Review Article

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Endodontic Healing

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ABSTRACT

Background: Endodontic healing involves a series of rapid increases in specific cell populations that prepare the site for repair, deposit new matrices and finally, mature the wound. Upon completing their tasks, these specific cell types must be eliminated from the site prior to the progression to the next phase of healing. The most logical method of cellular down-regulation is through apoptosis. Apoptosis allows for the eliminations of entire populations without tissue damage or an inflammatory response. This review discusses which cells dominate the various phases of tissue repair and how the cellular pattern may vary during different phases. The potential mechanisms involved in the down-regulation of inflammation and fibrosis are also covered. The studies that support the hypothesis that apoptosis is involved in the regulations of wound healing are discussed. The evidence supporting potential cell signals involved in the induction of apoptosis in tissue repair are examined and how dysregulation of apoptosis can lead to pathologic forms of healing such as excessive scarring and fibrosis also covered. By understanding the mechanisms controlling apoptosis and tissue repair, one may eventually develop therapeutic modalities to endodontic healing.

Keywords: Dentistry, endodontics, healing.

INTRODUCTION

Root-canal treatment aims to eliminate bacteria from the infected root-canal system to create an environment that is most favourable for healing.[2] Wound healing is as important as knowing the pathogenesis of disease, because satisfactory wound healing is the ultimate goal of treatment. If we are able to understand the mechanisms of periapical wound healing, we can design treatment approaches that maximize favourable conditions for wound healing to occur, such as effective disinfection of the root canal system in nonsurgical root canal therapy, control of periapical inflammation by medication, or incorporation of growth factors in bone grafts in surgical endodontic therapy.[3]

Interestingly, healing begins as soon as inflammation starts. When irritants (microbial and nonmicrobial) in the canal systems or in the periapical tissues are eliminated by nonsurgical or surgical endodontic therapy, inflammatory mediators are no longer produced in the periapical tissues because of reduction of immunoinflammatory cells. Inflammatory mediators already present are inactivated by the body's control mechanisms to prevent an inflammatory reaction from going unchecked. This process precedes wound healing.[3]

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Examples of host anti-inflammatory control mechanisms are:

1. Enzyme destruction of inflammatory activators;
2. Natural inhibitors of inflammatory mediators (e.g., opioids, somatostatin, glucocorticoids, etc.);
3. Relative balance between intracellular levels of cyclic AMP and cyclic GMP;
4. The antiphlogistic role of histamine;
5. Inhibitors of the complement system;
6. Antiinflammatory cytokines, such as IL-4, IL-10, IL-13 and TGF-β.

The major cellular inducer of inflammation neutrophilic leukocytes, undergo apoptosis and the major cellular player of wound healing, macrophages, secrete anti-inflammatory molecules.[3] Wound healing of apical periodontitis lesions after proper nonsurgical root canal therapy follows the general principle of wound healing of connective tissues elsewhere in the body, with the formation of fibrovascular granulation tissue, removal of necrotic tissue and dead bacteria by activated macrophages and finally repair and/or regeneration of the wounded tissue. Healing of apical periodontitis lesions is largely accomplished by regeneration and to some degree by fibrosis.[3]

The process of wound healing is tightly regulated by cell-to-cell and cell-to–extracellular matrix interactions, as well as temporal and spatial expression of a variety of cytokines, growth factors, and neuropeptides and apoptosis. All these cellular and humoral factors operate together in either an antagonistic or synergistic manner and are precisely orchestrated during wound healing. This results in a highly organized response permitting regeneration of the original tissue architecture. Wound healing appears to be a programmed event.[3]

Wound healing is a complex process, which requires interactions between different type of cells, interactions between cells and extracellular matrix and a wide variety of cytokines, growth factors, neuropeptides and apoptosis. This process in periapical pathosis follows the same fundamental mechanisms of wound healing of connective tissues elsewhere in the body, including granulation tissue formation and activation of macrophages in order to digest necrotic tissue remnants and dead bacteria, resulting in regeneration and/or repair of the involved tissue.[4]

Cellular changes after wound healing

After injury, a great variety of signals are released that not only initiate but regulate all aspects of tissue repair. Platelets arrive at the time of vascular disruption and have been shown to contain large amounts of growth factors in their alpha granules. Growth factors released by platelets initiate the tissue repair by attracting cells into the wound. Currently, neutrophils are felt to be primarily involved in the first-line defence against invading organisms and the elimination of foreign material. The oxygen free-radicals and proteases released by the neutrophils are effective for performing the defensive tasks but they also act as `friendly fire' to destroy viable tissues if not limited. The next cell that appears in a wound is the macrophage. The role of the macrophage in wound healing was investigated in 1975 by Leibovich and Ross who eliminated macrophages from the wound and discovered that wounds healed poorly. Since then, several investigators have concluded that the macrophage is a key orchestrator of tissue repair. Macrophages regulate tissue repair through the release of several growth factors and cytokines. They also have a role in the phagocytosis of nonviable materials. Soon after the arrival of macrophages there is an influx of lymphocytes. The inflammatory reaction induced by leukocy tes is essential for preparing the wound for the production of a new extracellular matrix that mainly consists of collagens and glycosaminoglycans. Cytokines and growth factors released by the inflammatory cells attract fibroblasts and myofibroblasts into the wound to initiate the `proliferative or collagen phase' of tissue repair. There is a rapid influx of fibroblasts at 3 - 5 days followed by the first deposition of collagen and glycosaminoglycans. During this phase there is a rapid increase in the amounts of collagen detected in the wound that is associated with a rapid increase in incisional tensile strength. Fibroblasts require oxygen and nutrients to manufacture the extracellular matrix so there is a requirement for angiogenesis. Macrophages in the hypoxic environment release angiogenic factors that stimulate post-venule endothelial cells to break free of their basement membrane and migrate into the

wound to create a highly vascular `granulation tissue'. This environment of fibroblasts, new capillaries and extracellular matrix create an adequate bed for the disrupted epithelium to migrate across the wound. The collagen produced is essential for the wound to regain much of the strength lost after injury. Eventually, (usually 2 - 3 weeks in an incision) collagen content in the wound levels off, marking the start of the final phase of tissue repair: the `maturation phase'. Collagen is still synthesized but collagenase production also increases to create a balance between collagen production and degradation. During this phase, collagen is remodeled and re-aligned along planes of stress to increase the strength of the incision. Wounds have persistent increases in vascularity and cellularity that persists for months as indicated by the continued presence of a red and thickened wound. Eventually, the wound becomes less cellular and vascular to end up with a wound that is flat and white. Usually the maturation phase lasts approximately one year before the wound develops its final state of a mature avascular and acellular scar.[1,4]

Mechanism of periapical wound healing

Local tissue resident cells involved in periapical wound healing are osteoblasts and bone marrow stromal cells in alveolar bone and multipotent stem cells in periodontal ligament. During periapical wound healing, many unwanted hyperplastic cells (e.g. endothelial cells, fibroblasts, epithelial cells) are deleted by apoptosis and the extracellular matrix is remodeled by metalloproteinases. Pathologic processes such as extensive fibrosis do not occur, and the damaged periapical tissues can be ideally restored to their original structure by the process of regeneration.[3]

The temporal and spatial relationship between alveolar bone, cementum, and periodontal ligament during periapical wound healing after nonsurgical root canal therapy cannot be clearly delineated. Nevertheless, wound healing appears to recapitulate the initial histogenesis of damaged tissues or organs in many instances. The process of periapical wound healing after nonsurgical root canal therapy may be similar to wound healing following guided tissue regeneration in periodontal therapy: regeneration of new periodontal ligament, new cementum and new alveolar bone. Both nonsurgical root canal therapy and guided tissue regeneration therapy are able to remove irritants and provide a favourable environment conducive to regeneration of periodontal tissues damaged by apical periodontitis and marginal periodontitis, respectively.[3]

During periapical wound healing, the cells of viable periodontal ligament from adjacent root surfaces proliferate to cover the root surfaces in which the periodontal ligament was damaged by apical periodontitis and removed by macrophages. Proteins derived from Hertwig's epithelial root sheath (i.e., enamel matrix proteins) are required for cementoblast differentiation from ectomesenchymal stem cells in the dental follicle during tooth development. The cells of Hertwig's epithelial root sheath are absent in mature teeth.[3]

Nevertheless, the extracellular matrix and growth factors of cementum (i.e.IGF-1, FGFs, EGF, BMP, TGF-β, PDGF) sequestered after cemental resorption in mature teeth are capable of inducing proliferation, migration, attachment and differentiation of multipotent stem cells in the periodontal ligament into cementoblast-like cells and produce cementoid tissue on the root surface denuded of periodontal ligament. This is similar to reparative dentin formation by pulp stem cells in direct pulp capping procedures where growth factors such as TGF-β are released from dentin matrix binding sites. Root resorption that involves cementum or both cementum and dentin can only be repaired by cementoid tissue because multipotent stem cells of the periodontal ligament are incapable of differentiating into odontoblasts that produce dentin.[3]

Bone has a remarkable capacity for regeneration in response to injury. During periapical wound healing, the osteoblasts or mesenchymal cells lining the surfaces of endosteum—stimulated by TGF-β, BMPs, IGFs, PDGF, VEGF, and cytokines released by stromal cells, osteoblasts, platelets, and bone matrix after bone resorption can undergo proliferation and differentiation into osteoblasts and produce bone matrix. When one of the cortical bone plates (buccal or lingual/palatal) is destroyed, mesenchymal cells in the inner layer of periosteum beneath the oral

mucosa stimulated by TGF-β, BMPs, IGFs, PDGF, and VEGF are also capable of proliferation and differentiation into osteoblasts and can produce bone matrix. If both buccal and lingual/palatal cortical bone plates are destroyed by large apical periodontitis lesions, it is possible that the lesion may be repaired with fibrous scar tissue because of extensive destruction of the periosteum beneath the oral mucosa. Accordingly, a guided tissue regeneration procedure using membrane barriers and bone grafts is recommended to prevent ingrowth of fibroblasts from periosteum or submucosa into the bony defect and to enhance periapical wound healing if periapical surgery is necessary. Growth factors/cytokines may play an important role in regulating fibroblast gene expression and excess scar tissue formation.[3]

The newly regenerated periodontal ligament will finally undergo remodeling into mature periodontal ligament, with one group of collagen fibers (Sharpey's fibers) inserted into the newly formed cementum and another group of collagen fibers inserted into the newly formed alveolar bone. Thereby, regeneration of damaged periapical tissues, cementum, periodontal ligament, and alveolar bone is completed.[3]

Down-regulation of inflammation and the healing process

Evidence suggests that the epithelium produces at least one protein that down regulates fibroblast proliferation. An epidermal cell-derived factor' has been described that decreases fibroblast proliferation. Other cytokines and growth factors appear to play a role in the resolution of the fibroblastic response. Transforming growth factor-β (TGF- β) has been suggested as having dual roles: as a down-regulator of inflammation as well as being the key growth factor for inducing fibrosis. The antagonism of TGF- β1 has been found to reduce scarring. Interestingly, TGF- β3 appears to have antifibrotic effects and may be an important factor in reducing pathologic scar. During the maturation phase, the wound hyper vascularity must also decrease. The mechanisms that decrease angiogenesis probably involve a negative feedback loop that involves macrophages. Once a macrophage resides in an environment rich in oxygen and low in lactate, then the stimuli for the production of angiogenic factors is lost. While losing the angiogenic stimuli is undoubtedly important as a signal, it does not address the mechanisms of eliminating vessels that are already present in the wound.[1]

Apoptosis as the method of cellular elimination in wounds

The cells involved in each phase disappear from a wound by one of three potential mechanisms: necrosis, emigration or apoptosis. Necrosis occurs in pathologic tissue repair but for most wounds, healing proceeds without excessive inflammation and resulting tissue damage. Necrosis clearly induces inflammation and so the mechanism of the decrease in cellularity in wounds is probably not dominated by necrosis. There is little evidence of cell migration out of the wound. The most logical mechanism for decreasing cell numbers with the various phases of healing is through apoptosis. Apoptosis or programmed cell death is the universal pathway for the elimination of unneeded cells and tissues in a phagocytotic process that does not elicit an inflammatory response. When enough collagen has been deposited (at the end of the proliferative phase) fibroblasts would start to undergo apoptosis. Finally, upon the completion of wound maturation, endothelial cells and remaining fibroblasts would silently disappear.[1]

Factors Influencing Periapical Wound Healing

Local and systemic factors may affect periapical wound healing. Infection will complicate and prevent wound healing, foreign bodies can impair wound healing and nutrition can also affect wound healing. Diabetes was reported to reduce the likelihood of healing of apical periodontitis lesions after nonsurgical root canal therapy. Impaired nonspecific immune response and disorders of the vascular system appeared to have a significant influence on the success rate of nonsurgical root canal therapy on teeth with apical periodontitis. However, immunocompromised patients, such as HIV patients, responded as well as counterpart patients after nonsurgical endodontic therapy. Although smoking has not been shown to be associated with increased incidence of apical periodontitis and prognosis of nonsurgical root canal therapy, smoking may increase complications

of periapical surgery, such as pain and swelling. Patients receiving radiotherapy of jaws and bisphosphonate therapy have a risk of developing osteonecrosis of jawbones, so nonsurgical root canal therapy is recommended for these patients.[3]

SUMMARY

Apoptosis plays an essential role in the orchestration of the rapidly changing populations of cells that are involved in the endodontic healing. The controls of proliferation lead to an expeditious closure of a site. Occasionally, the balance between increased and decreased cellular numbers loses its balance and leads to pathologic tissue repair. By understanding not only the cellular controls that promote proliferation but also decreasing cell numbers clinicians may treat or many pathologic processes.[1,7]

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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