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AMP-lification of wound healing

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Cutaneous wound healing is a highly complex biological process. The main goal of wound healing is to re-establish skin homeostasis and integrity and the "multi-level" cutaneous barrier functions (e.g. physico-chemical, immunological, biological). The physiological, regenerative-rejuvenating wound healing procedure contains mainly four major phases: the inflammatory, the proliferative, the granulation tissue formation and the tissue remodeling stages (1,s1). Traditional models for wound healing mainly emphasized the "almost exclusive" roles of inflammatory skin cells in skin repair. However, recent models (such as e.g. the 'seed versus soil' and ''dynamic reciprocity' ones) more comprehensively review the process, and propose that proper wound healing is not possible without the multi-directional communication of multiple skin cell populations and their interactions with a plethora of components of the extracellular environment (including e.g. matrix elements, intercellular communication mediators, cytokines, oxygen tension, mechanical shear forces, etc.) (2-3, s2-3). It can be proposed, therefore, that physiological skin repair involves practically all cellular and humoral elements of skin homeostasis.

In a recently published issue of *Experimental Dermatology*, Mangoni *et al* contribute to our understanding of the skin repair process by providing an excellent, comprehensive and up-to-date review on the roles of antimicrobial peptides (AMPs) as endogenous mediators of skin wound healing (4). Originally, AMPs (among which over two thousands were described in various species) were introduced as part of the innate immune system and members of the host-defense arsenal of the organism. As such, they play "unnoticeable housekeeping" roles to control unwanted microbial proliferation at epithelial surfaces (s4-5).

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Indeed, in human skin, several epithelial cell types (epidermal keratinocytes, sebaceous and eccrine sweat gland cells) constitutively produce multiple AMPs (e.g. RNases, psoriasin, β-defensins [hBDs], dermcidin, LL-37) which collectively control microbial growth (s6-7). Moreover, upon cutaneous inflammation/infection, AMPs can be strongly induced, either directly by invading microbes and their released products or by co-upregulated cytokines and growth factors. Interestingly, induction of AMPs takes place preferentially in the more outwards located epidermal layers whereas cytokine induction tends to occur primarily in the lower parts of the epidermis (5-6). This may facilitate the rapid encounter of invading microbes with AMPs.

In addition to their direct antimicrobial properties, AMPs exhibit diverse immunomodulatory functions (e.g. chemotactic activity, cytokine induction, induction of cell differentiation and proliferation as well as putative involvement in several skin diseases), making them important and versatile players in host defense (7-8, s8-9). Thus, it is not surprising that AMPs seem to play also an important role in wound healing.

The review of Mangoni *et al* (4) highlights that AMPs not only act as fist-line humoral guardians and "signal transducers" of the wound healing process towards certain skin cells, but can also directly promote skin repair mechanism. Indeed, multiple AMPs were implicated as endogenous regulators in one or more of the four phases of cutaneous wound healing (4). For example, hBD-3 (and, in part, hBD-2) induces cytokine/growth factor release (inflammatory phase) and promotes growth of epidermal keratinocytes as well as chemo-attraction of macrophages (proliferative phase); furthermore, hBD-3 also is also implicated in the resolution of inflammation after termination of tissue remodeling (s10-11). Likewise, LL-37 not only stimulates migration/proliferation of cutaneous epithelial and mesenchymal cell types (proliferative phase), but also promotes neovascularization and angiogenesis (granulation tissue formation phase) (s12). Finally, certain AMPs can activate collagen synthesis and extracellular matrix remodeling, and are involved in neutralizing bacterial lipopolysaccharide (reviewed in 4).

The above findings are translationally relevant: several ongoing human clinical trials are currently aiming at defining the therapeutic potential of AMP-based pharmaceuticals in skin wound healing. Indeed, in Phase III trials against chronically infected wounds, topical pexiganan (a synthetic analog of the natural AMP, magainin) exerted similar beneficial effect as orally applied ofloxacin; however, in contrast to the oral antibiotic, pexiganan did not promote the colonization of resistant bacteria on the wounds and was associated with fewer adverse effects (s13). Likewise, in a prospective trial involving a small number of patients, application of LL-37 (which is diminished in chronic wounds) also promoted wound healing in chronic leg ulcers (s14).

The current elegant review of Mangoni *et al* (4) raises numerous open questions which need to be addressed in future studies. A few of these exciting themes are as follows:

- It is now widely accepted that different skin regions (e.g. dry, moist, greasy) harbor markedly diverse communities of the commensal microbiota. Therefore, in order to better understand the roles of AMPs in wound healing and in skin biology in general, it should be determined whether "site-specific" and/or "microbiota-specific" AMP patterns exist and, if yes, what functional characteristics could be attributed to these differential configurations.

- As skin aging is accompanied by marked changes in both skin functions and skin microbiota, and, furthermore, wound healing rate and efficacy markedly decrease with age, it is also important to study the role of AMPs in cutaneous aging.
- In relation to the above, it should also be revealed how the "forward and reverse" microbiota-AMP signaling events contribute to the formation, integrity, and regeneration of the complex skin barrier, and hence wound repair.
- Likewise, it is necessary to further assess whether the altered expression patterns of AMPs, identified in lesional (and non-lesional) psoriatic and atopic skin and wounds, may have a causative, pathognomic role in the development of these (and possibly other) dermatoses.
- Evidently, it is also highly desired to uncover whether the wound healing-promoting actions of AMPs (found in either pre-clinical or clinical settings) are mainly due to their obvious anti-microbial effects and/or to their direct effects on cellular and humoral components of the cutaneous wound healing machinery.
- An alternative approach to be assessed is the strategy to facilitate wound healing by the application of AMP-inducers. For example, thrombocyte concentrate lysates induce the expression of AMPs in wounded skin. This may contribute to the reported beneficial effects of thrombocyte concentrate lysates for the healing of chronic and infected wounds (9).
- Finally, to facilitate the design of optimal AMP-based pharmaceuticals, the exact mechanisms of action of the selected AMPs (which, as suggested by numerous *in vitro* studies, exhibit quite "promiscuous polypharmacology") should be defined.

Taken together, one can postulate that AMPs might become integral components of future dermatologic practice in the management of chronic (mostly infected) wounds, whose prevalence is ever-increasing thus constituting a major health care burden and socioeconomic challenge. Yet, as highlighted by the authors (4), future studies should also carefully address the potential risks of (long-term) AMP application, as these interventions might interfere with homeostatic innate immune defenses and the commensal microbiota of the human skin.

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TB and JH wrote the paper.

Conflict of interest
The authors declare no conflicts of interest.

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