Characteristics of Fetal Wound Healing and Inspiration for Pro-Healing Materials

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Abstract:

Chronic non-healing wounds are a significant healthcare challenge. Various biomaterials have been developed to treat chronic wounds but there are still opportunities for improvement of biomaterial therapeutics. This review discusses how fetal wound healing could be used as inspiration to develop pro-healing materials. Compared to adults, fetuses have enhanced wound healing outcomes and healing without scarring. Scarless fetal wound healing is associated with various key differences in several growth factors, cytokines, extracellular matrix components, and coagulation parameters. Mimicking the fetal wound healing environment through bioinspired materials could create improved therapeutics to treat chronic wounds. This review addresses the key differences between adult and fetal wound healing that allow for enhanced scarless fetal healing and discusses how these differences can be used to develop pro-healing materials.

Introduction

Impaired wound healing contributes to a huge healthcare burden; nearly 6.5 million patients are affected by chronic, non-healing wounds in the United States [1]. Additionally, in many dermal injuries fibrotic scarring is a large concern because it leads to impaired skin function and has serious implications in overall healing [2]. Current biomaterials for wound healing have been fabricated from natural polymers, synthetic polymers, silicon-based materials, and metal-based materials [3]. These materials come is various forms, including sponges, hydrogels, particles, and nanofibers, that allow for the biomaterials to interface and actively augment the wound healing process [3]. Such materials have potential for addressing chronic wounds but there are still many opportunities to improve the pro-healing efficacy of existing materials. One potential strategy to improving material design is to take inspiration from fetal wound healing, which results in scarless healing and is in stark contrast to adult healing that frequently results in scar formation. Much work has gone into researching what factors create the fetal scarless wound healing environment [2]. Significant studies have been done on how cellular and molecular mechanisms can be modulated to limit scarring and promote skin regeneration after an injury [4]. This review provides an overview of the differences in wound healing factors between adult and fetal healing for treating chronic wounds (**Table 1**) and discusses how these differences could be used as inspiration to create pro-healing materials to treat chronic wounds.

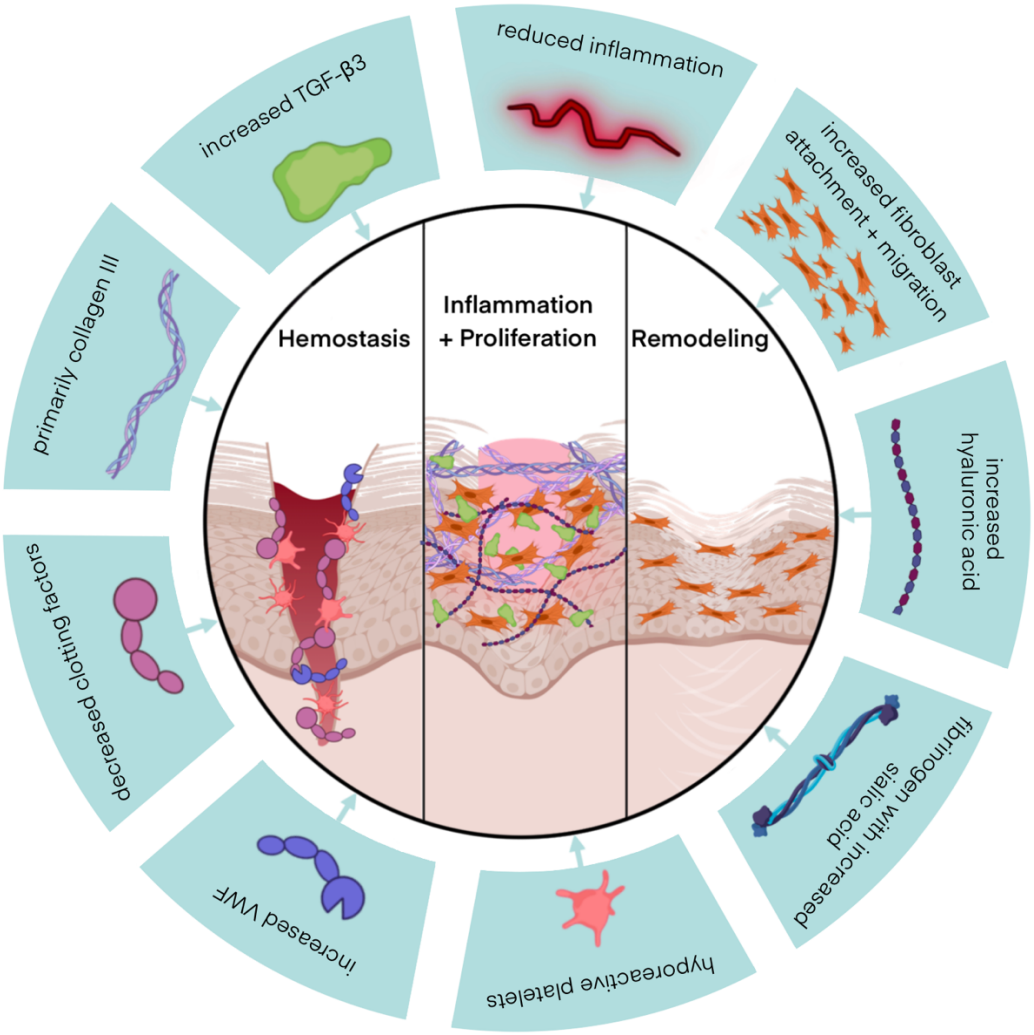

Fig. 1 Scarless fetal wound healing overview, including key characteristics that enable enhanced scarless healing.

Overview of Wound Healing

Wound healing is vastly different in fetuses and adults, most notably with fetal wound healing being scarless. In both fetuses and adults, wound healing consists of four distinct phases: hemostasis, inflammation, proliferation, and remodeling [5]. Hemostasis, the first step in the healing process, is characterized by platelet activation and coagulation [5]. After an injury, the clotting cascade is initiated, resulting in platelet aggregation, fibrin polymerization and the formation of a clot [6]. Subsequently the inflammation phase begins, resulting in a release of cytokines and growth factors [6, 7]. Neutrophils aggregate at the injury site due to the release of interleukin (IL)-1, transforming growth factor beta (TGF)-β, and other products [6, 7]. The proliferation phase is where epithelization begins [6, 7]. Epithelial cells at the wound's edge begin to proliferate and lay down the provisional matrix consisting of collagen [5–7]. Additionally, fibroblasts migrate into the wound area and deposit significant amounts of extracellular matrix (ECM) [8]. During the final stage of wound healing, collagen continues to be deposited and remodeled, and fibroblasts also secrete glycosaminoglycan and other proteins to support the new matrix [5–7]. At this point, wound contraction occurs through interactions between fibroblasts and the ECM, resulting in a healed wound [5, 6]. However, a longer remodeling phase occurs overs that can last for months or even years in which fibroblasts in the wound continue to alter the microenvironment.

While the phases of wound healing are generally the same in fetuses and adults, there are major differences within each of the phases. Critical differences in the macromolecules, growth factors, and proteins involved in wound healing allow for fetal wound healing to be enhanced with faster healing, minimal inflammation, and no scar formation (**Figure 1**). These differences are discussed in detail in the sections that follow.

Table 1: Adult vs Fetal Wound Healing Properties

Wound Healing Component	Adult	Fetus	Associated References
Hyaluronic Acid (HA)	Low HA content	Increased overall HA content	[9, 10]
TGF- β	Mainly TGF-β1 production	Increased TGF-β3 production Minimal TGF-β1 expression	[11, 12]
Collagen	Higher collagen I levels within wound Collagen deposition is delayed and remodeling takes longer	Deposited collagen is mainly collagen III Collagen deposition is rapid and occurs earlier in the wound healing process	[13–15]
Fibroblasts	Similar levels of proliferation but decreased migration	Increased migration Expression of genes associated with migrations and neovascularization	[16–18]

	Higher expression of fibrosis related genes		
Inflammatory Cells	Prolonged inflammation at the wound site	Little to no inflammation present in the wound site	[19–21]
ECM Modulators	Delayed cell migration Higher TIMP to MMP ratio, with increased collagen accumulation	Rapid cell attachment and migration Increased amounts of MMPs, which promote collagen turnover and remodeling	[14]
Coagulation Parameters	Increased clotting factors Increased bleeding times	Decreased clotting factors Increased von Willebrand Factor Hypoactive platelets and decreased bleeding times	[22–24]
Fibrinogen	Different subunit lengths Increased fibrin clotting times	Increased sialic acid content Increased phosphorylation and glycosylation	[22, 23]

Hyaluronic Acid

Hyaluronic acid (HA), a polysaccharide in the glycosaminoglycan family, plays a critical role in all steps of the wound healing process [3]. HA is a negatively charged disaccharide polymer, that exists in varying lengths. Long HA molecules are involved in the structural functions of wound healing, while short HA molecules are involved with inflammation and immunostimulation that occur during the wound healing process [24–26]. HA is also pro-angiogenic and correlates with upregulating several angiogenic signaling pathways [27, 28]. Additionally, HA interactions with the CD44 receptor promote cell attachment and cell adhesion [19, 28].

Total HA content in fetal wounds versus adult wounds is vastly different, and it is thought that HA plays an important role in the scarless healing process by modulating fibroplasia and neovascularization. Fetal wounds have a marked increase in HA content as compared to adult wounds [10]. West et al. determined an underlying reason for the increased HA levels in fetal wounds is lower hyaluronidase levels [9]. Hyaluronidase breaks down HA and is found at increased levels in adult wounds. The decrease in hyaluronidase in fetal wounds may promote a scarless healing environment [9]. Studies have shown that fetal wound fluid has increased levels of HA for up to two weeks after injury, while adult founds have elevated HA levels for only 3 days [29]. HA content affects the function and proliferation of fetal fibroblasts and plays a role in the amount of collagen present within a fetal wound [10]. Unlike adult fibroblasts, neonatal fibroblasts do not decrease HA production once confluent, resulting in elevated levels of HA within the fetal environment [30, 31]. Fetal fibroblasts have an increased number of HA receptors compared to adult cells, which correlates with increased fibroplasia in fetal wounds [30]. Adult wounds have decreased HA content, in part, due to the increased inflammation and pro-inflammatory cytokinesIL-1 and TNF-α that down-regulate HA. Mast et al. demonstrated that reducing HA content in fetal wounds leads to an adult-like healing response [10]. HA helps increase cellular motility, which contributes to scarless wound healing [32]. The size of HA also plays a critical

role in its wound-healing capabilities. Longer fragments of HA upregulate TGF-β3 expression and collagen III production, which is consistent with a fetal scarless wound healing-like environment. Since the amount of HA plays such a critical role in scarless wound healing, HA levels can be increased to promote a fetal-like healing response. Developing pro-healing materials that increase HA content or promote HA synthesis within a wound can be beneficial for mimicking the advanced fetal healing environment.

TGF-β

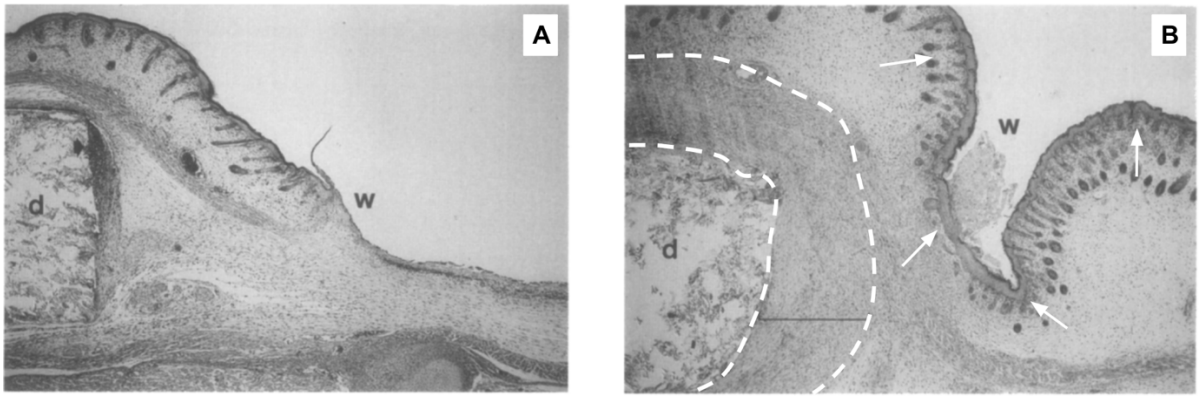

Fig. 2 Subcutaneous implantation of TGF-β1 within a fetal rabbit excisional wound leads to scarred healing. A) Control fetal skin shows no fibrosis B) Fetal excisional wound implanted with 1 μg of TGF-β1 forms a dense fibrous cap along the wounds edge (arrows). Figure 2 is reprinted from Lanning et al.*[33]* with permission from Elsevier.

TGF-β is a cytokine that modulates cellular responses and impacts healing. In mammals, TGF-β occurs in three isoforms, TGF-β1, TGF-β2, and TGF-β3. All three isoforms bind to two receptors, TβR1 and TβR1, and activate the same intracellular signaling pathway. However, the effect the isoforms have on wound healing is vastly different [34–36]. TGF-β1 expression results in fibroblasts contracting the ECM and forming scar tissue [35]. TGF-β3 expression downregulates collagen and fibronectin synthesis, resulting in scarless healing [37]. TGF-β can be released from platelets, neutrophils, macrophages, and fibroblasts at various points during the wound healing process [38]. The TFG-β isoforms are involved in inflammation, collagen synthesis, and remodeling of the extracellular matrix [36, 39, 40]. Additionally, TGF-β is essential for fibroblast migration and proliferation within a wound [38].

TGF-β levels are widely different in fetal wounds compared to adult wounds; the ratio of the TGF-β isoforms, as opposed to the total amount of TGF-β, is what leads to the regulation of fibrosis in fetal wounds [11, 12]. The ratio of TGF-β1 and TGF-β3 levels dictates scar formation [12]. Adult wounds have increased levels of latent TGF-β1 and a decreased expression of α-SMA. Additionally, MMPs upregulate the secretion of TGF-β1 [41] and α-SMA expression is inhibited by matrix metalloproteinase (MMP) inhibitors. An increase in TGF-β3 is observed during fetal wound healing, while TGF-β1 levels are nearly undetectable [42].

Several studies have shown manipulation of TGF-β1 and TGF-β3 levels in fetal wounds leads to a change in wound healing. Adding exogenous TGF-β1 to wounded fetal skin resulted in increased inflammatory response and the formation of a scar, which is consistent with adult wound healing response [43]. Eslami et al. determined the effect of TGF-β3 on scar formation in gingival wounds [12]. Co-localization of αvβ6, an integrin that can activate either TGF- β1 or TGF-β3, and TGF-

β3 was associated with scarless gingival healing. It was also determined that late expression of TGF-β3 could lead to anti-scarring effects [12]. In studies conducted by Krummel et al., polyvinyl alcohol sponges loaded with TGF-β1 were subcutaneously inserted into fetal wounds, which resulted in scarring and excess fibrosis[44]. The healing response in these studies was found to be more adult-like, with increased inflammation, more collagen accumulation, and adult-like fibroblast proliferation. Furthermore, exogenous TGF-β1 expression within fetal wounds results in increased fibrosis (**Fig. 2**)[33]. Shah et al. conducted studies where they neutralized TGF-β1 in adult wounds, resulting in no scar formation at the wound site[45]. In addition to age-related differences in TGF-β1 responses in healing, sex-specific differences have also been noted. Adult women have poor dermal wound healing due to the estrogen-induced increase of TGF-β1. This increase in TGF-β1 leads to more scarring at wound sites [46]. Based on these studies, pro-healing materials that can promote the upregulation of TGF-β3 and downregulation of TGF-β1 could minimize fibrosis formation at the wound site. For example, developing wound healing materials that deliver TGF-β3 within a wound site could be useful in promoting a scarless wound healing environment.

Collagen

Collagen, the most abundant protein in the body, is a major component of the ECM. Collagen type I and type III play an integral role in the wound healing process by supporting cell attachment, proliferation, and differentiation [47–51]. Collagen exposure at the site of an injury initiates the clotting cascade [47], contributing to fibrin clot formation to stop bleeding. Collagen also regulates inflammation. Specifically, collagen type I amplifies inflammation by attracting neutrophils to the wound site [47, 52]. Collagen also plays a critical role in scarring. Scars typically have high levels of collagen, fibronectin, and laminin [47, 53]. The difference in the level and type of collagen results in scarless wound healing in fetuses.

The timing and the pattern of collagen deposition differs between fetuses and adults [13]. While both adults and fetuses produce all types of collagen at a wound site, collagen is deposited for an increased amount of time within an adult wound. Whitby and Ferguson demonstrated that collagen is present in an adult wound at 5 days post-wound, while fetuses have collagen deposition much earlier, at 48 hours post-injury [13]. The difference in the type of collagen plays a role in scar formation and regulation. Within a wound, fetuses have a higher ratio of collagen III to collagen I, while adult collagen content is mostly collagen I [14]. The increased amounts of collagen III in a fetal wound are deposited in a fine pattern, similar to uninjured skin [15]. On the other hand, adult wound healing is characterized by collagen I bundles that are laid down in a disorganized pattern with high amounts of crosslinking between the bundles. Unlike collagen III, the strength and crosslinking of collagen I impede the movement of cellular mediators, which are critical for wound healing [15]. Collagen production is regulated by fibroblasts, and fetal fibroblasts produce increased amounts of collagen compared to adult fibroblasts [32]. Being able to control the type of collagen present within a wound can lead to an advanced healing environment. Focusing on developing wound healing scaffolds composed of collagen type III or scaffolds that drive enhanced collagen type III expression could hold promise in recapitulating the scarless wound healing environment.

Fibroblasts

The inherent differences between fetal fibroblasts and adult fibroblasts play an integral role in why fetal wound healing is enhanced compared to adult healing. Fibroblasts are critical in the wound healing process, as they lay down the ECM and proliferate within the wound. The ECM microenvironment that is critical for the enhanced wound healing environment in fetuses is largely due to fetal fibroblasts [16]. In general, fetal fibroblasts express higher amounts of collagen than adult fibroblasts, and collagen deposition correlates directly with scar formation [17]. Fetal fibroblasts and adult fibroblasts generally proliferate at similar rates, however fetal fibroblasts migrate more, as compared to adult fibroblasts [16]. For wound healing, increased migration directly correlates to a faster rate of wound closure. Fetal fibroblasts have much more plasticity as compared to adult fibroblasts; fetal fibroblasts can differentiate into adipocytes and chondroblasts, but this does not hold true for adult fibroblasts [16]. Adult fibroblasts are also much more responsive to injury [18]. When injured, adult fibroblasts express genes associated with fibrosis, including collagen type 1 α1 chain (Col1a1), collagen type 3 α1 chain (Col3al), and TGF-β, while fetal fibroblasts express genes associated with migration and neovascularization, including, fibronectin 1 (Fn1), insulin like growth factor 1 (Igf1), insulin like growth factor 2 (Igf2), and vascular endothelial growth factor A (VEGFa) [18]. Additionally, adult fibroblasts produce an excess of cytokines, which creates an environment not conducive for wound healing [54]. Broker et al. demonstrated that adult fibroblasts produce nearly twice as much TFG-β1 and an excess of cytokines, as compared to fetal fibroblasts, which creates a suboptimal wound healing environment [54]. Leveraging the wound healing capabilities of fetal fibroblasts may play a large role in the development of advanced wound healing materials that mimic the scarless wound healing microenvironment. For example, using biomaterials to deliver fetal fibroblasts could be useful for promoting healing in chronic wounds.

Inflammatory Cells

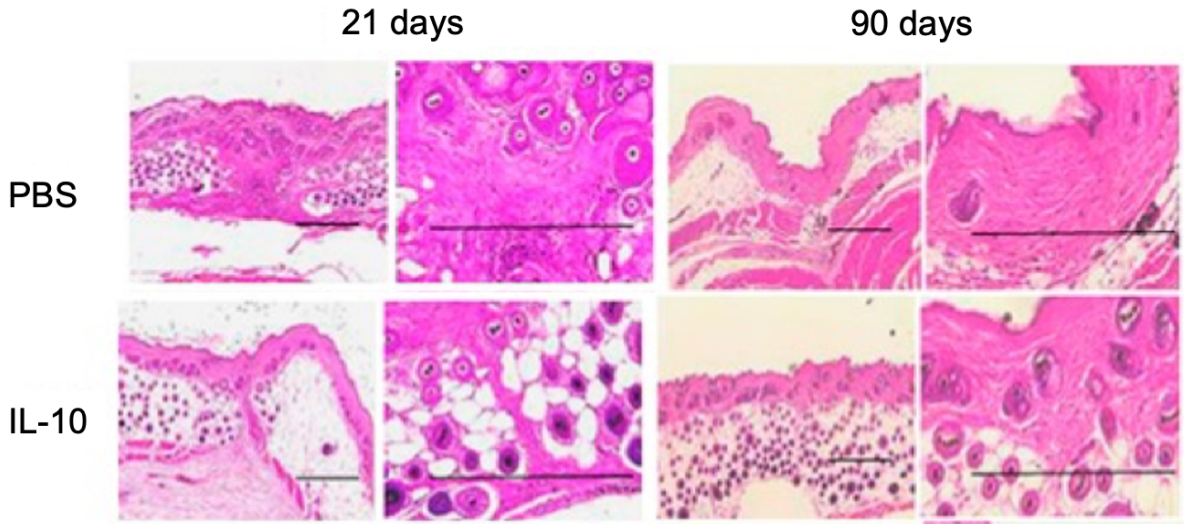

Fig. 3 Overexpression of IL-10 in adult wounds results in scarless healing. Low and high magnification microscopy of Hematoxylin & Eosin stained skin wounds 21 and 90 days after initial skin wound surgery (scale bars are all 150 μm). PBS treatment (top row) results in scarring and dense collagen deposition. Additional expression of IL-10 (bottom row) resulted in no scarring and organized collagen deposition. Figure 3 is reprinted from Gordon et al.*[55]* with permission from Elsevier.

Minimal to no inflammation is seen within the injury site or clot of a fetus during wound healing 24]. Adult wounds have high levels of granulocytes, macrophages, and lymphocytes, and inflammation occurs for an extended period. In adult wounds, inflammation lasts for upwards of 30 days, while neonatal wounds only have inflammation for around 3 days. The cytokine IL-8 plays an important role in regulating inflammation. IL-8 recruits neutrophils and other immune cells to the site of an injury. IL-8 is diminished within fetal wounds but is abundant in adult wounds. Fewer number of macrophages and monocytes are recruited to an injury for fetal wounds. These cells are also less persistent in fetuses as compared to adults [21]. Wagner and Whermanm studied how the cytokine activity and expression is different between fetal and adult wound healing; all seven cytokines that were studied had increased expression in adult wounds [37]. IL-6 is another important modulator of wound healing; a lack of IL-6 leads to impaired wound healing, while an excess of IL-6 causes scarring [20]. Studies have shown that fetal wounds do not have prolonged expression of IL-6 like adult wounds [20]. Additionally, an exogenous administration of IL-6 in a fetal wound causes scarring demonstrating the proinflammatory cytokine, IL-6, plays a role in the scarring response [20]. IL-10 is an anti-inflammatory cytokines that is implicated in scarless wound healing [55]. High levels of IL-10 are seen in fetal skin, but these levels drop significantly in adult skin [55]. Gordon et al. studied the over expression of IL-10 in postnatal human skin and determined the excess of IL-10 led to a reduction in the inflammatory response and an environment permissive for scarless wound healing (**Fig 3**)[55]. Developing materials that can actively decrease inflammation time within a wound would be advantageous. For example, this could be achieved by delivering IL-10 at levels seen in fetal wounds for short periods of time.

When delivering growth factors, the release kinetics of growth factors should match what is seen in fetal wounds to promote decreased scarring and an overall better wound environment.

ECM Modulators

The ECM consists of a variety of proteins and macromolecules that support and regulate cellular processes. For example, within the ECM, glycosaminoglycan chains are important for wound healing because they influence the mechanical properties of the tissues [56]. Proteoglycans are also involved in the wound healing process. Decorin, a small leucine-rich proteoglycan, has been shown to downregulate TFG-β production and influence wound healing [56]. Connective tissue proteoglycans impact wound healing by regulating critical growth pathways and by stimulating angiogenesis [56, 57]. Compared to adult ECM, fetal ECM has many differences in ECM modulators [56], including those that modulate collagen synthesis, maturation, and degradation.

Many ECM modulators like decorin, lysyl oxidase, and MMPs differ in their expression between adults and fetuses [14]. Adult wounds have upregulated amounts of decorin [14, 58]. Lysyl oxidase crosslinks and strengthens collagen and has increased expression during development. Fibromodulin, which has been shown to promote scarless wound repair, is downregulated in adult wounds compared to fetal wounds [14, 59]. Scarless fetal wounds have an increase in MMP1 and MMP9 and a decrease in MMP2, which have increased tissue-derived inhibitors (TIMPs) [14, 60]. This higher ratio of MMP to TIMP is associated with increased ECM remodeling. Fetal wounds have an increase in ECM adhesion proteins [61]. Whitby and Ferguson also demonstrated that fetal wounds have tenascin expression at 1 hour post-injury compared to 24 hours in adult wounds; tenascin is an ECM protein that regulates cell migration [13]. The rapid appearance of tenascin in fetal wounds is thought to influence the rapid closure of fetal wounds [13]. Since the ECM plays such a crucial role in wound healing, being able to recapitulate the fetal ECM environment could allow for a scarless wound healing environment. Developing materials that can regulate the expression of ECM modulators may potentially hold immense promise in creating pro-healing materials. For example, materials could be created that deliver MMP1 and MMP9 at ratios that are seen in fetal wounds.

Hemostatic System

Because coagulation is the first step in the healing process, and the fibrin clot that forms serves as the initial scaffold for cellular infiltration during early healing, it is important to consider age-related differences in hemostasis. Interestingly, the fetal and neonatal hemostatic system is considerably different from that of adults. This phenomenon, known as developmental hemostasis, has been identified and researched since the early 1980s and is characterized by age-dependent differences in clotting factors, platelets, and fibrin clot characteristics. Differences in these factors are most marked through the neonatal phase but can persist for the first year of life. In the healthy neonate, these age-dependent differences are thought to be part of typical development and do not pose a concern. In fact, many have considered that fetal/neonatal hemostasis serves a protective purpose in minimizing risks of thrombosis or bleeding [62, 63]. In general, the fetal/neonatal hemostatic system is considered balanced; many clotting factors that constitute the coagulation cascade are found to be in different proportions than in the mature, adult form. In particular, clotting factors II, VII, IX, and X are observed to be lower in the fetus/neonate. However, these

lower coagulation factor levels are overall balanced by increased concentrations of procoagulant von Willebrand Factor [63–65].

In addition to age-specific differences in concentrations of circulating clotting factors, quantitative distinctions have been identified in fetal/neonatal hemostatic proteins, most notably in fibrinogen . Although fibrinogen concentrations are similar, neonates possess a molecular variant of the protein termed fetal fibrinogen [64]. This fetal/neonatal specific protein has been shown to have different molecular weights of the subunits and distinct post-translational modifications compared to the adult form [22, 23]. Specifically, fetal/neonatal fibrinogen had higher levels of phosphorylation and glycosylation compared to the mature form. These differences result in lower activity reflected by longer fibrin clotting times compared to those observed in adults [22, 23].

Additionally, although circulating platelet counts and even morphology are generally equivalent between adults and neonates, platelets in newborns are observed to be hyporeactive compared to adults[66]. This hyporeactivity is demonstrated by lower activation and aggregation activity and leads to reduced intraclot thrombin levels [66]. This hyporeactivity is also reflected by, in response to various platelet agonists, overall less expression of surface P-selectin, a protein that functions as a platelet adhesion molecule and binding to fibrinogen [62, 67]. However, despite the documented hyporeactivity of neonatal platelets, bleeding time and platelet closure time have actually been found to be shorter in full term infants compared to adults [62, 67]. From a wound healing perspective, neonatal derived platelet-rich plasma (PRP) has been demonstrated to increase proliferation, differentiation, and migration of various cell types, including endothelial cells, mesenchymal stem cells, and dermal fibroblasts, all crucial for wound healing and may be a viable therapeutic for enhancing healing outcomes [68, 69]. Developing pro-healing materials that modulate the concentrations of various clotting factors, use fetal fibrinogen, or employ neonatal PRP could leverage the advanced properties of the fetal and neonatal hemostatic system to create a fetal-like healing environment.

Applications of Fetal Wound Healing Properties

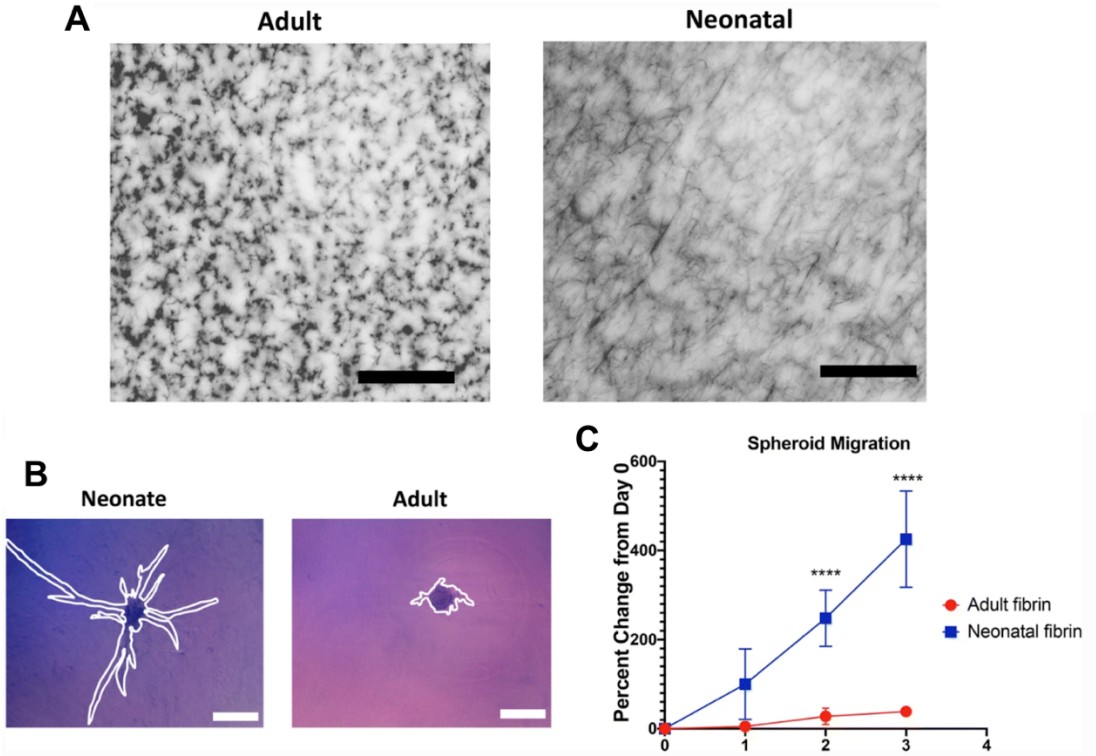

Fig. 4 Critical differences between neonatal and adult fibrinogen scaffolds allows for enhanced cellular migration on bulk neonatal fibrin gels A) Neonatal fibrinogen forms clots with increased porosity and fewer cross branching B) Neonatal fibrin scaffolds enhance fibroblast migrations withing the bulk gel. Figure 4 is reprinted from Nellenbach et al.*[1]* with permission from Elsevier.

The differences in fetal wound healing and adult wound healing can be leveraged to create novel materials that enhance wound healing. Nellenbach et al. developed neonatal fibrin scaffolds to augment wound healing. As compared to adult fibrin, neonatal fibrin networks form more porous structures with low cross branching (**Fig 4**). Fibroblast spheroids embedded between layers of either adult of neonatal fibrin clots exhibited significantly different amounts of migration; cells grown in between bulk neonatal fibrin scaffolds migrated more and at a much faster rate (**Fig 4**). *In vivo*, neonatal fibrin scaffolds promoted wound healing wherein full thickness dermal wounds treated with neonatal fibrin scaffolds had a significantly faster wound healing rate resulting in increasing angiogenesis and thicker epidermal layers, consistent with enhanced wound healing outcomes [1].

Chen et al. studied how scaffold developed from neonatal mouse skin could be used for adult cutaneous wound healing. Acellular dermal matrix scaffolds were sourced from 1-day old and 20-day old mouse skin. The scaffolds were then used to treat full thickness dermal wounds in adult mice. The scaffolds made from the 1-day old mouse show better reepithelization. Additionally, adult mice treated with the 1-day old scaffolds saw a downregulation in TGF- β1 expression, consistent with a fetal wound healing environment. The remodeling phase was also different between he the 1-day old and 20-day old scaffold treatments. Wounds treated with the 1-day old

scaffold induced and increase in collagen III deposition. Overall, the 1-day old scaffolds led to faster healing in an environment similar to a fetal wound healing environment [70].

As another example, neonatal bone marrow has been studied as a source of stem cells to aid in diabetic wound healing. A major complication with diabetes is chronic non-healing wound/ulcers. There has been increased research to develop therapeutics to aid in increasing the wound healing rate for diabetic wounds. Yamada et al. transplanted mesenchymal stem cells (MSC) from porcine neonates onto murine diabetic ulcers. Wounds treated with neonatal MSC as opposed to syngeneic MSCs had a significantly faster wound closure rate. The neonatal MSCs also lead to increase angiogenesis and lymphangiogenesis in the wound site. Additionally, wounds treated with neonatal MSCs had increased expression of VEGF, TGF- β1, and prospero homeobox protein 1 (PROX1), characteristics consistent with fetal wound healing [71]. As demonstrated, fetal derived materials can enhance wound healing even when taken out of the fetal system.

Together, these examples demonstrate the promise of mimicking fetal and neonatal wound healing environments to enhance wound healing outcomes.

Conclusions

There are many differences in growth factors, cytokines, and extracellular matrix components when comparing adult and fetal wound healing. Biomimetic scaffolds that mimic the fetal wound healing process, such as through the use of fetal isoforms of ECM components or delivery of ratios of growth factors that match those seen in the fetal microenvironment, could greatly improve treatment options for chronic non-healing wounds. A few examples of such scaffolds have been described but overall, using the fetal microenvironment as inspiration for pro-healing materials is a vastly untapped opportunity. Many fetal inspired healing materials to date only take into account a single element driving scarless healing. Much work remains to be done to integrate multiple components of scarless wound healing into a single pro-healing material. To develop novel wound healing materials that promote scarless wound healing, it is crucial to understand how the different factors of scarless wound healing work together to create the fetal wound healing environment. Biomaterial scientists and extracellular matrix biologists could consider these opportunities in designing new materials for chronic non-healing wounds.

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Data Sharing Statement

Data sharing not applicable to this review article as no datasets were generated or analyzed during the current study.

Conflict of Interest Statement

Dr. Brown is co-founder of Selsym Biotech, Inc., an NC State affiliated start-up company focused on development of hemostatic materials.

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