation and to corroborate the theorem proposed here.

The option of using oral mucosal fibroblasts instead of skin fibroblasts in various tissue-engineered skin substitutes is currently being explored. If multipotent stem cells are identified in the oral mucosa, clearly, in addition to direct clinical application, this finding would have further wide-ranging, positive ramifications in the fields of tissue engineering, tissue repair and regeneration. This is due to the easy accessibility of the oral mucosa and the fact that the oral mucosa is in an ideal and preferential position to provide the sample, for isolating and clonally expanding a population of progenitor cells, since it will heal quickly without scarring. These progenitor cells can then be cultured onto in vitro custom-designed, biologically compatible tissue-engineered materials that will be able to generate a functional tissue (or a tissue-engineered skin substitute).

The ability of wounds to heal in a scarless manner or the availability of a biologically developed surrogate that promotes scarless healing will be of immense benefit for patients whose injuries (such as burns or major trauma) result in a considerable amount of normal or excessive scarring, or cutaneous fibrosis and contractures, that, in addition to being aesthetically plain, result in significant functional morbidity. The oral mucosa, due to the aforementioned reasons, can be effectively used as an exemplar to further decipher the mechanics of scarless healing.

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## Key Points

- Visual and physical signs of inflammation (swelling, redness, pain, heat) within or around wounds are primarily caused by neutrophil leukocytes, together with the complement proteins, aided and abetted by tissue mast cells.
- Most of the immunological activities taking place in a chronic wound are mediated by the innate arm (or division) of the immune system.
- Neutrophil infiltration is the most prominent feature of the innate response, but neutrophils as a weapon of defence are a double edged sword. They are aggressive against microbes, but they cause major collateral damage by releasing a corrosive cocktail of protease enzymes and active oxygen species.
- Even though crucial for antibacterial defence, neutrophils can become an unwelcome, damaging presence in a wound, if they stay in residence for too long. Excessive proteases and/or chronic hypoxia can be root causes of these problems. New healing technologies will re-instate healing by dealing with these local causes.
- As a general rule, wounds dominated by neutrophils are in trouble, either because of infection or chronic inflammation, while macrophage domination is usually a sign that a wound is progressing well. But these are signs that clinicians cannot see. New diagnostic tests will reveal these changes to give crucial guidance to care strategies.