Dynamic regulation of the wound repair process: achieving one-stop scar-free repair

*Min Wang, Xianwen Wang**

School of Biomedical Engineering, Research and Engineering Center of Biomedical Materials, Anhui Medical University, Hefei, Anhui Province, China

***Corresponding author:**
Xianwen Wang,
xianwenwang@ahmu.edu.cn.

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At present, the clinical treatment of chronic refractory wounds still faces many challenges: on the one hand, the delivery efficiency of therapeutic drugs is seriously affected by physiological barriers such as bacterial membranes; on the other hand, how to dynamically deliver appropriate drugs at different stages of wound healing is also an important factor affecting wound healing.[1] The wound healing process is strictly controlled by many types of cells and is associated with cell migration and proliferation, extracellular matrix deposition, and tissue remodelling, which mainly include four dynamically overlapping and mutually differentiated stages: haemostasis, inflammation, proliferation, and remodelling.[2] Bacterial infection is an important factor in chronic wound healing, and the regulation of the immune microenvironment is the key factor in promoting the gradual process of wound healing.[3] However, immune regulatory dysfunction may lead to the occurrence of chronic wounds and arrest the healing process in the inflammatory phase. Notably, an early persistent inflammatory response leads to insufficient skin function and scar formation. The four stages of wound healing occur in a cascade that is step-by-step, highly coordinated and interacts with each other. Therefore, the programmed regulation of the chronic wound microenvironment at different repair stages may solve the bottleneck of clinical treatment.

In *Nature Communications*, Zhang et al.[4] designed a core-shell structured microneedle (MN) with programmed functions that can programmatically regulate wound healing and can dynamically adjust the wound immune microenvironment according to different healing stages to accelerate the healing speed of chronic wounds and improve the quality of wound repair (**Figure 1**). In this study, MN patches with reactive oxygen species (ROS)-responsive shells and immunoregulatory functional cores were designed to dynamically regulate inflammation, proliferation, and remodelling. Research teams have verified in mouse and rabbit models that the patch can not only promote wound healing but also promote scar-free repair of the wound.

MN with programmed function is composed of a ROS-responsive polyvinyl alcohol shell and a photo-crosslinked heparin core, while the photosensitizer verteporfin is loaded on the shell. In the early stage of wound appearance, MN s can effectively penetrate the bacterial biofilm formed by chronic wounds, and verteporfin loaded in the shell can produce ROS under laser irradiation to inhibit the bacterial biofilm. After entering the inflammatory phase, the MN shell can gradually degrade in the wound environment with high ROS levels, and heparin, which has a negative charge inside the MN, can be exposed to neutralise various pro-inflammatory factors to promote the transition of the wound from the inflammatory phase to the proliferative phase. In addition, the released verteporfin can inhibit scar formation by preventing the activation of the *Engrailed-1* gene in fibroblasts.

Cytokine delivery, implantation of natural or synthetic scaffolds, and cell therapy have been studied for treating chronic wounds by targeting the inflammatory microenvironment around the wound.[5,6] However, it is hampered by the natural skin barrier system. Bacterial infection and the formation of bacterial biofilms in wounds can further exacerbate inflammation, but conventional antibiotics often cannot eliminate biofilms produced by drug-resistant bacteria (such as methicillin-resistant *Staphylococcus aureus*), resulting in a sustained inflammatory response and delayed healing.[7] Photodynamic therapy has become a promising strategy for treating bacterial infections by producing highly toxic ROS, but its antibacterial efficacy is limited by the limited penetration of biofilms. Polymeric MNs, as effective tools for transdermal drug delivery through stratum corneum perforation, have been used in the diagnosis and treatment

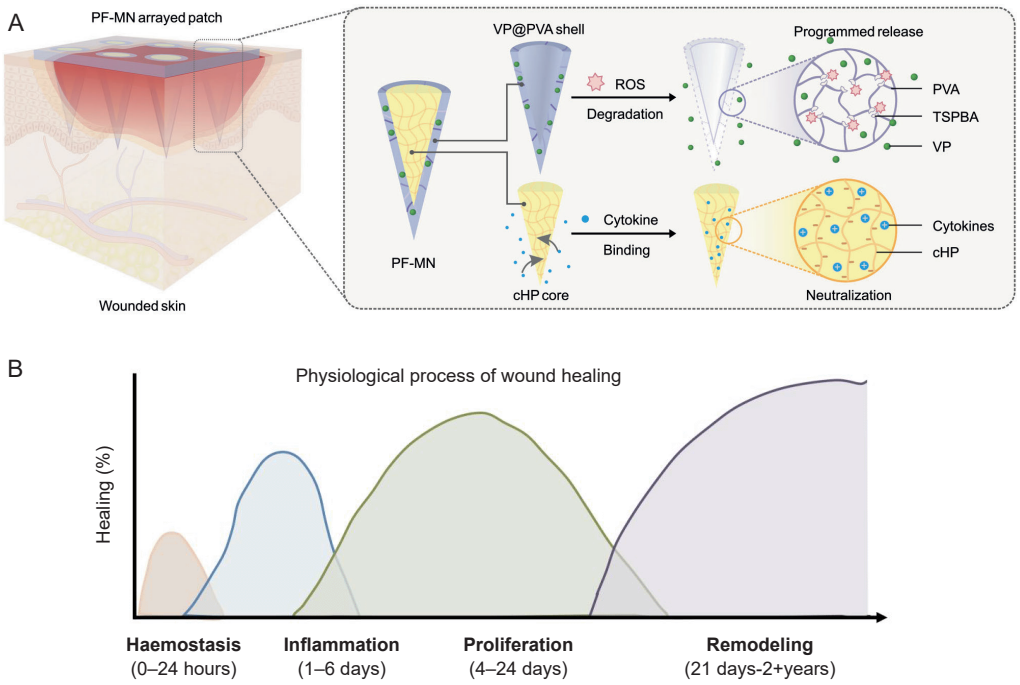

Figure 1. (A) Schematic illustration of the structure of PF-MNs. Reprinted from Zhang et al.[4] (B) Schematic illustration of the physiological process of wound healing (including haemostasis, inflammation, proliferation, and remodelling stages). Created with Microsoft PowerPoint. cHP: crosslinked heparin; PF-MN: microneedle with programmed functions; PVA: poly (vinyl alcohol); ROS: reactive oxygen species; TSPBA: N^1-(4-boronobenzyl)-N^5-(4-boronophenyl)-N^1,N^1,N^3,N^3-tetramethylpropane-1,3-diaminium; VP: verteporfin.

of a variety of diseases. However, most MNs inhibit bacterial infection only by enabling the controlled release of therapeutic drugs, and the dynamic program of the immune microenvironment corresponding to different healing stages has not been explored. Zhang et al.[4] developed a technique for programmed regulation of chronic wound healing and achieved scar-free wound healing by dynamically regulating the wound immune environment. This technology provides a new approach to the dynamic regulation of the microenvironment with physiological/pathological changes to achieve tissue repair and provides a new strategy for the clinical treatment of chronic refractory wounds.

However, the regulation of the wound immune microenvironment in this study involved the neutralisation of various proinflammatory factors through heparin, which has a negative charge within the MNs and has not yet been shown to be involved in the regulation of important immune cells involved in wound healing and the impact on innate and acquired immunity.[6] In the process of wound healing, immune cells such as neutrophils and macrophages are necessary to support the subsequent stage of skin reconstruction after injury, and it is necessary to develop a repair system with key immune cells such as macrophages for acute and chronic wound repair.[8] In addition, the study is still in the laboratory stage and has not been widely validated in clinical practice. Although the experimental results showed good effectiveness, further clinical trials are needed to evaluate the effectiveness, safety, and long-term tolerability of the stent. Only after sufficient verification can we determine its feasibility and effectiveness in clinical application.

Author contributions
MW conceived and wrote the draft, and XWW reviewed and edited the draft. Both authors approved the final version of the manuscript.
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Conflicts of interest statement
The authors declare no conflicts of interest.

1. Mu, R.; Campos de Souza, S.; Liao, Z.; Dong, L.; Wang, C. Reprograming the immune niche for skin tissue regeneration - From cellular mechanisms to biomaterials applications. *Adv Drug Deliv Rev.* **2022**, *185*, 114298.
2. Sun, B. K.; Siprashvili, Z.; Khavari, P. A. Advances in skin grafting and treatment of cutaneous wounds. *Science.* **2014**, *346*, 941-945.
3. Opdenakker, G.; Van Damme, J.; Vranckx, J. J. Immunomodulation as rescue for chronic atonic skin wounds. *Trends Immunol.* **2018**, *39*, 341-354.

4. Zhang, Y.; Wang, S.; Yang, Y.; Zhao, S.; You, J.; Wang, J.; Cai, J.; Wang, H.; Wang, J.; Zhang, W.; Yu, J.; Han, C.; Zhang, Y.; Gu, Z. Scarless wound healing programmed by core-shell microneedles. *Nat Commun.* **2023**, *14*, 3431.
5. Patil, P.; Russo, K. A.; McCune, J. T.; Pollins, A. C.; Cottam, M. A.; Dollinger, B. R.; DeJulius, C. R.; Gupta, M. K.; D'Arcy, R.; Colazo, J. M.; Yu, F.; Bezold, M. G.; Martin, J. R.; Cardwell, N. L.; Davidson, J. M.; Thompson, C. M.; Barbul, A.; Hasty, A. H.; Guelcher, S. A.; Duvall, C. L. Reactive oxygen species-degradable polythioketal urethane foam dressings to promote porcine skin wound repair. *Sci Transl Med.* **2022**, *14*, eabm6586.
6. Griffin, D. R.; Archang, M. M.; Kuan, C. H.; Weaver, W. M.; Weinstein, J. S.; Feng, A. C.; Ruccia, A.; Sideris, E.; Ragkousis, V.; Koh, J.; Plikus, M. V.; Di Carlo, D.; Segura, T.; Scumpia, P. O. Activating an adaptive immune response from a hydrogel scaffold imparts regenerative wound healing. *Nat Mater.* **2021**, *20*, 560-569.
7. Dieltjens, L.; Appermans, K.; Lissens, M.; Lories, B.; Kim, W.; Van der Eycken, E. V.; Foster, K. R.; Steenackers, H. P. Inhibiting bacterial cooperation is an evolutionarily robust anti-biofilm strategy. *Nat Commun.* **2020**, *11*, 107.
8. Sharifiaghdam, M.; Shaabani, E.; Faridi-Majidi, R.; De Smedt, S. C.; Braeckmans, K.; Fraire, J. C. Macrophages as a therapeutic target to promote diabetic wound healing. *Mol Ther.* **2022**, *30*, 2891-2908.

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