Scarless wound healing – a literature review

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ABSTRACT

The healing of skin lesions, such as traumas or burns, can often result in severe scarring causing important disabilities. The study of fetal skin particularities brings into light its ability of healing wounds in a scarless manner, through regeneration. Understanding the cellular and molecular mechanisms of fetal scarless phenotype is of utmost importance as it can result in new therapeutic targets that could have the potential to reduce scarring in postnatal wounds. The aim of this review is to summarize the unique features of fetal wound healing process that may facilitate a scarless wound repair.

Keywords: fetal skin, trauma, burns, healing, scarring

INTRODUCTION

A skin lesion can heal via two processes: regeneration or repair/scarring, and understanding the differences between these is of paramount importance. The regeneration process is represented by the replacement of the affected tissue with the same type of tissue, which entails keeping intact both the structure and function. The repair or scarring process is represented by the replacement of the tissue defect with another type of tissue, usually fibrous. Secondary to this process, the affected segment heals with changes to both structure and function (1).

The secondary effects to healing with scar tissue can be analysed as a pathologic entity that is separate from the initial acute event. The discovery of treatments that promote scarless healing or healing with minimal scarring through promoting tissue regeneration would have a major impact in this field. This would be beneficial both at an individual level, by improving patient quality-of-life, and also for the healthcare system as a whole, through improving quality of care and decreasing the inherent costs of the treatment of sequelae (2).

Novelties in the scarless healing process of fetal skin

The physiopathology of fetal injury healing is a subject of great importance, as understanding this phenomenon can have a major clinical impact through the potential for influencing the fibro-proliferative process that causes contractures and keloid scarring (3). Despite advanced research in this domain, the mechanisms of scarless healing have yet to be completely elucidated. An important step in the study of the healing process was made when, four decades ago, it was observed that a lesion occurring early in gestation on fetal skin has the particularity of healing without scars (4). Starting from this hypothesis, it was later proven that mammal fetuses have a pattern of healing that is similar to the regeneration process (5-7). Fraser et al. studied a comparative animal model of fetal tissue response versus a postnatal one, to a thermal injury that affects the deep dermis. The macroscopic, histopathologic and immunohistochemical analysis proved that fetal tissue heals in a manner that is similar to regeneration while postnatal tissue heals with scarring (8).

Currently it is considered that the differences in healing of fetal and postnatal tissues are due to consequential differences in the intensity of the inflammatory response, the extracellular matrix, cell mediators, the expression of certain growth factors, gene expression and stem cell function (9,10). The inflammatory response in fetal injuries is attenuated, involving a lower number of progenitor cells (11). Also, fetal tissue contains higher levels of morphogenic factors.

These two mechanisms create a qualitatively, quantitatively and temporally different growth profile of the fetal skin, compared to postnatal skin (5,12).

The capacity of fetal skin tissue to heal without a scar is dependent on gestational age. Animal model studies have demonstrated that the capacity for scarless healing is maximal throughout the second trimester and the first part of the third trimester of pregnancy, but as the pregnancy evolves, the process of healing through regeneration sustains a transition phase where healing capacity is kept but skin appendages no longer develop (13). In human embryos, the capacity for scarless healing is lost after 24 weeks of gestation, with a gradual transitional stage that is determined by the size of the injury (5). It was thought initially that the presence of the amniotic fluid, as a sterile environment that surrounds the fetus and that is rich in growth factors and adhesion molecules, has an important role in promoting the regeneration process. However, a series of later experiments demonstrated that its presence is neither essential nor sufficient in scarless healing of fetal tissue, regeneration being proven as an intrinsic characteristic of fetal tissue (14-16).

TABLE 1. *Main differences in the characteristics of the healing process of fetal vs. adult lesions (modified after Lorenz et al) (3)*

Features of the healing process	Foetus	Adult
Scarring	Absent	Present
Development and cellular growth	Present	Absent
Speed to closure of wound	Increased	Decreased
Forming an eschar	Absent	Present
Partial oxygen pressure	Decreased	Increased
Fluid environment	Present	Absent
Sterile environment	Present	Absent
Temperature	Increased	Decreased
Acute inflammatory reaction	Attenuated	Present
Synthesis of the extracellular matrix	Rapid	Slow
Angiogenesis	Reduced	Increased
Epithelialization	Rapid	Slow
Keratinization	Immature, periderm	Present

Fetal extracellular matrix

The extracellular matrix is a dynamic supportive structure that facilitates the migration and proliferation of cells, creating the premises for healing with minimal scarring (9).

Collagen is the most important structural protein in the organism and nowadays, 28 subtypes are known (17). There are phenotypic differences with regards to the distribution of all types of collagen between fetal tissue and the postnatal one, the predominant ones being types I and III (9). During the healing process of

lesions affecting fetal tissue, type III collagen is organized in a fine reticular pattern that cannot be differentiated from intact skin (3). In contrast, in postnatal lesions, type I collagen is predominant which creates a network of thick fibres that are displayed parallel to each other and perpendicular to the lesion – this generates a increased degree of tension and rigidity (9,10). Also, it was observed that the speed with which collagen forms deposits throughout the healing process is inversely proportionate to age (foetus > newborn > adult) (18). It is considered that the regulation of collagen synthesis is one of the most important mechanisms in the process of scarless healing (3).

Hyaluronic acid is a glycosaminoglycan that accumulates rapidly both in fetal injuries and in adult ones, thus generating resistance to deformity (10). Fetal skin has an increased level of hyaluronic acid that persists until day 21 post-injury, and fetal fibroblasts exhibit an increased number of receptors for it (14). In injuries on mature skin tissue, hyaluronic acid is found in smaller quantities, mixed with fibrin and platelets, and is rapidly removed by hyaluronidase, reaching a baseline level at 3 days post-injury (3,14). The modulators of the extracellular matrix are responsible for the synthesis, distribution and degradation of collagen. The main modulators are decorin, fibrinomodulin, chondroitin sulphate, lisil-oxydase, metaloproteinases and tissue inhibitors.

Increased levels of decorin and lisil-oxydase are found in the repair process of adult skin lesions while condroitin-sulphate and fibrinomodulin, a proteoglycan responsible for inactivating cytokine ß-TGF, both have higher levels in fetal injuries (9,10). Metalloproteinases and tissue inhibitors are responsible for the turnover of the extracellular matrix. Throughout the process of scarless healing, an increased ratio between metalloproteinases and tissue inhibitors can be found, which support remodelling to the detriment of collagen deposits (10).

Mediators of scarless healing

Inflammation is a complex pathologic process that represents a defensive body response to aggression. The inflammatory reaction is attenuated in the healing of fetal lesions, which generates a micro-medium that is favourable to the regeneration process. Also, it has been observed that a decrease in the inflammatory process in postnatal injury healing results in a decrease in scarring. Using this observation as a starting point, the role of inflammatory cells, cytokines and growth factors in the healing and regeneration processes was studied (10,19).

Main inflammatory cells

Fibroblasts are essential in the synthesis and re-modelling of the extracellular matrix, which is a vital component of the healing process. It is considered that fetal fibroblasts are the main cells responsible for scarless healing, as this process depends on their capacity of producing and organizing collagen and the other components of the extracellular matrix in quantities and ratios that are similar to intact skin (20). There are intrinsic differences between fetal and adult fibroblasts that are reflected in their capacity for synthesizing components of the extracellular matrix (9,10). Fetal fibroblasts have the capacity for simultaneous proliferation and synthesis of collagen, and more so types III and IV. Adult fibroblasts initially proliferate and later on, they start synthesizing collagen (10).

Myofibroblasts are fibroblasts that have similarities to smooth muscle cells, such as containing myofilaments of actin (α-SMA) and having contractile properties that are involved in creating scar tissue. These are absent or in a very low number in fetal injuries but are found in a high number in postnatal injuries (10).

Platelets have the capacity of releasing signals that initiate the inflammatory process in the early stages of healing. Although there is no microscopic difference between fetal platelets and adult ones, it has been observed that fetal ones have a low tendency for aggregation in the presence of collagen and also that they produce lower levels of platelet-derived factors, TGF-ß1 and TGF-ß2, compared to adult ones (10,21,22). In scarless healing, the absence or the presence of an attenuated inflammatory reaction is partially due to a low capacity of fetal platelets for aggregation and also to the secretion of minimal levels of cytokines (14,21).

The main function of neutrophils is the phagocytosis of bacteria and the removal of necrotic tissues. During the healing process, neutrophils are activated by cytokines TGF-β1, TNF-α, IL-1 and by platelet-derived growth factors (9). Once activated, neutrophils release self-stimulating cytokines and induce chemotaxis for fibroblasts and macrophages (20). As fetal platelets have a reduced capacity for secreting factors that are responsible for the activation of neutrophils, there will be a lower number of neutrophils involved in fetal injury healing (9,10).

Monocytes are recruited to the site of the lesion by PDGF and secondarily converted by TGF-β into macrophages. These will collect tissue debris through phagocytosis and will release numerous cytokines and growth factors (20).

Keratinocytes are the main cellular component of the epidermis, which play an important part in the maintenance and restoration of the barrier function of the skin. When the integrity of the skin is lost, they contribute to the re-epithelialization process as an integrated part of the healing process (23). Re-epithelialization is accelerated in fetal injury healing, usually occurring in the first 24 hours (18,24).

Mastocytes are the last cell type to migrate to the level of an injury. They are attracted by IL-33, a cytokine that is released from necrotic cells (25). Once they reach the injury, they secrete TNF-α, which helps in the recruitment of neutrophils. Thus, the presence of a low number of mastocytes is associated with a decreased migration of neutrophils and an attenuated inflammatory response (26).

Cytokines

β-TGF (transforming growth factor beta) is a growth factor that controls cell proliferation and differentiation. Isoforms TGF-β1, TGF-β2 and TGF-β3 are involved in all stages of the healing process, but have diverging effects. The expression of TGF-ß1 and TGF-β2 (which are secreted by thrombocytes and inflammatory cells) is increased in the repair of adult skin injuries and decreases in fetal injuries, were TGF-β3 (secreted by keratinocytes and fibroblasts) is predominant (5,27,28).

Interleukins are cytokines that are responsible with chemotaxis and activating inflammatory cells. The most important subtypes are pro-inflammatory interleukins 6 (IL-6) and 8 (IL-8) and anti-inflammatory interleukin 10 (IL-10). The initiation of the healing process determines a rapid increase in IL-6 and IL-8. These are depleted in the first 12 hours of healing for fetal injuries, but they persist to 72 hours in adult injuries (10,20). IL-10 has a protective role against excess collagen deposits, it maintains high levels of hyaluronic acid, impedes the differentiation of fibroblasts into myofibroblasts and prolongs the angiogenesis process (29). The attenuated inflammatory reaction in fetal injuries is partly due to an increased production of IL-10 and decreased levels of IL-6 and IL-8 (30,31).

Growth factors

VEGF (vascular endothelial growth factor) has an essential role in angiogenesis, having an increased expression in adult skin lesions, compared to fetal ones (20,32). Also, it is an accentuating factor for the inflammatory response, through an increase in vascular permeability and facilitation of inflammatory cell migration into the lesion (32).

PDGF (platelet derived growth factor) is a chemotactic agent for inflammatory cells and fibroblasts, causing their migration to the site of injury. Initially,

PDGF is present in both fetal injuries and postnatal ones, but it recedes faster in fetal injuries (33).

The FGF family (fibroblast growth factors) numbers 21 isoforms that, along with their receptors, have different distributions in fetal skin both throughout the healing process but also depending on the gestational age of the fetus. Intact skin has an increasing expression of isoforms FGF 5, 7, 10 as pregnancy advances compared to isoforms FGF 2 and 9, that do not change. In the case of a skin lesion, it has been found that isoforms FGF 7 and 10 have a decreased expression while isoforms FGF 5 and 9 do not change (34).

Gene expression

The genomic analysis has demonstrated that fetal injuries that have undergone scarless healing and postnatal ones that have healed with scarring have different genetic expression profiles (35). In the initial stages of healing fetal skin lesions there is a rapid increase in the expression of genes involved in cellular growth and proliferation, which likely contributes to expedited healing. After 24 hours, the genetic expression will exceed that of postnatal injuries (35). Studies have identified a group of transcription factors that was called homeobox genes, that have a crucial role in morphogenesis and embryologic development, regulating cellular migration and proliferation with subsequent development of differentiated tissues. Homeobox genes have been divided into two large families: a set of 39 HOX genes and a more diverse set of non-HOX genes, that include genes MSX and PRX (36). In fetal dermis, during development, specific homeobox genes are expressed: HOXA4, HOXA5, HOXA7, HOXB13, HOXD8, MSX-1, MSX-2, MOX-1 and PRX-2 (37,38). Genes HOXB13 and PRX-2 are only present in fetal skin injuries; they are absent in adult ones. The expression of HOXB13 decreases, while the one for PRX-2 increases, which suggests that the activation or deactivation of these genes plays an essential role in the regeneration process (38).

TABLE 2. *Fetal versus adult wound healing mechanisms (modified after Larson et al., Lo et al., Satish et al.) (9,10,20)*

		Fetal wound healing	Adult wound healing
Collagen	Rate of deposition	Immediate	Delayed
	Collagen type	Prevalence of type III collagen - optimal for cellular migration and proliferation	Prevalence of type I collagen – generates rigidity – impedes cellular migration and regeneration
	Histological pattern	Fine, reticular bundles	Dense parallel bundles
Extracellular matrix modulators		High matrix metalloproteinase to tissue-derived inhibitors ratio favours modulators turnover and remodelling	Low matrix metalloproteinase to tissue-derived inhibitors ratio favours accumulation of collagen
Glycosaminoglycans	Hyaluronic acid	High levels facilitate cellular movement and water absorption	Low levels inhibit cellular movement
	Heparan sulfate	Absent / Decreased	Present / Increased
	Chondroitin sulfate	Present / Increased	Absent / Decreased
Proteoglycans	Fibromodulin	Increased	Decreased
	Decorin	Absent / Decreased	Present / Increased
Adhesion proteins		Rapid up-regulation stimulates cell migration and attachment	Diminished up-regulation results in slower fibroblast migration
Platelets		Decreased degranulation and aggregation	Release of PDGF, TGF-β1 and TGF-β2
Inflammatory cells		Decreased number	Increased number
Inflammatory Response		Attenuated	Intense
Myofibroblasts		Absent	Present
Interleukins	IL-6, IL-8	Decreased expression	Increased expression
	IL-10	Increased expression	Decreased expression
TGF-β	TGF-β1 and TGF-β2	Low levels	High levels
	β3-TGF	High levels	Low levels
Growth factors	VEGF	High levels	Low levels
	PDGF	Transient	Sustained
	FGF	Low levels	High levels
Gene expression responsible of cell growth and proliferation		Rapid up-regulation	Delayed up-regulation
Progenitor cells		Increased number	Decreased number

Stem cells

Multiple studies have underlined the possible role of stem cells in the healing process, especially of epidermal and mesenchymal stem cells. The reservoir of stem cells for the skin is found in the superior dermal layer and is represented by a specific population of mesenchymal cells that are responsible for the regulation of hair follicle growth and that also have a potential for differentiation into a wide variety of cells (39). The inferior dermal layer is composed of reticular fibroblasts that are responsible for synthetizing the extracellular matrix; they are the first cells to migrate to the site of a skin lesion at the beginning of the healing process (40).

The main end-point of studying stem cells remains developing therapeutic strategies that will act at a cellular level to promote healing through regeneration, in both the adult and pediatric age groups.

New advances and theories in research regarding scarless healing

One of the future avenues of research is trying to modulate the healing process by slowing down the fibrotic response and providing enough time for multipotent stem cells to differentiate, thus replacing the scarring process with a regenerative one (6). Currently, different therapeutic strategies that have this potential are being studied. One strategy suggests placing epidermal progenitor cells at the level of a biomimetic matrix, which represents a manipulated environment through optimizing mechanical stress and oxygen tension in order to reproduce similar conditions to those present in the healing process of fetal lesions (6).

As fetal tissues heal with an attenuated inflammatory reaction, the modulation of the inflammatory process has been attempted by using molecules with anti-inflammatory properties. De Souza et al. demonstrated that systemic administration of alpha-melanocyte stimulating hormone, which possesses anti-inflammatory and immunomodulatory properties,

participates in healing wounds with minimal scarring by organizing collagen fibres in a network similar to the normal skin (41). Gay et al. demonstrated that fibroblast growth factor IX (FGF9) facilitates neogenesis of hair follicles. This observation can have a significant impact in the research of the regeneration process as mature skin heals with formation of scar tissue that is characterized by the lack of cutaneous appendages (42).

Some of the methods of manipulating the healing of a mature skin wound are: inhibition of the inflammatory response by blocking cytokines TGF-β1, FGF-β and PDGF, adding exogenous fibronectin or tenascin and transplantation of fetal fibroblasts into the wound or adding exogenous hyaluronic acid in order to stimulate fibroblasts migration and tissue regeneration (14).

Bioengineered fetal tissues can replace the skin that is traditionally used for grafting in patients with second and third degree burns. Hohlfeld et al. developed fetal skin constructs using harvested skin after elective pregnancy termination. They treated a number of pediatric patients and obtained a rapid healing, with an excellent functional and cosmetic result (43).

CONCLUSIONS

Wound healing is a complex process that involves a close partnership between inflammatory cells, growth factors, cytokines, extracellular matrix components and stem cells. The fetal phenotype has the ability to regenerate due to a different profile in growth factors and extracellular matrix and an attenuated inflammatory response. The exact process of healing fetal wounds remains unknown at present, this field being open to research, as understanding the cellular and molecular mechanisms of the regeneration process has the potential to provide insights into developing therapies that can minimize the development of scar tissue secondary to burns or other traumas.

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