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Neurovascular interactions in skin wound healing

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ABSTRACT

Skin wound healing is a complex and dynamic biological process that involves many different cell types, the extracellular matrix, and mediators, such as neuropeptides, growth factors, and cytokines. Similar to diseases of the central nervous system, neurovascular interactions have been shown to play a pivotal role in skin wound healing, for example, as seen in the delayed healing of denervated skin. In aspects involving neurovascular interactions, while angiogenesis is considered important, physiological and pathological roles of these interactions in skin wound healing remain unclear. In this review, we discuss recent findings on neurovascular interactions in skin wound healing, with a particular focus on angiogenesis.

1. Introduction

Skin integrity is required for maintaining homeostasis of the human body. Indeed, major damage to skin integrity from trauma or illness can lead to major disabilities and substantially impair quality of life. Skin wound healing is a complex and dynamic biological process that involves many cell types, the extracellular matrix (ECM), and mediators that interact in a highly refined temporal sequence (Singer and Clark, 1999). Immediately after the skin is wounded, various intra- and intercellular pathways are activated and coordinated in order to restore tissue integrity and homeostasis. This process involves significant changes in gene expression and phenotypes of numerous cell types, including keratinocytes, fibroblasts, peripheral nerve cells, vascular cells, and immune cells, leading to cell proliferation, migration, and differentiation (Gurtner et al., 2008). Although advances in science have deepened our understanding of skin wound healing, the underlying mechanisms are not yet fully understood.

Recent studies have demonstrated that interactions between neural networks and vascular networks play an important role under physiological and pathological conditions, particularly in the context of central nervous system diseases. This review aims to highlight neurovascular interactions in skin wound healing, with a focus on their roles in angiogenesis.

2. Skin wound healing process

Skin wound healing can be divided into three overlapping phases: inflammation, proliferation, and remodeling. None of these phases corresponds to an exactly defined period, and all phases overlap to some extent (Baum and Arpey, 2005).

Inflammation, the first phase of wound healing, occurs immediately after damage to the skin and begins with hemostasis, which is achieved initially by the formation of a platelet plug, followed by fibrin matrix formation (Gurtner et al., 2008). Platelets not only produce a hemostatic plug, but also secrete several mediators, such as platelet-derived growth factor (PDGF), that attract and stimulate fibroblasts and macrophages (Singer and Clark, 1999). Subsequently, neutrophils infiltrate the wound area and remove bacterial degradation products. Monocytes are then recruited to the wound and differentiate into macrophages in response to chemoattractants, such as ECM protein fragments, transforming growth factor beta (TGF-β), and monocyte chemoattractant protein 1 (Singer and Clark, 1999). Macrophages not only remove pathogens and tissue debris, but also secrete a variety of cytokines, chemokines, and growth factors, such as vascular endothelial growth factor (VEGF) and PDGF, initiating the formation of granulation tissue (Gonzalez et al., 2016; Singer and Clark, 1999).

Proliferation, the second phase of wound healing, is characterized by re-epithelialization, granulation tissue formation, and neovascularization. In the early stages of this phase, keratinocytes migrate from the wound edge and skin appendages, such as hair follicles. Keratinocytes contribute to the degradation of collagen and ECM by producing collagenase and plasminogen activator (Bugge et al., 1996; Pilcher et al., 2017). These cells proliferate, mature, and reconstruct the barrier function of the epithelium. Fibroblasts play a leading role in granulation tissue formation. They are recruited to the wound area from the edge of the wound or from the bone marrow and are stimulated by growth factors, particularly TGF-β1 and PDGF secreted by macrophages, leading to the production of ECM that provides a structural

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framework for endothelial cells to generate new vessels in a process referred to as angiogenesis (Profyris et al., 2012). A portion of these fibroblasts differentiate into myofibroblasts, which are contractile cells required for the reconstruction of connective tissue and ECM production during skin wound healing (Hinz, 2007). The high contractile force produced by myofibroblasts is required for physiological wound healing, but can be detrimental to tissue function when it leads to excessive deposition of ECM, resulting in hypertrophic scars and keloids (Hinz, 2007). In order to maintain the newly formed granulation tissue, new blood vessels are essential. Angiogenesis depends on the migration and mitogenic stimulation of endothelial cells as well as appropriate ECM formation. Local changes in the tissue environment, such as hypoxia, increased lactate, and decreased pH, not only reflect poor tissue perfusion but also stimulate angiogenesis by inducing a variety of growth factors and cytokines (Baum and Arpey, 2005). Among these growth factors, fibroblast growth factor (FGF), VEGF, TGF-β1, and angiopoietins are known to play crucial roles in wound angiogenesis (Li et al., 2003).

Remodeling is the third phase of wound repair, and is characterized by scar maturation, which includes degradation and reorganization of ECM. This final phase can continue to develop over a period of weeks, months, or even years. During the remodeling phase, a majority of responsible cells, such as vascular cells, inflammatory cells, and fibroblasts, decrease in number in the wound area due to apoptosis or other unknown mechanisms (Gonzalez et al., 2016). This process is important to ensure completion of normal wound healing and avoid excessive scar formation (Hinz, 2007; Profyris et al., 2012). With ECM maturation, type III collagen is gradually replaced by type I collagen, which increases scar strength. Matrix metalloproteinases secreted by macrophages, endothelial cells, and fibroblasts stimulate this process of collagen replacement (Gurtner et al., 2008).

3. Effects of skin denervation on skin wound healing

Many studies have reported on the effects of nerves and related molecules in the skin wound healing process. In clinical settings, patients with impaired sensory and autonomic innervation, such as those with spina bifida and spinal cord injury, often show impaired wound healing below the level of the spinal cord lesion (Basson and Burney, 1982; Groah et al., 2015; Srivastava, 1995). Moreover, systemic disorders involving neuropathy, such as diabetes, can impair skin wound healing. For example, pressure ulcers in diabetes patients are caused by long-term compression and impaired blood circulation due to sensory loss. However, even with proper depressurization and wound treatment, these ulcers are often intractable and delay wound healing.

Although the reasons underlying the delay in wound healing are unclear, some have suggested the involvement of differences between denervated skin and normal skin in every phase of the wound healing process (Rappl, 2008). For example, transporting molecules important for wound healing (e.g., cytokines and growth factors) is difficult due to reduced blood supply and flow resulting from impairment of the vasomotor pathway of the spinal cord (Bennett et al., 1984; Patterson et al., 1993). This could hinder the inflammation phase of the skin wound healing process. Another potential reason is a reduced amino acid pool and activity of lysyl hydroxylase, an enzyme required for collagen synthesis, in insensitive skin relative to sensitive skin (Claus-Walker et al., 1977; Rodriguez and Claus-Walker, 1988). This could lead to poor quality collagen production, which would be detrimental for the remodeling phase.

In animal models, wound healing is delayed in denervated skin. For example, in a unilateral denervated rat hindlimb model in which the sciatic and saphenous nerves are severed, healing of dry-ice blisters was significantly slower compared to controls (Carr et al., 1993). Moreover, when a full-thickness skin defect was created on the dorsal side, and spinal nerves corresponding to the area of the open wound were divided in rats, wound contraction was significantly delayed (Engin et al., 1996). In yet another study, sensory denervation by capsaicin injection in rats was associated with increased wound surface area and volume resulting from increased mitosis in granulation tissue and decreased apoptosis of wound cells (Smith and Liu, 2002). This enlarged wound surface was observed during the inflammation and proliferation phases in denervated rats, and the contracture process in skin wound healing was also impaired in these rats.

These studies suggest that skin denervation affects every phase of the wound healing process in animal models, as well as in clinical settings. However, the reason underlying the delayed healing of denervated skin remains unclear. According to some sources, direct contact of fibroblasts with neuronal processes is important for their differentiation into myofibroblasts, which secrete collagen fibers and induce wound contraction, leading to wound healing. Thus, the delay of healing in denervated skin may result from insufficient differentiation of fibroblasts, since neuronal processes are diminished due to Wallerian degeneration in denervated skin compared with normal skin (Fujiwara et al., 2013; Liu et al., 1999). Another factor may be reduced neuropeptide secretion from nerve endings, which has been reported to delay wound healing in denervated skin (Engin et al., 1996).

4. Neurovascular interactions in skin wound healing

Although not to the extent observed in recovery from central nervous system diseases, studies have demonstrated the involvement of neurovascular interactions in skin wound healing. Many reports on these neurovascular interactions have focused on neovascularization during the three phases of skin wound healing. This angiogenic process plays a crucial role in wound healing and requires intact endothelial and peripheral nervous systems (Hao et al., 2015). Neovascularization involves three processes—angiogenesis, arteriogenesis, and vasculogenesis. Angiogenesis involves capillary sprouting or splitting from preexisting blood vessels. Arteriogenesis refers to the enlargement of preexisting smaller vessels through vascular remodeling or collateral growth. Vasculogenesis involves *de novo* formation of blood vessels from the migration and differentiation of angiogenic progenitor cells. Vasculogenesis was previously thought to occur only during fetal development, but recent evidence suggests it can also occur after birth, although the extent of its involvement in skin wound healing is unclear (Bauer et al., 2005).

Angiogenesis is regulated by a balance between inducers and inhibitors, and requires a tip in the balance toward inducers in order to occur. Various types of molecules, such as cytokines and neurotrophic factors, participate in angiogenesis during skin wound healing. The regulation of angiogenesis during this process is very complicated, with main regulatory factors differing based on the site and timing of angiogenesis. There are also differences in regulatory factors involved in physiological and pathological angiogenesis (Iruela-Arispe and Dvorak, 1997).

Previous studies have hinted at the involvement of a complex network of mediators, such as neuropeptides, growth factors, and cytokines, in the regulation of skin wound healing. We next focus the discussion on the effects of these molecules on vascular tissue during skin wound healing.

5. Neuropeptides

5.1. Substance P (SP)

SP (an 11-amino acid peptide), neurokinin A (NKA), and neurokinin B, all of which are structurally related peptides belonging to the tachykinin family, bind to G-protein coupled receptors called neurokinin receptors (NK-1, NK-2, and NK-3) (Severini et al., 2002). SP is found throughout the central and peripheral nervous systems, including skin (Schäffer et al., 1998). It is produced in the dorsal root ganglion, and distributed centrally to the dorsal horn of the spinal cord and peripherally to the nerve endings of sensory neurons in the dermis and epidermis (Ashrafi et al., 2016; Schäffer et al., 1998).

SP impacts the wound healing process in many ways. For example, exogenous administration of SP can accelerate skin wound healing in animal models (Delgado et al., 2005; Khalil and Helme, 1996). The actions of SP are regulated mainly through high affinity binding to the NK-1 receptor, which is expressed not only in neurons, but also in keratinocytes, fibroblasts, endothelial cells, smooth muscle cells, and various types of immune cells (Schäffer et al., 1998). In rats depleted of sensory neuropeptides by treatment with capsaicin, it was suggested that the inhibition of peripheral neuropeptide release into the wound might delay wound closure induced by morphine and was related to reduced NK-1 receptor expression in inflammatory and parenchymal cells (Rook et al., 2009).

SP also exerts various effects on neurovascular interactions in skin wound healing. For instance, SP can stimulate vasodilation, vascular permeability, and plasma extravasation (Hughes et al., 1990). SP can also promote endothelial cell proliferation, migration, and differentiation into capillary-like structures, leading to angiogenesis (Wiedermann et al., 1996; Ziche et al., 1994). Most of these effects of SP may involve nitric oxide in endothelial cells.

SP acts as an immunoregulator by stimulating the activity of inflammatory cells, such as lymphocytes, monocytes, macrophages, and mast cells, and modulating the synthesis and release of multiple proinflammatory cytokines, including interleukins and tumor necrosis factor-α, which are important in the inflammation phase of wound healing and may contribute to angiogenic or anti-angiogenic effects (Ashrafi et al., 2016; Luger and Lotti, 1998; O'Connor et al., 2004). SP also enhances wound closure by promoting the proliferation of endothelial cells, keratinocytes, and fibroblasts, which play essential roles in the proliferation phase of wound healing (Muangman et al., 2009; Tanaka et al., 1988; Ziche et al., 1990a; Ziche et al., 1994). Moreover, SP regulates the activity of matrix metalloproteinases and increases collagen remodeling during skin wound healing (Fong et al., 2013).

5.2. Neurokinin a (NKA)

NKA (also known as substance K), a 10-amino acid peptide, is a member of the tachykinin family and its biological activities are closely related to those of SP (Chéret et al., 2013). In wound healing, NKA stimulates the proliferation of fibroblasts, and NKA released from peripheral neurons has been suggested to not only contribute to inflammatory responses, but also act as a mitogen by stimulating the proliferation of connective tissue cells (Nilsson et al., 1985). NKA exhibits angiogenic activity in microvascular endothelial cells of human bone marrow (Pelletier et al., 2002). However, several studies have also found that NKA and a NK-2 receptor agonist had no significant angiogenic effect on human or bovine endothelial cells (Haegerstrand et al., 1990; Ziche et al.,1990b). Therefore, NKA may either exert its angiogenic effect specifically in marrow microvascular endothelial cells, or its angiogenic effect might be modulated only by stromal cells (Pelletier et al., 2002). NKA and SP can both directly induce the expression of nerve growth factor (NGF) mRNA and secretion of NGF protein in human and murine keratinocytes, leading to various effects on skin wound healing (Burbach et al., 2001).

5.3. Calcitonin gene-related peptide (CGRP)

CGRP is one of the most abundant neuropeptides in the body and has various effects on skin wound healing. CGRP is a 37-amino acid peptide that is widely expressed in neuronal tissue, including peripheral sensory nerves with extensive perivascular localization (Russell et al., 2014). There are two major CGRP isoforms, α-CGRP and β-CGRP, which have similar structures and biological activities but are synthesized from two distinct genes at different chromosomal sites in humans. α-CGRP is predominantly distributed in the central and peripheral nervous systems, whereas β-CGRP was considered to be found mainly in the nervous system of the intestinal tract, but now is known to be released alongside α-CGRP in the vascular system (Russell et al., 2014). The effects of CGRP are mediated through high affinity interactions with a heterodimeric receptor consisting of calcitonin receptor-like receptor and receptor activity modifying protein 1, which is expressed in epidermal cells such as keratinocytes and melanocytes (Hara et al., 1996; Hou et al., 2011).

In rats, intraperitoneal and intradermal injections of CGRP promote wound healing by increasing the rate of wound contraction in normal but not denervated areas. This suggests that the trophic effect of CGRP depends on the integrity of the neural supply related to the axonal transfer of CGRP (Chéret et al., 2013; Engin, 1998). CGRP promotes the proliferation and migration of keratinocytes, resulting in re-epithelialization, proliferation, adherence, and differentiation of fibroblasts into myofibroblasts, thereby promoting granulation tissue remodeling (Chéret et al., 2014; Seike et al., 2002). CGRP also increases the enzymatic activities of matrix metalloproteinases and affects collagen remodeling (Chéret et al., 2014).

In terms of neurovascular interactions, one of the prominent effects of CGRP on skin wound healing is the stimulation of angiogenesis by enhancing the proliferation of endothelial cells (Haegerstrand et al., 1990; Mapp et al., 2012). CGRP is a more potent vasodilator than most prostaglandins and other vasodilators such as SP (Russell et al., 2014). CGRP has been reported to selectively relax arterial contractions induced by endothelin-1 (Meens et al., 2009), which is involved in pulmonary hypertension and organ fibrogenesis including excessive scar formation (Kiya et al., 2017). CGRP stimulates microvascular permeability and edema formation induced by neuropeptides such as SP and NKA, which are co-released with CGRP from sensory neurons in the skin (Scholzen et al., 1998). CGRP is also involved in immune responses. For example, c-fiber-derived CGRP can stimulate human dermal microvascular endothelial cells to secrete interleukin 8 (IL-8), which is a neutrophil chemotactic factor and facilitates their vascular transmigration (Ansel et al., 1997; Chéret et al., 2013).

5.4. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP)

VIP and PACAP are members of a superfamily of structurally related peptides including glucagon, secretin, and growth hormone-releasing hormone, and act through the same family of receptors, which are widely distributed in the central and peripheral nervous systems (Harmar et al., 2012). VIP immunoreactivity is observed in nerve fibers near dermal arteries, capillaries, sweat glands, apocrine glands, meibomian glands, and hair follicles in the skin (Chéret et al., 2013).

Many studies have reported the proliferation and migration of keratinocytes during skin wound healing, leading to re-epithelialization via an adenosine 3′,5′-cyclic monophosphate (cAMP) dependent pathway (Haegerstrand et al., 1989). Keratinocyte proliferation has been shown to result from the paracrine activity of VIP and autocrine activity of PACAP (Granoth et al., 2000). The N-terminal portion of VIP is required for VIP-induced migration (Wollina et al., 1997). In addition, VIP may be involved in reinnervation of wound tissue in a manner similar to NGF, since it has been shown to enhance sciatic nerve regeneration in rats after transection (Rayan et al., 1995). Similar to SP and CGRP, VIP promotes the release of NGF and inflammatory cytokines, such as IL-1α and IL-8, in keratinocytes, and affects collagen remodeling during skin wound healing by modulating matrix metalloproteinase activity (Chéret et al., 2014; Dallos et al., 2006).

In terms of neurovascular interactions, VIP exerts angiogenic effects both *in vitro* and *in vivo* by promoting VEGF production through the extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen activated protein kinase (MAPK) signaling pathway, particularly in skin keratinocytes (Collado et al., 2007; Yang et al., 2009; Yu et al., 2010). Both VIP and PACAP induce vasodilatation, but different mechanisms may underlie the vasodilatory effects of these two peptides in different regions, such as cerebral and coronary vessels (Dalsgaard et al., 2003).

6. Growth factors

6.1. Vascular endothelial growth factor (VEGF)

Among growth factors, VEGF is one of the most potent and extensively studied stimulators of angiogenesis in the wound healing process. VEGF was originally identified as a vascular permeability factor (VPF), and subsequently found to act as a mediator of angiogenesis and promote endothelial cell functions, such as migration, proliferation, and differentiation (Johnson and Wilgus, 2014). Most early studies on the effects of VEGF in skin wound healing focused mainly on endothelial cells. However, recent studies have shown that VEGF can influence cell types other than endothelial cells, such as inflammatory cells and fibroblasts, and play an important role in multiple aspects of wound healing (Johnson and Wilgus, 2014).

VEGF is released from various cells, such as macrophages, vascular smooth muscle cells, and fibroblasts, and is predominantly secreted by keratinocytes during skin wound healing (Greaves et al., 2013). VEGF secreted by keratinocytes was initially thought to stimulate endothelial cells in the dermis in a paracrine fashion, but studies have now shown that VEGF can directly act on keratinocytes to regulate their proliferation, migration, and survival (Brown et al., 1992; Johnson and Wilgus, 2014). VEGF expression is also regulated by many other cytokines, as well as hypoxia (Greaves et al., 2013; Johnson and Wilgus, 2014).

Little evidence exists in terms of whether the influence of VEGF's angiogenic activity during skin wound healing involves the peripheral nervous system around the wound. However, in embryonic mouse limb skin, VEGF derived from peripheral nerves has been reported to promote arterial differentiation *in vitro* and *in vivo* (Mukouyama et al., 2005, 2002), and the expression of VEGF has been confirmed in neurons, astrocytes, and Schwann cells (Eichler et al., 2004; Taurone et al., 2015). This suggests the possibility that neural tissue-derived VEGF is involved in skin wound healing.

6.2. Fibroblast growth factor (FGF)

The FGF family plays a crucial role in multiple aspects of wound repair, including angiogenesis in skin wound healing. Among FGF family members, FGF-2, FGF-7, and FGF-10 are thought to be the most important in skin wound healing (Barrientos et al., 2008). FGF-2 participates in granulation tissue formation by regulating the synthesis and deposition of various ECM components, re-epithelialization by increasing keratinocyte motility, and tissue remodeling by stimulating the migration of fibroblasts and promoting them to produce collagenase (Barrientos et al., 2008; Powers et al., 2000). Indeed, recombinant basic FGF is one of the few growth factors used to treat refractory ulcers and has been shown to be effective in clinical settings.

Many reports have been published on FGFs and FGF receptors in endothelial cells and their involvement in angiogenesis during wound healing. FGFs exert their angiogenic activity by interacting with multiple endothelial cell surface receptors, including heparan-sulfate proteoglycans, tyrosine kinase receptors, and integrins (Presta et al., 2005). For example, FGF-2 promotes endothelial cell migration by inducing the expression of integrin $\alpha v\beta 3$ on the surface of endothelial cells, thereby recruiting matrix metalloproteinase (MMP)-2 to the cell surface, which leads to collagen degradation and endothelial cell migration (Brooks et al., 1996; Sepp et al., 1994). The pro-angiogenic activity of FGFs is exerted in close association with various cytokines and growth factors, including VEGF (Presta et al., 2005). FGFs are produced by various cells involved in skin wound healing, such as keratinocytes, fibroblasts, and endothelial cells. FGF-2 is also expressed in cultured Schwann cells (Duobles et al., 2008), raising the possibility that some FGFs involved in skin wound healing may be derived from nervous system tissue.

6.3. Transforming growth factor-β (TGF-β)

TGF-β is a member of the structurally related but functionally distinct TGF-β superfamily, which also includes members such as bone morphogenic proteins and activins. In mammals, TGF-β has three isoforms (TGF-β1, -β2, -β3) which are secreted as inactive latent precursors that are modified in the extracellular space. These proteins exhibit overlapping functions mainly via the downstream intracellular SMAD pathway. It is widely accepted that TGF-β not only plays a crucial role in normal development and physiology, but also is associated with the pathogenesis of many diseases such as connective tissue disorders, fibrosis, and cancer.

In skin wound healing, TGF-β, especially TGF-β1, is a key regulator of various processes such as inflammation, re-epithelialization, fibroblast proliferation and differentiation, ECM synthesis, and remodeling. In addition, TGF-β is associated with angiogenesis in skin wound healing, although conflicting reports exist regarding its *in vitro* and *in vivo* angiogenic effects. While *in vivo* studies have shown that TGF-β stimulates angiogenesis (Roberts et al., 1986; Roesel and Nanney, 1995; Yang and Moses, 1990), *in vitro* studies have shown that it inhibits endothelial cell proliferation (Baird and Durkin, 1986; Fràter-Schröder et al., 1986; Heimark et al., 1986). This discrepancy may result, in part, because TGF-β exerts its angiogenic effect by recruiting monocytes and inducing them to express angiogenic factors such as TNFα *in vivo* (Wiseman et al., 1988). Another possible reason is that changes in the matrix environment could regulate the expression of TGF-β receptors on endothelial cells, thereby altering the effect of TGF-β on these cells (Sankar et al., 1996).

TGF-β is widely expressed throughout the body, and the presence of its receptors has been confirmed in most cells. In skin wound healing, the major cellular sources of TGF-β are considered to be platelets, macrophages, keratinocytes, and fibroblasts (Barrientos et al., 2008). TGF-β is also produced in the nervous system, for example, in Schwann cells (Einheber et al., 1995; Ridley et al., 1989). Although TGF-β produced by Schwann cells reportedly plays a role in nerve injury and regeneration (Sulaiman and Nguyen, 2016), it may also influence skin wound healing in combination with TGF-β produced by other cell types.

6.4. Nerve growth factor (NGF)

NGF is one of the most well-known neurotrophins, which are essential for the survival, differentiation, and functioning of the central and peripheral nervous systems. NGF is produced by many cell types in the nervous system, immune and inflammatory systems, and various tissues including the skin (Sofroniew et al., 2001). NGF has various effects in distinct phases of skin wound healing and may be useful for treating skin ulcers. In a human case study, pressure ulcers treated with topical NGF showed more rapid healing compared to ulcers in cases that received only conventional topical treatment (Aloe, 2004; Bernabei et al., 1999). In addition, chronic vasculitic leg ulcers with poor curative tendency in patients affected by long-term rheumatoid arthritis rapidly healed upon topical application of NGF (Tuveri et al., 2000).

Molecular mechanisms of NGF-mediated acceleration of wound healing are not fully understood. However, its promotion of skin wound healing might be attributed to the acceleration of keratinocyte proliferation and promotion of angiogenesis (Matsuda et al., 1998; Tuveri et al., 2000; Wilkinson et al., 1994). With regard to its angiogenic effect, NGF injection has been shown to increase capillary and arteriole density and decrease apoptosis of endothelial cells and myofibers in ischemic limbs of mice, possibly via a VEGF-Akt−NO−dependent mechanism (Emanueli et al., 2002).

Although NGF is expressed by several cell types in skin tissue, such as keratinocytes, smooth muscle cells, adipocytes, and fibroblasts, the effects of wounding on NGF expression differ by cell type (Hasan et al., 2000). Interestingly, cell types that express NGF also express α-SMA, a widely used myofibroblast marker. Staining for both markers increases after wounding, suggesting that NGF synthesis and myofibroblast differentiation are regulated in a coordinated fashion (Hasan et al., 2000). NGF also has various immunological effects on activating mast cells, which play a key role in wound healing by secreting various cytokines and growth factors (Kawamoto and Matsuda, 2004).

7. Sympathetic nerves

Skin contains a rich supply of sympathetic nerves. According to various reports, these nerves are involved in skin wound healing, including angiogenesis. Dopamine (DA), an endogenous inhibitor of angiogenesis, inhibits VEGF/VPF-mediated microvascular permeability, proliferation, and migration of endothelial cells via D2 receptors by inhibiting the phosphorylation of VEGF receptor 2, focal adhesion kinase, and mitogen-activated protein kinase (Basu et al., 2001; Sarkar et al., 2004). Consistent with this, a D2 receptor antagonist was shown to accelerate skin wound healing in mice by inducing angiogenesis (Shome et al., 2011). There are also reports that in cancer cells, catecholamines such as norepinephrine and epinephrine enhance the production of proangiogenic factors such as VEGF, thereby promoting angiogenesis and tumor progression (Lutgendorf et al., 2003; Yang et al., 2006).

Regarding effects other than angiogenesis, an α1-agonist was shown to stimulate cell migration and production of several cytokines, including TGF-β1 and insulin-like growth factor-1, in human fibroblasts (Liao et al., 2014). In addition, β2-adrenergic receptor activates a Src-dependent pro-migratory pathway and a PKA-dependent pro-proliferative pathway in dermal fibroblasts (Pullar and Isseroff, 2006). In contrast, a β-adrenergic receptor antagonist was shown to promote human keratinocyte migration and re-epithelialization in a chronic wound healing model (Pullar et al., 2006).

8. Conclusions

Skin wound healing is a complex process involving hemostasis, inflammation, re-epithelialization, new tissue formation, and tissue remodeling. During this dynamic biological process, the nervous system plays a crucial role, as is evident by the delayed skin wound healing in clinical and experimental studies of denervated skin. Many neuropeptides, growth factors, and cytokines that are derived from or can be derived from nervous system tissue stimulate and/or regulate various events in skin wound healing. Among these events, angiogenesis is important for proper wound healing and is greatly affected by neurovascular interactions, the focus of this review. However, few reports have been published on neurovascular interactions in skin wound healing compared to other central nervous system diseases, and many unclear points remain. A better understanding of the mechanisms underlying neurovascular interactions in skin wound healing will contribute to the identification of new therapeutic targets and improve patient care.

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