Chapter 1
Antimicrobial Peptides in Cutaneous Wound Healing

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Abstract Injury that breached the physical skin barrier increases the likelihood of infection. The wound healing process is divided into hemostasis, inflammation, proliferation, and tissue remodeling. Antimicrobial peptides play a major role for the antimicrobial defense at all these stages in wound healing, but the main sources of antimicrobial peptides vary with the different stages of wound healing coming from plasma proteins, neutrophils, and keratinocytes. Apart from being part of the antimicrobial defense, antimicrobial peptides play other important roles in wound healing as in angiogenesis, attraction of leukocytes, resolution of inflammation, and proliferation. Future studies will demonstrate whether antimicrobial peptides can be used therapeutically to improve the wound healing processes and reduce scar formation in chronic wounds.

1.1 Introduction

The intact skin constitutes a very efficient physical barrier toward surrounding microbes. Indeed, skin infections are rarely found in intact healthy skin. However, injury or wounding causes breach in the physical barrier of the skin increasing the likelihood of infections. Keeping the wound free of overt infection is a prerogative for successful wound healing (Edwards and Harding 2004). Indeed, chronic non-healing cutaneous wounds are most often infected with *Staphylococcus aureus* or *Pseudomonas aeruginosa* (Edwards and Harding 2004). Antimicrobial peptides (AMPs) play a major role for the antimicrobial defense during wound healing. Indeed, studies of the remarkable ability of the African frog *Xenopus laevis* to keep its wounds free of infections under non-sterile conditions led to the first identification of antimicrobial peptides (AMPs) from the skin (Zasloff 1987).

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Wound healing following injury is traditionally divided into four stages: (1) hemostasis, (2) inflammation, (3) proliferation, and (4) tissue remodeling (Singer and Clark 1999). AMPs are found at all stages of wound healing; however, the sources of AMPs are different at each of these stages of wound healing.

1.2 Generation of AMPs at the Different Stages of Wound Healing

1.2.1 Injury

Injury by itself leads to generation of AMPs. In frog skin, the injury-induced nervous stimulation leads to release of antimicrobial peptides from skin glands (Simmaco et al. 1998). Though similar mechanisms have not been described in mammals, injury does lead to activation of proteases that release membrane-bound growth factor like HB-EGF and amphiregulin that possess antimicrobial activity (Malmsten et al. 2007). Furthermore, these growth factors play a major role as inducers of the epidermal AMP expression at later stages in the wound healing process (Sørensen et al. 2006, 2008; Roupé et al. 2010). Surely, tissue injury may generate additional AMPs but a systematic study of antimicrobial peptides released by tissue injury is still to come.

1.2.2 Hemostasis

After injury, there is extravasation of plasma proteins into the wound with activation of complement and coagulation cascades. Activation of the complement system leads to generation of fragments of C3a with antimicrobial activity (Nordahl et al. 2004; Sonesson et al. 2007; Pasupuleti et al. 2007). The coagulation cascade is one of the principal host defenses in insects and activation of the human coagulation cascade leads to cleavage of several proteins like kininogen, fibrinogen, and thrombin involved in the coagulation cascade, which leads to generation of several antimicrobial peptides (Frick et al. 2006; Påhlman et al. 2013; Papareddy et al. 2010). Thrombin knockout mice have increased susceptibility to infection with *Staphylococcus aureus* infection in their limited life span (Mullins et al. 2009), which may indicate an important role of the thrombin-derived AMPs.

1.2.3 Inflammation

After hemostasis follows influx of neutrophils followed by monocytes and lymphocytes to the wounds in the inflammatory stage of wound healing (Singer and Clark 1999). Neutrophils contain large amounts of antimicrobial peptides (Levy 1996;

Borregaard and Cowland 1997; Borregaard et al. 2007) important for the microbicidal activity of these cells (Flannagan et al. 2009). During the inflammatory phase, the major AMPs present in the wound will be derived from the neutrophils. The AMPs in neutrophils are found both in neutrophil granules and cytosol (Levy 1996; Borregaard and Cowland 1997). Neutrophils even produce an AMP like elafin after migration to the skin (Theilgaard-Mönch et al. 2004); however, the main antimicrobial peptides found in neutrophils are the α-defensins (HNPs) in azurophil granules (Ganz et al. 1985), cathelicidins in specific granules (Sørensen et al. 1997), and calgranulins (S100A8/S100A9) in the cytosol (Hessian et al. 1993).

The main antimicrobial activity of neutrophil defensins is exerted in the neutrophil phagolysosome (Joiner et al. 1989), but neutrophil defensins are also secreted to the exterior (Ganz 1987; Faurschou et al. 2002). Apart from their direct antibacterial and antiviral activity (Ganz et al. 1985; Daher et al. 1986), defensins also boost bacterial phagocytosis by macrophages (Soehnlein et al. 2008a). Neutrophil defensins have other functions of importance in wound healing. Human neutrophil defensins have chemotactic activity toward monocytes (Territo et al. 1989), T cells (Chertov et al. 1996), and immature dendritic cells (Yang et al. 2000a). Furthermore, these peptides are mitogenic for epithelial cells and fibroblasts (Murphy et al. 1993). Neutrophil defensins do not seem to have a nonredundant function in wound healing since mice neutrophils lack defensins (Eisenhauer and Lehrer 1992).

The cathelicidins present in specific granules (or large granules in rudiments) are stored as inactive proteins in the granules and the biological function is unleashed following extracellular cleavage with serine proteases from azurophil granules (Zanetti 2004). In porcine and bovine neutrophils, the cathelicidins are processed by elastase (Panyutich et al. 1997; Scocchi et al. 1992) while proteinase 3 is responsible for the processing of the human cathelicidin hCAP-18 to the antimicrobial peptide LL-37 (Sørensen et al. 2001), a peptide with broad-spectrum antimicrobial activity (Turner et al. 1998). The elastase-mediated processing porcine cathelicidins has been shown to be important for clearance of bacteria from wounds (Cole et al. 2001). Cathelicidins have other important functions in wound healing, both in the recruitment of mononuclear cells and in the tissue regeneration. It has long be recognized that neutrophils play a major role for the subsequent recruitment of monocytes (Ward 1968), and it has now been recognized that LL-37 plays a role for the recruitment of monocytes (Soehnlein et al. 2008b). Indeed, LL-37 has been shown to be a chemotactic factor toward monocytes as well as T cells and neutrophils (Yang et al. 2000b). Porcine and murine cathelicidins have importance for angiogenesis (Li et al. 2000; Koczulla et al. 2003) and both the porcine PR-39 and the human LL-37 induce expression of VEGF (Rodriguez-Martinez et al. 2008). Furthermore, treatment of wounds with the gene delivery of the human cathelicidin LL-37 promotes wound healing (Jacobsen et al. 2005; Steinstraesser et al. 2014; Carretero et al. 2008). Transactivation of the epidermal growth factor (EGFR) occurs in cutaneous wound healing (Tokumaru et al. 2000) and LL-37 has been shown to cause EGFR transactivation (Tjabringa et al. 2003) and thereby induce keratinocyte migration (Tokumaru et al. 2005). Furthermore, LL-37 suppresses both keratinocyte and neutrophil apoptosis (Chamorro et al. 2009; Nagaoka et al. 2006).

S100A8/S100A9 constitutes 40 % neutrophil cytosolic protein (Edgeworth et al. 1991) and is a potent antifungal agent (Steinbakk et al. 1990). In wounds, neutrophil-derived S100A8/S100A9 is probably released from dying neutrophils or from neutrophil extracellular traps (NETs) and contributes to killing of *Candida albicans* (Urban et al. 2009). Apart from the direct antifungal effect, S100A9 enhances microbicidal activity of neutrophils by enhancing phagocytosis (Simard et al. 2011) and S100A8/S100A9 is important for neutrophil accumulation in response to LPS (Vandal et al. 2003) and induces neutrophil chemotaxis and adhesion (Ryckman et al. 2003). S100A8/S100A9 mediates proinflammatory activities mediated by binding to TLR-4 (Vogl et al. 2007) or the receptor for advanced glycation end products (RAGE) (Hofmann et al. 1999). Additionally, calgranulins have functions that may limit tissue damage or are anti-inflammatory. S100A8/S100A9 is very sensitive to oxidation (Raftery et al. 2001; Lim et al. 2008) and may, thus, act as oxidant scavenger. S100A8 induces expression of the anti-inflammatory cytokine IL-10 and protects against tissue injury (Hiroshima et al. 2014) and may, thus, play a role in resolution of inflammation.

1.2.4 Proliferative Phase

As the inflammatory cells recede from the wound, the epidermal keratinocytes become a major source for AMPs during the proliferative phase of wound healing. While non-injured epidermis contains constitutively expressed AMPs like hBD-1 and RNase 7, the expression of many AMPs is induced during wound healing and inflammation. Indeed, many AMPs like hBD-2, hBD-3, RNase 7, and psoriasin were originally isolated from inflamed epidermis (Gläser et al. 2005; Harder et al. 1997, 2001; Harder and Schröder 2002). Though some epidermal expression of the human cathelicidin hCAP-18/LL-37 may also be found in the inflammatory stage of wound healing (Dorschner et al. 2001), the peak expression of epidermal AMPs is found during the proliferative phase of wound healing (Roupé et al. 2010). The AMPs with increased epidermal expression during the proliferative phase of wound healing include hBD-2 (Schmid et al. 2001), hBD-3 (Sørensen et al. 2006), psoriasin (S100A7) (Lee and Eckert 2007), S100A8/S100A9 (Thorey et al. 2001), S100A15 (Roupé et al. 2010), elafin (vanBergen et al. 1996), SLPI (Schmid et al. 2001; Wingens et al. 1998), lactoferrin (Roupé et al. 2010), midkine (Frick et al. 2011), and NGAL (Sørensen et al. 2006). Since the various defensins arise from a common ancestral gene (Bevins et al. 1996), it is remarkable that neutrophils and keratinocytes share many of the same AMPs and antimicrobial proteins (see Table 1.1); however, the AMPs in keratinocytes are induced only during wound healing and inflammation while the AMPs in neutrophils are synthesized during normal neutrophil differentiation in the bone barrow (Borregaard et al. 2005). However, this means that the antimicrobial proteins and peptides are present in the wound over and extended time, though the cellular source varies.

Table 1.1 Antimicrobial peptides and proteins present in both neutrophils and keratinocytes

AMPs in neutrophils and keratinocytes	
Neutrophils	Keratinocytes
Azurophil granules	
α-defensins (HNP-1-4)	β-defensins (hBD-1-3)
Lysozyme	Lysozyme
Specific and gelatinase granules	
Lactoferrin, NGAL, hCAP-18/LL-37	Lactoferrin, NGAL, hCAP-18/LL-37
Transcobalamin, SLPI, lysozyme	Transcobalamin, SLPI, lysozyme
Cytosol	
Calgranulins (S100A8/S100A9)	Calgranulins (S100A8/S100A9)
Produced following extravasation	
Elafin	Elafin
	Keratinocyte AMPs not present in neutrophils
	Psoriasin, RNase7, S100A15

Since α- and β-defensins arise from an ancestral gene, it is remarkable how many other antimicrobial peptides and proteins found in keratinocytes are also found in neutrophils. See text for references

The expression of some AMPs during wound healing is dependent on inflammation, i.e., cytokines from infiltrating inflammatory cells as in the case of the IL-1-dependent hBD-2 expression (Liu et al. 2003; Sørensen et al. 2005). However, the expression of other AMPs, like hBD-3, is induced by the injury-induced EGFR activation in epidermal keratinocytes, even in the absence of inflammatory cells (Sørensen et al. 2006; Roupé et al. 2010), thus directly linking growth and tissue regeneration with AMP expression. Deficiency in the injury-induced hBD-3 expression has been linked to the severity of skin infections and nasal carriage of *S. aureus* (Zanger et al. 2010, 2011; Nurjadi et al. 2013). Additionally, many AMPs like S100A8/S100A9, SLPI, and NGAL are induced both by injury-induced GFR activation and proinflammatory cytokines (Roupé et al. 2010; Mork et al. 2003; Sørensen et al. 2003; Liang et al. 2006).

Though AMP expression mainly is induced during wound healing and inflammation, inflammatory stimuli seem to downregulate the expression of certain AMPs during wound healing. The antimicrobial chemokine CXCL14 is normally expressed in the epidermis (Maerki et al. 2009) but downregulated during wound healing and inflammation (Frick et al. 2011; Maerki et al. 2009). Likewise, RNase 7 protects healthy skin from *Staphylococcus aureus* infection (Simanski et al. 2010). The expression of RNase 7 is induced both by IFN-γ/IL-17 (Simanski et al. 2013) and significantly by EGFR activation in injured skin *ex vivo* (Wanke et al. 2011). Though RNase 7 is significantly induced through EGFR activation in injured skin *ex vivo*, the expression level of RNase 7 is the same in skin wounds *in vivo* as in non-injured skin (Roupé et al. 2010) indicating that some inflammatory mediators may downregulate the injury-induced RNase 7 expression.

The epidermal AMPs induced by wound healing generate a broad spectrum on antibacterial activity, e.g., hBD-3 against *S. aureus* and *S. pyogenes* (Harder et al. 2001), psoriasin against *E. coli* (Gläser et al. 2005), and calgranulins against *C. albicans* (Steinbakk et al. 1990). Though, for example, psoriasin has been implicated in defense against *E. coli* (Gläser et al. 2005) and hBD-3 and RNase 7 against *S. aureus* (Zanger et al. 2010; Simanski et al. 2010), the appearance of AMPs during the proliferative phase of wound healing raises the question of whether these peptides may play additional roles beyond antimicrobial defense of the wound. Notably, some AMPs seem to remain intracellular or cell associated while other AMPs are secreted. hBD-2 is readily secreted into the medium from multilayer epidermal keratinocyte cell cultures (Sørensen et al. 2005), while hBD-3 remains cell associated, both in multilayer epidermal keratinocytes cell cultures (Sørensen et al. 2005) and in whole epidermis (Sørensen et al. 2006). Though, the antimicrobial S100A proteins psoriasin (S100A7), calgranulins (S100A8/S100A9), and S100A15 are cytosolic, at least psoriasin is also found extracellularly (Gläser et al. 2005). For AMPs to interact with other cells, the AMPs must – at least partially – be found extracellularly.

Numerous cytokine-line functions have been attributed to hBD-2. hBD-2 activates dendritic cells through TLR-4 (Biragyn et al. 2002) and is a chemoattractant toward immature dendritic cells and memory T cells through CCR6 (Yang et al. 1999) and toward neutrophils, monocytes, and macrophages through CCR2 (Röhrl et al. 2010). hBD-2 has been found to promote intestinal wound healing *in vitro* (Otte et al. 2008) and stimulate proliferation, migration, and cytokine production of epidermal keratinocytes (Niyonsaba et al. 2007).

Likewise, non-antimicrobial functions have been attributed to hBD-3 including chemoattractant properties (Röhrl et al. 2010), antagonism of CXCR4 (Feng et al. 2006), and activation of mast cells with increase of vascular permeability (Chen et al. 2007). However, the fact that hBD-3 appears to remain cell associated in the skin (Sørensen et al. 2005 2006) questions whether these functions play a major role during wound healing.

The non-antimicrobial functions of psoriasin include chemotactic activity toward T lymphocytes and neutrophils (Jinquan et al. 1996) mediated by binding to RAGE (Wolf et al. 2008). This also promotes proliferation of endothelial cells (Shubbar et al. 2012). Psoriasin induces VEGF (Shubbar et al. 2012) and the expression of keratinocyte differentiation markers (Hattori et al. 2014) as wells as strengthens the tight junction barrier in the skin (Hattori et al. 2014).

Though SLPI (secretory leukocyte protease inhibitor) is also found in neutrophils, keratinocytes are the major source of SLPI in wound healing (Jacobsen et al. 2008). SLPI is found to be secreted both in multilayer epidermal keratinocytes cell culture (Sørensen et al. 2003) and whole epidermis (Sørensen et al. 2006). SLPI has antimicrobial activity against bacteria (Hiemstra et al. 1996), fungi (Tomee et al. 1997), and HIV-1 (McNeely et al. 1995). During wound healing, the secreted SLPI has nonredundant functions (Ashcroft et al. 2000) by inhibiting the elastase-mediated cleavage the epithelial growth factor proepithelin to the growth-inhibitory epithelin (Zhu et al. 2002).

1.2.5 Tissue Remodeling Phase

Tissue remodeling in cutaneous wound healing involves increased expression of collagen VI (Betz et al. 1993) that has antimicrobial activity (Abdillahi et al. 2012). Interestingly, collagen VI expression in fibroblasts is induced by neutrophil defensins (Li et al. 2006). The regulation of expression of antimicrobial proteins and peptides in the underlying connective tissue of skin will likely receive more interest after the finding that the normal skin microbiome extends to the connective tissue (Nakatsuji et al. 2013).

1.2.6 Chronic Wounds

Though many studies demonstrate how microbial products induce AMP expression in keratinocytes mainly through TLR activation (Abtin et al. 2008; Büchau et al. 2007, 2008; Li et al. 2013; Nagy et al. 2005; Gariboldi et al. 2008; Gerstel et al. 2009; Liu et al. 2002), the possible significance of this in acute wound healing in noninfected wounds is not clear. The bacteria-induced AMP expression may be more important in chronic wounds with infections (Edwards and Harding 2004). Furthermore, in this instance, the bacterial proteases could play contradictory roles, either by induction of AMP expression through protease-activated receptors (Chung et al. 2004) or by AMP degradation (Schmidtchen et al. 2002). Chronic wounds like chronic venous ulcers are characterized by chronic inflammation with continuous recruitment of inflammatory cells, and indeed neutrophil AMPs like neutrophils defensins are found in high amounts (Lundqvist et al. 2008). The epidermal expression of hBD-2 and psoriasin is induced in chronic venous ulcers (Butmarc et al. 2004; Dressel et al. 2010), while the expression of LL-37 is decreased (Heilborn et al. 2003). In diabetic wounds, the high glucose levels may suppress the expression of both hBD-2 (Lan et al. 2012) and hBD-3 (Lan et al. 2011) in keratinocytes. To understand the role of AMPs in chronic wound pathology or chronic wound infections, more detailed studies are needed to delineate the AMP expression in different types of chronic wounds and how this is related to wound infection or underlying disease such as diabetes.

1.3 Concluding Remarks and Future Perspective

AMPs provide part of the antimicrobial defense during wound healing. Topical application of antimicrobials do not improve normal wound healing (Lipsky and Hoey 2009), demonstrating adequate antimicrobial defenses. While the AMPs originating from the coagulation and complement cascades, the neutrophils, and epidermal keratinocytes undoubtedly contribute to the antimicrobial defense in the

wound healing process, it is difficult to decipher the role of individual AMPs due to overlapping antimicrobial activities. Apart from SLPI (Ashcroft et al. 2000), no AMP has been demonstrated to possess nonredundant functions during wound healing.

Though mice models provide useful insight, it is important to note that differences exist between humans and mice – also when it comes to both wound healing and AMPs. Wound contractions are important for wound healing in rodents such as mice, but not in humans (Davidson 1998). Neutrophils and keratinocytes are major sources of AMPs during wound healing, but mice have far fewer neutrophils than humans (Mestas and Hughes 2004) and the mouse epidermis contains far fewer keratinocytes than human epidermis. Accordingly, though no directly comparative studies exist, it seems reasonable that the mouse wounds will contain fewer AMPs than human wounds. There will also be qualitative difference in the AMPs. The mouse contains many more different β-defensins than humans (Schutte et al. 2002), while there will be no neutrophil α-defensins in mouse wounds (Eisenhauer and Lehrer 1992). The neutrophil α-defensins play a role for the antimicrobial function of the neutrophils (Sørensen et al. 2014), and this will undoubtedly be important for the antimicrobial defense also in wounds.

While even infected wounds only in some instances benefit from topical treatment with antibiotics (Lipsky and Hoey 2009), gene delivery of AMPs has been found to have beneficial effects for wound healing (Jacobsen et al. 2005; Steinstraesser et al. 2014; Carretero et al. 2008). This clearly indicates that AMPs have beneficial effects in wound healing beyond its antimicrobial properties. AMPs are generated at all stages of wound healing and it does seem like AMPs participate in the regulation of some aspects of the wound healing processes, for instance, LL-37 plays a role for recruitment of monocytes (Soehnlein et al. 2008b). Resolution of inflammation is now recognized as a regulated process (Serhan and Savill 2005; Ortega-Gomez et al. 2013), and in wounds, AMPs may play an important role here. Dying and necrotic neutrophils are anti-inflammatory due to the release of neutrophil defensins (Miles et al. 2009) and calgranulin S100A8, which induce the anti-inflammatory cytokine IL-10. Later, IL-10 may play a role for downregulation of AMP expression in keratinocytes (Howell et al. 2005). Both defensins and LL-37 promote proliferation of keratinocytes (Niyonsaba et al. 2007; Heilborn et al. 2003). Accordingly, AMPs may play a role for inflammation, resolution of inflammation, and proliferation during wound healing. One of the paradoxes of psoriasis, a disease with very prominent AMP expression (Harder and Schröder 2005), is the lack of scarring following the chronic inflammation (Nickoloff et al. 2006). Future studies will further address the role of AMPs for regulation of the wound healing process and scar formation. This will hopefully pave the way for new treatment modalities for chronic wounds and wound infection.

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