Current and Emerging Treatments for Postsurgical Cleft Lip Scarring: Effectiveness and Mechanisms

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Abstract

Cleft lip with or without cleft palate is the most common congenital malformation of the head and the third-most common birth defect. Surgical repair of the lip is the only treatment and is usually performed during the first year of life. Hypertrophic scar (HTS) formation is a frequent postoperative complication that impairs soft tissue form, function, or movement. Multiple lip revision operations are often required throughout childhood, attempting to optimize aesthetics and function. The mechanisms guiding HTS formation are multifactorial and complex. HTS is the result of dysregulated wound healing, where excessive collagen and extracellular matrix proteins are deposited within the wound area, resulting in persistent inflammation and resultant fibrosis. Many studies support the contribution of dysregulated, exaggerated inflammation in scar formation. Fibrosis and scarring result from chronic inflammation that interrupts tissue remodeling in normal wound healing. Failure of active resolution of inflammation pathways has been implicated. The management of HTS has been challenging for clinicians, since current therapies are minimally effective. Emerging evidence that specialized proresolving mediators of inflammation accelerate wound healing by preventing chronic inflammation and allowing natural uninterrupted tissue remodeling suggests new therapeutic opportunities in the prevention and management of HTS.

Keywords: wound healing, fibrosis, scar, inflammation, lipoxins, fish oils

Introduction

Cleft lip with or without cleft palate (CL/P) is the most common congenital malformation of the head and the third-most common birth defect. According to the Centers for Disease Control and Prevention, in the United States, CL/P affects approximately 1 in 700 live births, with wide variability across geographic origin, racial and ethnic groups, environmental exposures, and socioeconomic status (Dixon et al. 2011). Cleft lip is about twice as common in males (Watkins et al. 2014). Cleft lip is a physical split or separation of the 2 sides of the upper lip. It appears as a narrow opening or gap between the philtrum and the lateral upper lip (incomplete cleft), or it may extend beyond the base of the nose and include the bones of the upper jaw and/or upper gum (complete cleft). CL/P originates from failures in the fusion of the maxillary process to the ipsilateral medial nasal process within the first 5 to 6 wk of gestation (Dixon et al. 2011).

Clinical management of cleft lip is a unique ongoing challenge in maxillofacial plastic surgery. The repair of the lip is usually performed during the first year of life, as early as safe for the patient (mean age of 4 mo at time of surgery), while cleft palate repair follows between 12 and 18 mo of age (Owusu et al. 2013). The surgical goals of CL/P repair are to achieve normal facial appearance, feeding, speech, and hearing without significantly affecting the ultimate facial and psychosocial

development of the child. The multidisciplinary management team comprises of surgeons, speech pathologists, social workers, audiologists, and nutritionists. The outcomes of primary surgical repair are often less than ideal, requiring many revision operations due to loss of function and compromised aesthetic outcomes.

Hypertrophic Scars

Hypertrophic scar (HTS) formation is a frequent postoperative complication of cleft lip repair, which impairs soft tissue form, function, or movement and restricts facial growth (Soltani et al. 2012). HTS generally occurs within 3 to 6 mo following

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Figure 1. Hypertrophic scar formation after unilateral cleft lip defect repair on an infant: (A) preoperative, (B) 2 wk after cleft lip repair, (C) 1 y after cleft lip repair.

the initial surgery. Rates of HTS formation following primary cleft lip repair are sparsely reported and vary widely, from 8% to 47% (Wilson and Mercer 2008; Soltani et al. 2012). Surgeons, patients, and caregivers are often dissatisfied with the surgical results, and multiple lip revision operations are required throughout childhood to optimize aesthetics and function. Revision operations may be performed at any time after the initial repair, but they are generally performed between 5 and 8 y of age or later during adolescence (Trotman et al. 2010). Based on a recent systematic review, there is substantial variation in the incidence of lip revision surgery as well (Sitzman et al. 2016). These cleft lip revisions can cause increased parental and patient stress, added anesthetic and surgical risks, and further financial and societal costs (Soltani et al. 2012). Health expenditures are approximately 8 times higher in the first 10 y of life for children with CL/P (Sitzman et al. 2016).

Mechanisms of HTS Formation

HTSs represent abnormal healing responses secondary to surgical procedures, burn injuries, and traumatic injuries (Butzelaar et al. 2016). Wound repair requires the integration of complex cellular networks to restore tissue homeostasis. The mechanisms guiding HTS formation are multifactorial and complex. Given the significant impact of HTS on the facial growth, dental development, function, and aesthetics of the patient following cleft lip repair, understanding the biological processes that regulate wound healing and HTS formation will provide valuable insight into the underlying pathogenic mechanisms and help prevent or more effectively treat HTS formation early in life.

HTS is the result of a dysregulated wound-healing process that includes a failure of fibrotic scar remodeling with excessive collagen and extracellular matrix (ECM) protein accumulation within the wound (Butzelaar et al. 2016). The net result is a scar that is raised above the skin surface, and skin of normal texture, elasticity, and resilience is replaced by a nonfunctional mass of tissue. The failure of this tissue to further remodel creates major functional and aesthetic problems (Lian and Li 2016; Fig. 1). The scar tissue contains dense

parallel-oriented collagen fibers with perpendicularly oriented capillaries, diminished hyaluronic acid content, and nearly absent to very sparse elastic fibers (Sahl and Clever 1994). Despite the clinical importance of HTS in children with cleft lip, there remain significant gaps in understanding the exact mechanisms underlying HTS formation. A limited number of studies have been conducted to identify conditions or risk factors associated with HTS (Butzelaar et al. 2016).

When a cutaneous injury occurs, wound healing consists of 4 successive and overlapping phases: hemostasis, inflammation, proliferation, and remodeling (Xue and Jackson 2015). These phases and their biophysiologic functions are programmed and temporally regulated, must occur in proper sequence and at a specific time point, and continue for a specific duration at optimal intensity. The first phase of healing begins with hemostasis immediately after injury, with vascular constriction, platelet aggregation, and fibrin clot formation. Platelets play a critical role in this phase, not only as initiators of the coagulation, but also through the release of multiple growth factors and cytokines that stimulate the recruitment of neutrophils, monocytes, and fibroblasts, ultimately affecting the dynamics of ECM synthesis (Satish and Kathju 2010). The signaling network regulating the wound-healing process involves cytokines and growth factors, including transforming growth factor β (TGF- β), epidermal growth factor, fibroblast growth factor, and platelet-derived growth factor (Grieb et al. 2011). Normal wound healing requires the coordinated action of all cells, such as neutrophils, macrophages, lymphocytes, endothelial cells, and fibroblasts.

Once bleeding is controlled, inflammatory cells migrate into the wound (chemotaxis) and promote the inflammatory phase. The goal of neutrophils and macrophages is the clearance of invading microbes, cellular debris, and apoptotic cells in the wound. As macrophages clear apoptotic cells, they undergo a phenotypic transition to a reparative phenotype that stimulates keratinocyte and fibroblast proliferation and to angiogenesis to promote tissue regeneration (Meszaros et al. 2000). In this way, macrophages promote and regulate the subsequent proliferative phase in the wound-healing process (Singer and Clark 1999).

The proliferative phase generally follows and overlaps with the inflammatory phase and is characterized by epithelial proliferation, formation of granulation tissue that replaces the fibrin clot, and epithelial cell migration over the provisional matrix within the wound (reepithelialization). The deposition of granulation tissue, collagen, and ECM proteins in the proliferative phase is regulated by fibroblasts (Xue and Jackson 2015). In the reparative dermis, fibroblasts and endothelial cells are the most prominent cell types present and support capillary growth, collagen formation, and formation of granulation tissue at the site of injury. Within the wound bed, fibroblasts produce collagen as well as glycosaminoglycans and proteoglycans, which are major components of the ECM (Guo and Dipietro 2010). At the completion of this phase, there is a fibrotic scar clinically. The fourth phase, remodeling, takes the damaged tissue back to homeostasis, or normal tissue that is indistinguishable from the original tissue. This is also the phase where resolution of inflammation is the most important. Persistence of inflammation (chronicity with failure to resolve) blocks the remodeling phase, leading to persistence of fibrosis and scarring (Levy et al. 2001; Levy et al. 2003).

In the remodeling phase, which can last for up to a year after injury, there is ongoing synthesis, degradation, cross-linking, and reorientation of collagen fibers. Regression of many of the newly formed capillaries occurs so that vascular density of the wound returns to normal. The abundant ECM is degraded, and the immature type III collagen of the early wound can be modified into mature type I collagen (Gauglitz et al. 2011). The wound also undergoes physical contraction, which is believed to be mediated by contractile fibroblasts (myofibroblasts) that appear in the wound (Hinz et al. 2007). Myofibroblasts are a specialized form of fibroblasts that contribute to connective tissue remodeling by exerting traction forces and synthesizing ECM components. In normal healing, myofibroblasts regress and disappear by apoptosis after wound reepithelialization, while in inflammation-induced fibrotic situations, they persist and cause organ dysfunction. Myofibroblasts and α -SMA have been investigated as possible antifibrotic targets (de Andrade and Thannickal 2009).

Multiple factors can lead to impaired wound healing resulting in fibrosis and scarring. The transformation of a wound clot into granulation tissue requires a delicate balance between ECM protein deposition and degradation. Aberrations in any step of the reparative process are likely to interfere with the remodeling phase, lead to an excessive accumulation of collagen type I and III and ECM proteins (e.g., fibronectin and laminin), and result in a disorganized fiber structure and HTS formation (Oliveira et al. 2009; Grieb et al. 2011). HTS tissues have greater numbers of fibroblasts and myofibroblasts than do normal skin healing lesions (Nedelec et al. 2001). In addition, histologic analysis has demonstrated an increased number of neutrophils within scar granulation tissue (Qian et al. 2016). Wound tension is also known to be a causative factor for the development of wide HTS in humans (Wong et al. 2011). Mechanical stimuli trigger local inflammatory responses and disturb the regular cell-matrix interactions, inducing fibrosis and scar hypertrophy (Wong et al. 2011).

Numerous studies have implicated excessive persistent inflammation as being detrimental to proper healing that promotes fibrosis and scar tissue formation, underscoring the importance of early control of inflammation to improve wound-healing outcomes (Pierce 2001; Dovi et al. 2003; Qian et al. 2016). During healing, orchestrated resolution of inflammation is crucial for restoration of homeostasis and tissue integrity (Serhan, Yacoubian, and Yang 2008).

Inflammation and HTS

A fundamental question in wound biology involves a better understanding of the relationship between inflammation and wound repair. The correlation between inflammation and scarring is illustrated in aging. The inflammatory response increases with age. It is instructive that normal adult healing results in a fibrous scar, whereas early fetal wounds result in very little, if any, inflammatory response and exhibit scarless healing with complete restoration of the normal skin architecture (Xue and Jackson 2015). While early wound signals participating in the inflammatory phase of the healing process are considered important drivers of the regenerative response (Karin and Clevers 2016), it is generally believed that if inflammation does not resolve, wound healing and regeneration will not occur (Eming et al. 2014). Our understanding of the cellular and molecular mechanisms of impaired inflammation resolution in HTS formation remains relatively poor mainly because of the lack of studies investigating the early events that determine the development of HTS.

A plethora of studies have reported that enhanced and prolonged inflammatory responses during wound healing and repair are strongly implicated in HTS formation and repair (Gurtner et al. 2008; Eming et al. 2014; LeBert and Huttenlocher 2014; Qian et al. 2016; Table 1). Although the recruitment of inflammatory macrophages and neutrophils at the site of tissue injury is important for the wound-healing process, these cells secrete a variety of toxic mediators, including reactive oxygen and nitrogen species that are harmful to the surrounding tissues. Neutrophil-derived proteases degrade ECM, fibrin clot components, and other proteins and inhibit keratinocyte migration and proliferation (Dovi et al. 2003). Consequently, if the inflammatory macrophages and neutrophils are not cleared quickly, they can exacerbate the tissue-damaging inflammatory response that can result in chronic unresolved inflammation and lead to tissue fibrosis and scarring. In many cases, this may be directly or indirectly the result of an imbalance of bioactive substances. For instance, prolonged persistence of neutrophils and macrophages at the wound site due to a sustained induction of chemokines results in impaired diabetic healing in mice (Wetzler et al. 2000). However, neutrophil-depleted mice exhibit accelerated rate of wound epithelial closure without any alteration of the overall quality of the dermal healing process (Dovi et al. 2003). A prolonged inflammatory period with increased immune infiltrate contributes to increased fibroblast activity with greater and more sustained ECM deposition (Qian et al. 2016).

Several cytokines and growth factors secreted by innate inflammatory cells have emerged as potential targets of antifibrotic

Table 1. Impact of Inflammation on Hypertrophic Scarring.

Inflammatory Cells/Mediators	Outcome	Reference
Neutrophils	Histologic analysis has demonstrated an increased number of neutrophils within scar granulation tissue in New Zealand white rabbits.	Qian et al. 2016
Neutrophils	1) Dermal wounds of neutrophil-depleted mice exhibited significantly accelerated reepithelialization. 2) Neutrophil depletion alleviated the healing impairment of reepithelialization displayed in diabetic mice.	Dovi et al. 2003
Neutrophils, macrophages, TNF α , IL-1 β	A prolonged persistence of neutrophils and macrophages at the wound site due to a sustained induction of chemokines (TNF α , IL-1 β) results in impaired healing in diabetic mice.	Wetzler et al. 2000
TNF α , IL-1 β	Mice that overexpress IL-1 β or TNF- α in the lung develop highly progressive pulmonary fibrosis.	Kolb et al. 2001
IL-1 β	Higher levels of IL-1 β are expressed in the dermis of untreated ear wounds that heal with larger hypertrophic scar as compared with occluded wounds that heal with a smaller scar in New Zealand white rabbits.	Gallant-Behm and Mustoe 2010
IL-10	Overexpression of IL-10 in adult murine wounds reduces inflammation and collagen deposition and creates improved wound-healing conditions.	Peranteau et al. 2008

IL, interleukin; TNF- α , tumor necrosis factor α .

therapy. Interleukin 1 β (IL-1 β), TNF- α , IL-6, and monocyte chemotactic protein 1 are considered major factors that regulate fibrosis and scarring, since they can modulate inflammatory cell adhesion and migration as well as fibroblast proliferation and regulation to maintain balance between ECM production and degradation (van der Veer et al. 2009). Excessive production of proinflammatory cytokines disrupts normal wound healing and results in fibrosis. Mice that overexpress IL-1 β or TNF- α in the lung develop highly progressive pulmonary fibrosis (Kolb et al. 2001). Higher levels of IL-1 β are expressed in the dermis of untreated ear wounds that heal with larger HTS, as compared with occluded wounds that heal with a smaller scar in New Zealand white rabbits (Gallant-Behm and Mustoe 2010). IL-10, a key anti-inflammatory cytokine, may play an important role in wound healing by regulating proinflammatory cytokines. Overexpression of IL-10 in adult murine wounds reduces collagen deposition and improves wound healing (Peranteau et al. 2008).

A substantial body of evidence implicates the TGF- β family of proteins in the pathogenesis of HTS (van der Veer et al. 2009). TGF- β has 3 isoforms with pleiotropic actions. While TGF- β 3 appears to reduce collagen type I and scarring (Hosokawa et al. 2003), elevated levels of TGF- β 1 and TGF- β 2 are expressed in HTS formation in rabbit ear wounds (Kryger et al. 2007).

Active Resolution of Inflammation

Although the processes underlying HTS formation have not been completely elucidated, the contribution of dysregulated, exaggerated inflammation in scar formation is clear (LeBert and Huttenlocher 2014; Karin and Clevers 2016; Qian et al. 2016). Uncontrolled and prolonged inflammation leads to tissue injury, tissue scarring, and fibrosis. In the face of uncontrolled host immune defense mechanisms, tissue regeneration and reconstruction of diseased and injured oral and craniofacial tissues are significantly hampered (Gurtner et al. 2008).

Inhibition of proinflammatory activity of innate myeloid-lineage cells and the secretion of proinflammatory mediators for the management of fibrotic diseases, including HTS, has met limited success (Gauglitz et al. 2011; Sidgwick et al. 2015). Efforts have been also made to block scar formation with antibodies and small molecules directed against TGF- β and other proinflammatory mediators, such as IL-1 β and TNF- α (Ferguson and O’Kane 2004). However, these single-agent therapies have not led to substantial advances in patient care (Gurtner et al. 2008). These disappointing results have generated significant interest in other options for the regulation of inflammation. Investigations into the molecular mediators that regulate the active resolution of inflammation during wound healing demonstrate improved wound healing with less scarring and continuous scar remodeling in different biological systems.

Early wound signals participating in the inflammatory phase of healing are considered important drivers of the regenerative response (Karin and Clevers 2016). However, cessation of those signals and resolution of the inflammatory phase are just as important. It is now clear that resolution of inflammation is an active, receptor-mediated process orchestrated by specialized proresolving lipid mediator–derived arachidonic acid and dietary ω -3 polyunsaturated fatty acids. Specialized proresolving mediators (SPMs) have opened the door for new therapeutics for management of wound-healing abnormalities (Kenchegowda and Bazan 2010; Van Dyke 2011; Tang et al. 2013; Herrera et al. 2015).

Effective resolution of inflammation, including efficient removal of leukocytes and return to homeostasis, is an active biological process orchestrated by endogenous signals derived from eicosanoid pathways that signal the physiologic end of the acute inflammatory phase (Levy et al. 2001; Serhan, Chiang, and Van Dyke 2008). SPMs include lipoxins, aspirin-triggered lipoxins (ATLs), resolvins (Rvs), protectins, and maresins (Serhan, Chiang, and Van Dyke 2008; summarized in Fig. 2). This family of endogenously produced mediators initiate resolution temporally in the inflammatory phase of wound

Figure 2. Biosynthetic cascades and actions of specialized proresolving mediators (SPMs) derived from arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). 5-LO, 5-lipoxygenase; 12/15-LO, 12/15-lipoxygenase; 14S-HpDHA, 14S-hydroperoxy docosahexaenoic acid; 15R-HETE, 15-R-hydroxy-eicosatetraenoic acid; 15S-HETE, 15-S-hydroxy-eicosatetraenoic acid; 17S-HpDHA, 17(S)-hydroperoxy docosahexaenoic acid; 17S-HDHA, 17-hydroxy docosahexaenoic acid; 18R-HEPE, 18R-hydro-peroxyeicoapentaenoic acid; AT-LXA₄, aspirin-triggered lipoxin A₄; COX-2, cyclooxygenase-2; LTA₄, leukotriene-A₄; LTB₄, leukotriene-B₄; LTC₄, leukotriene-C₄; LXA₄, lipoxin A₄; MaR1, MaR2, MCTRs, maresin 1, 2 CTRs; P-450, cytochrome P-450; PD1, protectin D1; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PGH2, prostaglandin H2; RvD1, RvD2, RvD3, RvD4, RvD5, RvD6: resolvins D1, D2, D3, D4, D5, D6; RvE1, RvE2, RvE3: resolvins E1, E2, E3.

healing emerging late (Van Dyke 2011). Chronic inflammation—including the failure to clear infection, fibrosis, and failure of scar remodeling—is a result of failure of resolution of inflammation (Levy et al. 2001). The early response after tissue injury results in the release of endogenous mediators that initiate acute inflammation: prostaglandins and leukotrienes. As the acute inflammatory response matures, accumulation of cells containing lipoxygenases and corresponding proinflammatory products, such as leukotrienes and hydroxy acids, favors lipid mediator metabolism class switching, leading to the synthesis of proresolving molecules through newly activated pathways separate from the pathways leading to the production of proinflammatory lipid mediators (Levy et al. 2001). Disruption of production of sufficient SPMs or availability or expression of SPM receptors delays the response and leads to establishment of chronic inflammation and fibrosis (Basil and Levy 2016; Van Dyke 2017).

There is an important distinction between resolution of inflammation and pharmacologic anti-inflammation. Resolution of inflammation through the actions of SPMs is clearly distinguishable from pharmacologic anti-inflammatory drugs; SPMs act through a feed-forward, receptor-mediated mechanism to actively resolve inflammation, promote clearance of inflammatory cells from the wound milieu, and restore tissue

homeostasis without immunosuppression. Anti-inflammatory drugs are enzyme inhibitors or receptor antagonists that block inflammation often with severe side effects, such as immune suppression. Resolution of inflammation induced by the interaction of SPMs with specific receptors is mainly characterized by limiting neutrophil migration into inflamed sites and promoting neutrophil apoptosis, as well as by activation of monocytes to a “nonphlogistic” (proresolving) phenotype and the regulation of NF- κ B gene products. Resolution macrophages exhibit enhanced phagocytosis of apoptotic neutrophils and clearance of bacteria at mucosal surfaces, promoting tissue regeneration and return to tissue homeostasis (Serhan, Chiang, and Van Dyke 2008).

Emerging evidence that SPMs accelerate wound healing in diabetic wounds (Tang et al. 2013), corneal wounds (Kenchegowda and Bazan 2010), and skin fibrosis (Herrera et al. 2015) suggests new therapeutic opportunities for the prevention and management of HTS (Table 2). Administration of proresolving mediators and ligation of ERV1 (ChemR23), a multifunctional receptor that transduces the proresolving actions of RvE1, stimulates macrophages and accelerates wound closure by altering fibroblast-mediated collagen deposition and alignment and reduces dermal scarring (Cash et al.

2014). Administration of RvD2, acting through a different receptor (GP18) in mouse burn wounds, promoted long-term survival of deep dermal components after the initial thermal insult by reducing the infiltration of neutrophils and release of proinflammatory mediators (Bohr et al. 2013). Local delivery of RvD1, which signals through the GP32 receptor, enhanced wound closure and restored defective macrophage-mediated resolution in type 2 diabetic mice (Tang et al. 2013). LXA₄ and RvD2 counterregulate fibroblast proliferation and migration directly at early time points, playing an active role in limiting fibrosis and allowing wound healing and collagen deposition in the ECM to proceed normally (Herrera et al. 2015). All of the above are examples of how SPMs can promote wound healing and tissue regeneration through their anti-inflammatory and proresolving actions by limiting neutrophil influx and activity, improving phagocytosis by macrophages, and decreasing proinflammatory cytokine production, stimulating the clearance of inflammatory debris and allowing for the return to tissue homeostasis (Dalli et al. 2015). Thus, the active regulation of inflammation promoted by SPMs actually affects the same proinflammatory mediators that are the targets of pharmacologic inhibitors used for the management of several fibrotic diseases (Gauglitz et al. 2011; Sidgwick et al. 2015). The difference is that a feed-forward, receptor-mediated response

Table 2. Impact of SPMs on Wound Healing and Scarring.

SPM	Outcome	Reference
RvD2	RvD2 prevents secondary thrombosis of the deep dermal vascular network and subsequent dermal necrosis by inhibiting TNF- α , IL-1 β , and neutrophil PECAM-1 expression.	Bohr et al. 2013
LXA4, RvD2	LXA4 and RvD2 enhance wound healing and limit fibrosis in part by counterregulating fibroblast migration and proliferation in fibroblast cultures.	Herrera et al. 2015
RvD1	RvD1 accelerates closure of diabetic wounds in mice by decreasing accumulation of apoptotic cells and macrophages.	Tang et al. 2013
Statins	Statins reduce scar elevation and hypertrophic scar formation in a rabbit ear wound model and inhibit the production of CTGF.	Ko et al. 2012
Proinflammatory / proresolving mediator gene expression	Patients with prolonged, complicated recovery after blunt trauma have higher ratio of expression between endogenous proinflammatory (LTs) and proresolving (SPM) lipid mediator pathway genes.	Orr et al. 2015
Fish oil oral supplementation	Boosting plasma levels of EPA and DHA with fish oil oral supplementation accelerates wound healing in patients by altering lipid mediator ratios in acute wound microenvironments, reducing neutrophil infiltration, and promoting wound reepithelialization.	McDaniel et al. 2011
LXA4 analog	Topical application of LXA4 analog in children with infantile eczema significantly reduced the severity of eczema.	Wu et al. 2013

CTGF, connective tissue growth factor; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL-1 β , interleukin-1 β ; LTs, leukotrienes; LXA4, lipoxin A4; PECAM-1, platelet–endothelial cell adhesion molecule 1; RvD1, RvD2: resolvin D1, D2; SPM, specialized proresolving mediators; TNF- α , tumor necrosis factor α .

of active counterregulation of proinflammatory signals (not inhibition) is coordinated temporally and encompasses all relevant pathways, some of which may remain to be discovered.

Control of inflammation with statins in a rabbit ear wound model reduces scar elevation (Ko et al. 2012). Statins play a critical role in inhibiting the production of connective tissue growth factor, which contributes significantly to fibrosis by stimulating angiogenesis, granulation tissue formation, fibroblast proliferation, ECM deposition, and wound contraction (Ko et al. 2012). Interestingly, the anti-inflammatory and proresolving actions of statins are mediated in large part by resolvins (Dalli et al. 2015).

Why then is there a failure of resolution leading to fibrosis and scarring? Dysregulated lipid mediator signaling may also lead to impaired resolution of inflammation and compromised healing outcomes. The ratio of endogenous proinflammatory (leukotrienes) and proresolving (SPM) lipid mediator pathway genes was significantly higher in patients with prolonged, complicated recovery after blunt trauma (Orr et al. 2015).

Current and Emerging Therapies for HTS

Current therapies for the management of HTS are minimally effective (Sidgwick et al. 2015). Prevention of pathologic scarring will likely be more effective in the long run than treatment. All therapies for HTS after cleft lip repair target the skin, although the healing after cleft lip repair involves skin and oral mucosa. Wound healing in the oral mucosa is known to result in significantly reduced scar formation when compared with skin, which is also a common finding after cleft lip repair operations (Glim et al. 2013). Oral wounds contain fewer immune cells and mediators, as well as fewer blood vessels and profibrotic signals, as compared with dermal wounds and can

Figure 3. Failure of resolution of acute inflammation after surgery will lead to chronic inflammation with scarring and fibrosis. Modulation of inflammatory resolution pathways in acute and chronic wounds via the topical application of specialized proresolving mediators (SPMs) may provide a novel therapeutic avenue to improve healing and reduce scarring.

provide a useful model to dissect the biological processes that result in scarless healing (Glim et al. 2013).

Mechanical offloading of incisions can decrease HTS formation. Proper surgical technique, including minimization of tension and meticulous closure with wound edge eversion, reduces scar width and hypertrophy (Khansa et al. 2016). Wound eversion is usually achieved with deep dermal sutures that relieve tension of the epidermis and produce skin edge eversion, with subcuticular sutures that reapproximate the epidermis superficially. Today, silicone-based treatments remain the foundation of abnormal scar prevention and continue to be widely used in clinical practice. Silicone gel sheeting and other similar tissue adhesives that replace the subcuticular sutures have been shown to increase hydration of the stratum corneum

and decrease evaporation of water from the skin, suggesting hydration, increased oxygen permeability, and occlusion with reduction of wound tension as the mechanisms of action of silicone-based products (Sidgwick et al. 2015). The proliferative activity of fibroblasts and the production of collagen and ECM are reduced in well-hydrated tissues providing the rationale for this approach (Chang et al. 1995). Hypoallergenic microporous paper tapes have been frequently used, since they were shown to reduce the occurrence of HTS development versus untreated controls after surgical incisions (Atkinson et al. 2005). Their effectiveness stems from their ability to reduce tension and dehydration of the wound. Injections of botulinum toxin into the orbicularis oris muscle immediately after wound closure in adults undergoing cleft lip scar revision to reduce wound tension and subsequent inflammation in wound edges showed promising results by minimizing the frequency and severity of HTS (Chang et al. 2014).

Intralesion steroid injections, especially triamcinolone, combined with topical administration of corticosteroid creams historically are the preferred treatment for HTS, but varying success has been reported (Sidgwick et al. 2015). Steroids can block inflammation in the wound and can also diminish fibroblast proliferation and collagen synthesis and inhibit collagenase inhibitors (Jalali and Bayat 2007). However, steroids do not actively resolve inflammation, and they fall into the category of pharmacologic blockers, inducing significant side effects, including granulomas and skin atrophy, that lead to reduced wound strength and telangiectasia. Intralesion steroid injections show improved efficacy when used with other therapies, including cryotherapy, laser, and 5-fluorouracil, that mainly targets fibroblast activity (Gauglitz et al. 2011; Sidgwick et al. 2015), but all fall short of the desired outcome.

Inflammation resolution pathways in acute and chronic wounds may provide a novel therapeutic avenue to improve healing and reduce scarring (Fig. 3). Boosting plasma levels of eicosapentaenoic acid and docosahexaenoic acid with fish oil oral supplementation alters lipid mediator ratios in acute wounds, reduces neutrophil infiltration, and promotes wound reepithelialization, accelerating wound healing (McDaniel et al. 2011). Topical application of 15(R/S)-methyl-LXA₄ in children with infantile eczema demonstrated the first successful treatment with an SPM in humans (Wu et al. 2013).

Looking Forward

HTS after cleft lip repair surgery remains a challenge for surgeons and patients. There is a critical need for new improved therapeutics to prevent or minimize scar tissue formation. A failure of natural resolution of inflammation pathways leads to excess inflammation with resultant fibrosis and scarring. The topical application of SPMs as a therapeutic adjunct after cleft lip repair surgery has the potential to limit fibrosis and scarring and promote scar remodeling. SPMs are safe and already approved for human use in different applications. Resolution of inflammation principles for the prevention and treatment of post-CL/P surgery HTS potentially holds great promise for the treatment of a significant problem in a vulnerable population.

Author Contributions

E. Papathanasiou, contributed to conception, design, and data interpretation, drafted and critically revised the manuscript; C.A. Trotman, A.R. Scott, T.E. Van Dyke, contributed to conception, design, and data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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