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"Sugar-coating wound repair: A review of FGF-10 and dermatan sulfate in wound healing and their potential application in burn wounds"

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Abstract

Thousands of patients suffer from burn injuries each year, yet few therapies have been developed to accelerate the wound healing process. Most fibroblast growth factors (FGFs) have been extensively evaluated, but only a few have been found to participate in wound healing. In particular, FGF-10 is robustly increased in the wound microenvironment following injury and has demonstrated some ability to promote wound healing *in vitro* and *in vivo*. Glycosaminoglycans (GAGs) are linear carbohydrates that participate in wound repair by influencing cytokine/growth factor localization and interaction with cognate receptors. Dermatan sulfate (DS) is the most abundant GAG in human wound fluid and has been postulated to be directly involved in the healing process. Recently, the combination of FGF-10 and DS demonstrated the potential to accelerate wound healing via increased keratinocyte proliferation and migration. Based on these preliminary studies, DS may serve as a cofactor for FGF-10, and together, they are likely to expedite the healing process by stimulating keratinocyte activity. As a specific subtype of wounds, the overall healing process of burn injuries does not significantly differ from other types of wounds, where optimal repair results in matrix regeneration and complete re-epithelialization. At present, standard burn treatment primarily involves topical application of anti-microbial agents, while no routine therapies target acceleration of re-epithelialization, the key to wound closure. Thus, this novel therapeutic combination could be used in conjunction with some of the current therapies, but it would have the unique ability to initiate wound healing by stimulating keratinocyte epithelialization.

Keywords

Burns; wound healing; FGF-10; dermatan sulfate

Introduction

For the 45,000 burn patients admitted to the hospital each year (1), the average length of stay is more than eight days and costs more than $60,000 (2). Although the average burn patient is a young, previously healthy male (2), many older burn patients suffer from comorbid conditions, such as diabetes and/or vascular disease, prior to burn injury. These

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patients are consequently at a higher risk for developing chronic, non-healing wounds. While significant progress in topical antimicrobial agents and local wound care has substantially reduced the morbidity and mortality from burn wound sepsis (3), no routine therapies currently target keratinocytes and/or stimulating re-epithelialization, which could potentially accelerate wound closure.

Overview of FGF Structure and Function

One important area of interest in wound healing includes the normal biologic role and potential therapeutic application of fibroblast growth factors (FGFs). FGFs serve in numerous capacities, including regulation of cell proliferation, cell migration, cell differentiation, development, response to injury, wound healing, and tumorigenesis (4). FGFs are differentially expressed in many tissues with significant variability in the pattern and timing of expression, which has been shown to be important during development (4). In humans, there are 22 known FGFs, ranging in size from 17 to 34 kDa and sharing 13–71% amino acid identity (5). The prototypical FGF gene consists of three exons, and their protein structures are characteristically composed of multiple beta strands with a common core containing 28 highly conserved amino acid residues and six identical amino acid residues (5, 6).

Furthermore, ten of these highly conserved residues interact with one of the six known FGF receptors (FGFRs) (5), which allow for FGF signaling. In general, the receptor binding sites are believed to be distinct from the ligand binding sites (5). The typical structure of these tyrosine kinase receptors consists of an extracellular ligand-binding domain, a single transmembrane domain, and a cytoplasmic domain (7). The extracellular ligand-binding domain contains three immunoglobulin-like domains, designated D1-3. D2 is positively charged and contains a highly conserved region that serves as a binding site for ligands, such as glycosaminoglycans (7). Alternative splicing of FGFR mRNA is regulated in a tissue-specific manner, dramatically affecting ligand-receptor binding specificity. The variable region in the D3 segment of FGFR1-3 permits receptor-ligand binding and infers unique characteristics. For example, FGFR2-IIIb (also known as keratinocyte growth factor receptor, KGFR) is exclusively expressed in epithelial cells (8). It is activated during wound repair upon binding of FGF-7 or FGF-10, thus promoting receptor dimerization and inducing multiple transduction pathways, including the mitogen-activated protein kinase (MAPK) pathway (9). Expression of a dominant-negative form of FGFR2-IIIb results in significant wound healing delays from reduced keratinocyte proliferation and subsequently delayed re-epithelialization (10). A recent study showed that FGFR1-IIIb and FGFR2-IIIb are essential for the maintenance of skin appendages and epidermal barrier function, and they appear to cooperate in regulating epidermal homeostasis (11). Therefore, FGF signaling diversity is partially due to the different splice variants and gene products for FGFR.

FGFs are grouped into subfamilies based upon similarities and differences in their structural and functional characteristics. For example, FGF-7, -10, and -22 share similar genetics and functions, and all three FGFs strongly activate FGFR2-IIIb (8, 12). During homeostasis, FGF-7, -10, and -22 are significantly expressed in non-injured mouse skin. However, FGF-7 and FGF-10 protein levels robustly increase following wounding (13). In addition, the abundance of FGF-binding protein is amplified during wound healing and binds FGF-7, -10, and -22 to enhance ligand activity at low concentrations (14). FGF-22 shares ~40–45% amino acid homology with FGF-7 and FGF-10, and it has been shown to be preferentially expressed in keratinocytes (15), where it functions in an autocrine manner. FGF-7, also known as keratinocyte growth factor (KGF), is a paracrine growth factor for epithelial cells and is expressed mainly by fibroblasts (16). Both FGF-7 and FGF-10 appear to enhance cell migration via kinase activation to promote cortical cytoskeleton reorganization (17).

Although FGF-7 has been shown to accelerate wound repair in several animal models, it showed only a modest improvement in re-epithelialization in a porcine deep partial-thickness burn model and showed no significant improvement after a full-thickness burn (18). Interestingly, aged mice have shown not only a decreased basal expression of FGF-7 and FGF-10, but they also demonstrated a blunted response after wounding (13), suggesting a possible contributory factor in the delayed healing and mortality observed in elderly burn patients. In parallel, elderly burn patients (≥ 65 years of age) tend to suffer from more severe burns at the time of admission, exhibiting a greater proportion of deep/superficial burns (41% vs. 23.3%) in a Chilean subpopulation (19). This resulted in a 12-fold higher mortality rate when adjusted for the %TBSA (total body surface area) burn and the TBSA/DTBSA (deep TBSA) proportion (19).

FGG-10 and its Role in Wound Healing

Under normal conditions, keratinocyte progenitor cells divide and proliferate to allow for the multi-layered epidermis. This intricate process of epidermal regeneration is dependent upon intracellular signaling cascades via keratinocyte-receptor interactions with the skin micro-environment through both autocrine and paracrine pathways. During the healing process, cross-talk between healthy keratinocytes on the periphery and other cells involved in wound repair is critical for optimal wound closure. Basal keratinocytes along the wound edges and dermal appendages, such as sweat glands, hair follicles, and sebaceous glands, are the primary cells responsible for the epithelialization phase of wound repair. Keratinocyte migration and proliferation is stimulated by cytokines and growth factors, such as FGF-10, produced during the inflammatory phase of wound healing. Injury also triggers an inflammatory keratinocyte response that results in secretion of cytokines, chemokines, and antimicrobial peptides required for immune defense against invading microbes. Thus, keratinocytes are considered active participants in both regeneration, where FGF-10 likely plays a key role, and in epidermal immune defense. [Reviewed in (20–22)]

FGF-10 is referred to as keratinocyte growth factor 2 (KGF-2), acts as a paracrine mediator of epithelial cell proliferation, and is expressed primarily by fibroblasts (22, 23). The human FGF-10 gene is located on 5p13-p12 and encodes a protein of 208 amino acids weighing ~19 kDa (23). Mouse FGF-10 mRNA was originally found to be expressed most abundantly in lung, skin, brain, and heart tissue (16). Notably, FGF-10 demonstrates significant thermal liability and is stabilized by a variety of polyanions, possibly affecting its functional capacity when not present (24, 25); thus, a small molecule, such as dermatan sulfate, may serve as an FGF-10 stabilizer and improve its functionality when readily available.

Comparable to FGFR2-IIIb-deficient mice, FGF-10-deficient mice die shortly after birth, demonstrate abnormal lung and limb development (26, 27), and exhibit defects in whisker formation and cutaneous epidermal differentiation resulting in hypoplasia (28, 29). More recently, FGF-10 was shown to have a stimulatory effect on hair growth *in vitro*, using isolated human hair follicles (30). Initial *in vitro* wound healing studies demonstrated that FGF-10 promotes both proliferation and differentiation of human keratinocytes, suggesting a likely role in epidermal growth and differentiation (31, 32). In addition, insertion of cells expressing wnt-2b/FGF-10 concurrently with wounding led to re-induction of the apical ectodermal ridge, suggesting new possibilities for limb regeneration in higher vertebrates (33). Using a rabbit model of corneal CO2 laser injury, topical FGF-10 was shown to accelerate corneal epithelial wound healing and to reduce inflammation, stromal edema, and fibrosis (34). A similar benefit was seen after applying topical FGF-10 to rabbit alkali burned cornea, noting a significantly enhanced rate of corneal epithelial wound healing (35).

With regard to cutaneous wound healing, the regulation of FGF-10 expression following injury has been controversial. Beer et al. concluded that FGF-10 mRNA expression was not induced during cutaneous wound repair using a murine excisional wound model, but noted that its protein form may be stored and released upon injury (16). However, Tagashira et al. demonstrated that FGF-10 mRNA was upregulated one day after injury, but normalized by day 3 in a mouse wounding model (36). Nevertheless, further studies have demonstrated that topical application of FGF-10 induces wound repair. A single topical application of FGF-10 to full-thickness incisional wounds in rats augmented and accelerated wound healing, characterized by an increase in the wounds' mechanical strength and an increase in wound collagen content (37). Similarly, topical FGF-10 promoted re-epithelialization and enhanced granulation tissue formation in an ischemia-impaired rabbit ear model without a significant difference in scar formation (38). In order to further characterize the impact of FGF-10 on wound repair, one study employed three distinct animal models (39). These experimental models included human meshed skin grafts explanted to athymic "nude" rats, surgical incisions in rats, and contaminated excisional rat wounds. Using these models, FGF-10 accelerated epithelialization in the explanted meshed skin grafts and increased the gain in breaking strength of the surgical incisions (although no improvement in the contaminated excisional wounds was demonstrated). Based on these results, FGF-10 was suggested as a potential wound healing agent for stimulating epithelialization in venous stasis ulcers, partial-thickness burn wounds, skin graft donor sites, or other various wounds (39).

FGF-10 and its use in Clinical Trials

In 2001, preliminary clinical trials using a recombinant form of FGF-10 topically applied to venous ulcers in humans demonstrated an ability to expedite wound healing (40). However, this effect was no longer significant in follow-up studies, and the clinical trials were aborted (41). Although initial research also showed promise in the treatment of cancer therapy-induced mucositis, follow-up studies were again disappointing, and the trials were discontinued (42). Similarly, FGF-10 appeared to promote healing of small intestinal ulcerations in rats (43) and reduced mortality, weight loss, and stool score in a murine colitis model (44). Nevertheless, a randomized, prospective clinical trial evaluating its use in the treatment of active ulcerative colitis demonstrated no benefit, although it was well tolerated (45). Other preliminary studies have shown that FGF-10 accelerated healing of meshed skin grafts used to close deep burn wounds (46). Therefore, FGF-10 alone has demonstrated significant promise in its potential ability to promote re-epithelialization and wound healing in multiple models of tissue injury.

Overview of GAG Structure and Function

Glycosaminoglycans (GAGs) play a critical role in FGF signaling by facilitating the formation of the FGF-FGFR complex and enhancing FGF oligomerization (47). FGFs have a high affinity for GAGs, and as such, their interaction stabilizes FGFs against thermal denaturation and proteolysis (4). In addition, GAGs limit the ability of FGFs to diffuse and be released into interstitial spaces, thus generating a reservoir of growth factors for the surrounding environment (4, 5). Therefore, most FGFs require GAGs for binding and signaling through their FGF receptor to enhance stabilization and/or accumulation of growth factors (4, 48–51).

GAGs, the most abundant heteropolysaccharides in mammalian tissues, are composed of long, unbranched polysaccharides containing repeating disaccharide units and vary in molecular weight from 10–100 kDa on average (52). Their synthesis involves several enzymes, which ultimately determine the identity of the GAG being created (53). Subsequent epimerization, sulfation, or deacetylation modifications distinguish the specific

GAG chains necessary for their particular activity. GAG classification includes heparin, heparan sulfate, chondroitin sulfate, dermatan sulfate, keratan sulfate, and hyaluronan. Most GAGs are linked to protein cores to form proteoglycans and include several sulfation sites, with the exception of hyaluronan. Typically, they are highly negatively charged at a physiologic pH and located on the cell surface or within the extracellular matrix (ECM) (52). Like FGFs, GAG functions vary widely and contribute to a variety of cellular processes, including development, homeostasis, wound repair, and disease. For example, some microorganisms such as herpes simplex virus and malaria recognize GAGs as cell surface receptors and exploit them to promote disease pathogenesis (54). They serve diverse roles and modulate biologic responses by acting as (1) stabilizers, cofactors, and/or coreceptors; (2) regulators of enzyme activity; (3) signaling molecules in response to cellular damage; and (4) targets for microbial virulence factors (55).

Hyaluronan is a large polymer (molecular weight ranging from 4–8,000 kDa) with shock absorbing and lubricating capacities, and it is typically found in synovial fluid, vitreous humor, and the ECM of loose connective tissue (52). Chondroitin sulfate is the most abundant GAG in mammalian tissues residing in cartilage, tendon, ligament, bone, and heart valves, where it binds large molecules to form proteoglycan aggregates. Considered the most heterogeneous GAG, keratan sulfate is expressed in cornea, bone, and cartilage, and frequently aggregates with chondroitin sulfates (52). Heparan sulfate is expressed primarily on cell surfaces and in the ECM as a part of proteoglycan complexes. Heparin, however, accumulates in granules of mast cells and is actually more sulfated than heparan sulfate (52). Both are well known for their ability to sustain FGF-2 signaling (56), while heparin is also commonly known for its ability to activate anti-thrombin II, which inhibits the serine proteases in the coagulation cascade (57). In addition, heparin participates in and stabilizes the interaction of specific FGF molecules and their FGF receptors (5, 52).

DS and its Role in Tissue Repair

Dermatan sulfate (DS), also known as chondroitin sulfate-B, is expressed in numerous mammalian tissues and is typically found on the cell surface or in the ECM. Structurally, DS is a linear polysaccharide composed of disaccharide units containing hexosamine, N-acetyl galactosamine, or glucuronic acid. The presence of iduronic acid, however, distinguishes DS from other forms of chondroitin sulfate and presumably plays a key role in the binding site specificity for GAG-binding proteins (55). DS also contains variable sulfation patterns on specific iduronic acid residues, which are critical for cell proliferation (9, 58). Altogether, the variability in the DS chain length, disaccharide composition, and iduronic acid residues likely influences its binding affinity and functional interactions (55, 57, 59). Moreover, some of its protein cores have demonstrated altered expression patterns during development, pathogenesis, and wounding (60–63). DS has been specifically shown to interact with numerous molecules important in several aspects of wound repair, including thrombin, activated protein C, collagen, fibronectin, α-defensin, interferon-γ, and transforming growth factor-β (54, 55). In addition to these distinct interactions, DS can participate in nonspecific binding with several plasma proteins, which likely influences its functional capacity (64).

Proteoglycans that contain DS as a major GAG include decorin, biglycan, versican, thrombomodulin, epiphycan, and endocan (55). DS and its related proteoglycans have been implicated in cardiovascular disease, tumorigenesis, infection, wound repair, and fibrosis (55, 65). For example, CS/DS can stimulate cancer progression and tissue regeneration in repair of the central nervous system and liver (54). In the skin, DS is the predominant glycan and is released at high concentrations during wound repair to serve as a cofactor for growth factors important in the proliferative phase of wound healing (59, 66). A shift in syndecan-1 GAG chains from predominantly HS to a mixture of DS/HS is observed during murine

wound repair (67), which likely supports the ability of DS to potentiate keratinocyte proliferation via FGFs after injury to a greater extent than heparin-GAG moieties (9). These data suggest a pivotal role for DS in stimulating the wound repair process, particularly during the proliferative phase.

In mouse skin, decorin deficiency causes abnormal collagen morphology, increased skin fragility, and reduced tensile strength of the skin (68). *In vitro*, fibroblast cultures from post-burn hypertrophic scars were found to synthesize less decorin than normal dermal fibroblasts, which may have implications for the development of such scars (69). In more recent studies, DS blocked P-selectin activity, which may indicate a potential therapeutic target for DS to minimize thrombosis, inflammation, and metastasis (70). DS has also been shown to increase intercellular adhesion molecule-1 (ICAM-1) expression and nuclear factor-κb activity, suggesting a potential role in cell signaling during injury response (71). With regard to autoimmune disease, DS displays preferential affinity for apoptotic and dead cells. It has been suggested that molecules with an affinity for DS have a high propensity to become autoantigens, thus causing autoreactive B-1a cells to be positively selected and expanded by DS-autoantigen complexes (72, 73).

DS and its use in Wound Treatments and Clinical Trials

Using a murine induced-colitis model, a subcutaneous injection of DS limited colon inflammation by reducing inflammatory cytokine production, attenuating lymphocyte and macrophage recruitment, and reducing collagen-mediated fibrosis (74). Similar effects were noted using a murine unilateral ureteral obstruction model following 14 days of DS injections (75). Subsequent to arterial injury in mice, treatment with DS and bone marrow mononuclear cells inhibited the initial thrombotic and inflammatory processes, where DS is hypothesized to assist in the recovery of injured endothelium (76). Recent grafting of DS onto polyethylene terephtalate (i.e. Dacron ®), the main polymer component of vascular prostheses, demonstrated improved endothelial cell proliferation *in vitro* and enhanced biointegration following subcutaneous implantation *in vivo* (77).

DS has been shown to inactivate thrombin via heparin cofactor II (47), and it has been investigated for its antithrombotic properties (78, 79). Clinical studies have explored the utility of DS for patients undergoing dialysis for renal failure, with disseminated intravascular coagulation (DIC) syndrome, and/or with arterial atherothrombotic disease (80). These studies have revealed pharmacologic properties of DS with possible clinical relevance: a predictable dose-response based on its dose-proportional and linear, concentration-dependent pharmacokinetics (81), and overall clinical safety when used for venous thromboembolism prevention (78). To date, no studies have demonstrated bleeding complications associated with DS therapy, which makes DS a promising candidate for wound healing applications and in patients with blood clotting disorders (80).

Overview of Wound Healing and Current Therapeutic Targets

As a subtype of acute wounds, it is important to recognize that the overall healing process for most burn injuries does not significantly differ from other types of wounds. The inflammatory phase initiates wound healing, which is characterized by fibrin clot formation, platelet degranulation, infiltration of inflammatory cells, phagocytosis, and the robust release of growth factors and cytokines. Stimulated by factors produced during the inflammatory response, the proliferative phase involves wound closure, angiogenesis, and matrix deposition. The final remodeling phase encompasses the cross-linking of collagen, and the production of degradative enzymes and additional matrix proteins, which together contribute to further maturation of the injured tissue [reviewed in (20, 22, 82–87)]. With this fundamental basis, acute burns ultimately close by re-epithelialization, wound contraction,

skin grafting, or a combination of these processes. A skin autograft is preferred for deeper burn wound closure, although it may also be achieved using biosynthetic dressings or skin/dermal substitutes (3, 88). In addition, donor autograft sites heal similar to a shallow burn, but can also result in a prolonged hospital stay if healing is delayed (86).

According to a rolling review by the American Burn Association, seven of the top ten clinically relevant complications among burn patients over the past decade were infectious (2). Consequently, most current therapies serve as anti-microbials targeting the most common infectious agents found in burn wounds: staphylococci, streptococci, and pseudomonas (89, 90). While these topical anti-microbial agents have significantly reduced the morbidity and mortality from burn wound sepsis (3), they may also prolong the healing time (3) and likely promote the development of multi-drug resistant bacteria. Furthermore, they do not address the process of burn wound repair itself. Several studies have been done using hyperbaric oxygen as a potential therapy to promote burn wound healing, but most reviews conclude that there is insufficient evidence to support or refute its effectiveness (91). Although a recent review suggested that cellular therapies using keratinocyte cultures are continuing to advance, several obstacles remain and prevent current practicality (92). Successful therapies, however, need to prevent infection and promote keratinocyte migration and proliferation early in the wound repair process. Few therapies today effectively target wound repair acceleration, but rather focus on preventing delays in wound healing from local infections or other systemic complications. Appropriate wound care currently requires multiple treatment modalities with variable timing to yield optimal repair (88). Therefore, the combination of FGF-10 and DS may serve as a novel adjunct by promoting keratinocyte proliferation and migration, and thus expediting re-epithelialization and wound healing.

The Potential of FGF-10 and DS in Wound Healing

Burn injuries constitute a subset of wounds that often heal by secondary intention, but may require more invasive treatment as well. Furthermore, they may occur in compromised individuals harboring local or systemic underlying conditions that hinder normal wound repair, such as diabetes and/or vascular disease. These comorbidities predispose them to the development of chronic, non-healing wounds which fail to respond to established medical and surgical therapies (93). In addition to burn wounds, ulcers from vascular disease, traumatic wounds, surgical wounds, pressure ulcers, and diabetic ulcers also frequently heal by secondary intention and represent a significant number of wounds treated on a daily basis. Specifically, more than 500,000 pressure ulcers were documented during hospitalizations in 2006, often resulting in longer hospital stays and higher mortality rates (94). Among the nearly 24 million diabetics in the United States (95), the estimated lifetime risk of developing a foot ulcer is 15% (96) with the average episode lasting 87 days and costing an average of $13,179 per episode (97). Unfortunately, secondary complications result in amputation for at least 15% of diabetics with foot ulcers (98). Although the incidence of such conditions would not be altered, accelerating the wound healing process of chronic wounds would likely decrease the subsequent development of their associated secondary complications, while also expediting the patient's recovery and return to baseline functional status.

Similar to burn wounds, chronic wounds are often complicated and are steadily becoming more prevalent. In the industrialized world, an estimated 1% of the population is anticipated to battle a chronic wound during their lifetime (99). Chronic, non-healing wounds are believed to be a result of quiescent or damaged cells induced by wounding and inflammation. Keratinocytes secrete several growth factors, proteases, and basement membrane proteins necessary for the proliferative phase of wound healing to proceed (22). Thus, any defect in keratinocyte migration or proliferation may have detrimental effects on

subsequent cellular responses during this phase (22). Furthermore, delayed epithelialization increases the risk for secondary infection and impairs the proliferative capacity of endothelial cells and fibroblasts responsible for angiogenesis and regeneration, respectively. Burn wounds specifically tend to have extensive areas of necrosis, increased inflammation, variable levels of inflammatory mediators, and increased levels of endogenous proteases, leading to a slower healing process (18). For current therapies to be successful, treatment needs to enhance re-epithelialization of the wound by further stimulating the regenerative capacity of keratinocytes.

FGF-10 has been shown to promote keratinocyte migration and proliferation in preliminary studies (9), but no clinical trials to date have confirmed significant findings *in vivo*. Similar to the role heparin plays in stabilizing FGF-FGFR interactions, perhaps the addition of DS could enhance the ability of FGF-10 to further potentiate keratinocyte migration and proliferation, and consequently re-epithelialization. More specifically, it is known that resident T cells within the skin's epidermis provide a robust supply of FGF-10, while mice lacking dendritic epidermal T cells display delayed keratinocyte proliferation and re-epithelialization, which correlated with decreased epidermal FGF-10 expression (100). Investigative studies have indicated that DS acts as a cofactor for FGF-10 to augment the ability of keratinocytes to migrate, which highlights the importance of DS as a cofactor for maximal cellular responsiveness to FGF-10 during wound repair (9). As proposed by Radek et al., DS fragments generated subsequent to wounding may act in a paracrine manner to facilitate, localize, and/or stabilize the FGF-10–FGFR2-IIIb interaction, resulting in receptor dimerization and subsequent signal transduction to promote burn wound re-epithelialization [as illustrated in Figure 1, modified from (9)]. Interestingly, desulfated DS preparations, even when combined with FGF-10, were no longer able to stimulate keratinocyte migration or proliferation *in vitro*, which suggests that a defect in DS sulfation in burn and/or chronic wounds may contribute to delayed or defective wound repair (9). Further studies are needed to asses the contribution of specific DS fragments as potential facilitators of the FGF-10–FGFR2-IIIb interaction in the wound, and to determine if this delicate balance is disturbed in abnormal wound repair. Collectively, these studies suggest that DS serves as a cofactor for FGF-10 in wound repair, and together, they have the potential to serve as a novel therapeutic agent in the treatment of burn injuries to stimulate re-epithelialization of the wound bed earlier in the process to minimize infection and further potentiate the proliferative phase of tissue repair.

Although many burn wounds heal without complications, most types of wounds could benefit from a therapy that would expedite the healing process. More specifically, the proposed combination of FGF-10 and DS could potentially eliminate the need for surgical intervention for some burn patients. Such a novel therapy may also have a significant advantage over other treatments, as most other therapies indirectly promote wound healing by targeting host microbial defense or inflammatory cascades to either enhance or suppress the body's immune response, respectively. FGF-10 and DS could likely be used in combination with current therapies, but serve as a novel adjunct by promoting epithelialization and thus, wound healing directly. Furthermore, its therapeutic implications could be applied to numerous acute and chronic wounds currently debilitating thousands of Americans.

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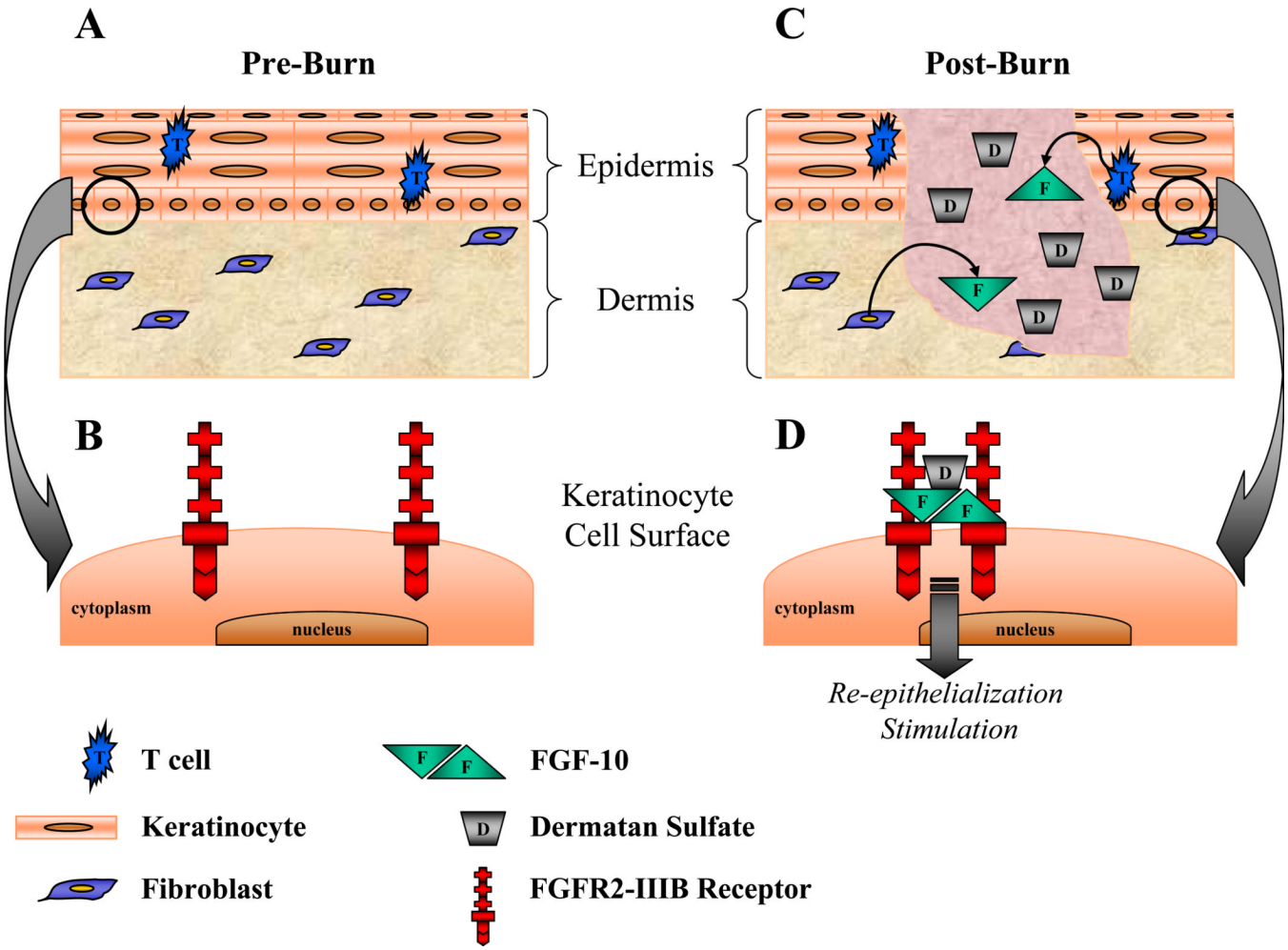

FIGURE 1.

Theoretical model for the role of DS in FGF-10 signaling through FGFR2-IIIb in burn wound re-epithelialization [modified from Radek et al., (9)]. (A) In non-burn-injured skin, T cells and fibroblasts reside in the epidermis and dermis, respectively. (B) In keratinocytes, the FGF receptor, FGFR2-IIIb, exists as a monomer on the cell surface. (C) Following burn injury, T cells and fibroblasts secrete FGF-10 into the wound, while small fragments of DS are released into the wound from the extracellular matrix. (D) Enabled by DS, the increase in FGF-10 acts in a paracrine manner through FGFR2-IIIb on keratinocytes. DS promotes receptor dimerization by facilitating the interaction between FGF-10 and FGFR2-IIIb. This interaction ultimately results in downstream signaling that stimulates burn would re-epithelialization by keratinocytes. DS, dermatan sulfate; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor.

TABLE 1

Selected articles highlighting significant findings related to FGF-10 and DS. GAG, glycosaminoglycan; DS, dermatan sulfate; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; DSS, dextran sulphate sodium; ICAM, intercellular adhesion molecule; IdoA, iduronic acid.

Author(Ref#)	Experimental Model	Animal/Tissue/ Cells	Treatment	Pertinent Conclusions (*based on each Author's interpretation*)
Beer (16)	Full-thickness excisional wounds	Balb/c 3T3 mice	FGF-10	No significant induction of FGF-10 mRNA expression was detected during wound healing and levels possibly declined after skin injury.
Han (43)	Intestinal ulcers	Rats	FGF-10	Intravenous FGF-10 significantly decreased acute intestinal injury and chronic ulceration.
Jang (30)	Cell culture	Human hair-follicles	FGF-10	FGF-10 significantly stimulated human hair-follicle cell proliferation and may be a promising therapeutic agent for stimulating human hair growth.
Jimenez (37)	Full-thickness incisional wounding	Sprague Dawley rats	FGF-10	A single topical application of FGF-10 at the time of wounding markedly accelerated healing, as suggested by an increased mechanical strength and increased wound collagen content.
Komi-Kuramochi (13)	Wounding	Hairless mice	FGF-10	FGF-10 mRNA is strongly expressed in healthy mice skin and expression is increased after wounding. Aged mice have a decreased basal expression and blunted response after wounding.
Liu (35)	Corneal wound (alkali burn)	New Zealand white rabbits	FGF-10	Topical FGF-10 enhanced corneal epithelial healing in rabbit alkali burned cornea.
Marchese (31)	Primary cell culture	Human keratinocytes	FGF-10	FGF-10 is a potent mitogen for human keratinocytes and promotes the expression of both early and late differentiation markers
Miceli (44)	DSS-induced colitis	Mice	FGF-10	FGF-10 enhanced weight recovery after discontinuation of DSS treatments. It also reduced mortality and stool scores, suggesting possible usefulness in treating inflammatory bowel disease.
Robson (40)	Chronic venous ulcers	Humans (clinical trial)	FGF-10	Topical FGF-10 appeared to accelerate wound closure in chronic venous ulcers, and it was particularly effective in smaller wounds and wounds with shorter ages.
Sandborn (45)	Ulcerative colitis	Humans (clinical trial)	FGF-10	Intravenous FGF-10 was well tolerated, but demonstrated no improvement in clinical remission rates at the doses tested.
Smith (46)	Skin graft explantation	Athymic "nude" rats	FGF-10	Wounds treated with topical FGF-10 showed a significantly increased rate of interstitial closure, suggesting acceleration of epithelialization.
Soler (39)	Skin graft explantation	Athymic "nude" rats	FGF-10	FGF-10 significantly accelerated the rate of epithelialization in the meshed skin graft model.
	Surgical incisions	Sprague Dawley rats	FGF-10	FGF-10 resulted in a modestly more rapid gain in breaking strength of surgical incisions.
	Contaminated excisional wounds	Sprague Dawley rats	FGF-10	Similar to FGF-7, FGF-10 did not accelerate wound closure by contraction of contaminated excisional wounds.
Stump (41)	Chronic venous ulcers	Humans (clinical trial)	FGF-10	Although it was well tolerated, FGF-10 did not significantly accelerate wound closure compared to placebo.
Stump (42)	Cancer therapy-induced mucositis	Humans (clinical trial)	FGF-10	FGF-10 was not significantly effective at reducing the incidence of cancer therapy-induced mucositis, although it was well tolerated.
Tagashira (36)	Wounding	Mice	FGF-10	FGF-10 mRNA was highly induced 1 day after injury and decreased rapidly by 3 days, suggesting a role in wound healing.

Author(Ref#)	Experimental Model	Animal/Tissue/ Cells	Treatment	Pertinent Conclusions (*based on each Author's interpretation*)
Wang (34)	Corneal wound (CO2 laser)	Japanese white rabbits	FGF-10	Topical FGF-10 accelerated corneal epithelial wound healing, inhibited corneal neovascularization, and reduced inflammation, stromal edema, and fibrosis.
Xia (38)	Ischemic full-thickness dermal ulcer	New Zealand white rabbits	FGF-10	Topical FGF-10 promoted re-epithelialization, increased dermal cell proliferation, and stimulated granulation tissue formation in full-thickness excisional wounds with no significant difference in scar formation. This effect was delayed in older rabbits.
Yang (32)	Primary cell culture	Human keratinocytes	FGF-10	FGF-10 had a significant proliferative effect on human keratinocytes, suggesting its ability to support the healing of chronic wounds.
Radek (9)	Primary cell culture	BaF3 cells	FGF-10, DS	DS promoted FGF-10-dependent cell proliferation, which was influenced by DS length, IdoA residues, and sulfation.
	Wound scratch culture	NHEK cells	FGF-10, DS	The combination of DS and FGF-10 resulted in maximal proliferation and migration of keratinocytes, suggesting a novel interplay between DS and FGF-10 in mediating wound repair.
Belmiro (74)	Murine induced-colitis	Wistar rats	DS	DS inhibited colon inflammation by reducing inflammatory cytokine production, attenuating lymphocyte and macrophage recruitment, and reducing collagen-mediated fibrosis.
Belmiro (75)	Murine unilateral ureteral obstruction	Swiss Mice	DS	By reducing macrophage recruitment, myofibroblast population and fibrosis, DS attenuates kidney inflammation in mice subjected to unilateral ureteral obstruction.
Dhahri (77)	Subcutaneous implantation	Rats	DS	Grafting of DS onto polyethylene terephtalate surfaces enhanced its biointegration following subcutaneous implantation in rats.
Godoy (76)	Murine arterial injury	Mice	DS	Following arterial injury, DS inhibited the initial thrombotic and inflammatory processes, and promoted migration of bone marrow mononuclear cells to the lesion site to aid in recovery.
Kozlowski (70)	Murine metastasis	Mice	DS	DS attenuated metastasis of MC-38 colon carcinoma and B16-BL6 melanoma cells.
	Murine peritonitis	Mice	DS	In a thioglycollate peritonitis model, DS attenuated inflammatory cell infiltration.
	Murine arterial injury	Mice	DS	Following arterial injury, DS reduced platelet deposition and thrombus size, suggesting inhibition of P-selectin and thereby binding of activated platelets during thrombus formation.
Lee (67)	Primary cell culture	NIH3T3 fibroblasts	n/a	The transfer of fibroblasts from a monolayer to a 3D culture induced synthesis of decorin, and GAG extracts from the 3D culture had the ability to potentiate FGF-7 activity.
	Incisional wounding	Balb/c mice	n/a	The incisional wounds demonstrated an increase in DS-GAG chain synthesis on the cell surface of the proteoglycan syndecan-1.
Penc (66)	Primary cell culture	Human wound fluid; F32 Cells	DS	Human wound fluid contains abundant amounts of DS, which supports the ability of FGF-2 to signal cell proliferation, suggesting DS as a mediator of FGF-2.
Penc (71)	Wounding	Human wound fluid	DS	DS activated endothelial cells in the absence of supplemental costimulatory molecules. It increased mRNA and cell surface ICAM-1, and it was a significant activator of nuclear factor-κB.
Saivin (81)	Blood coagulation	Humans (clinical trial)	DS	DS showed improved intramuscular absorption with plasma concentrations reaching steady state more quickly, suggesting continuous drug coverage with a once daily regimen.

Author(Ref#)	Experimental Model	Animal/Tissue/ Cells	Treatment	Pertinent Conclusions (*based on each Author's interpretation*)
Scott (69)	Post-burn hypertrophic scars	Fibroblast cultures	n/a	Fibroblasts from post-burn hypertrophic scars have a reduced capacity to synthesize decorin.
Trowbridge (59)	Primary cell culture	Human wound fluid; BaF3 cells	n/a	Both FGF-7 and FGF-1 showed a dose-dependent increase in cell proliferation in response to DS. In addition, the size, sulfation level, and concentration of DS affected both proliferation and receptor binding.