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Role of Schwann cells in cutaneous wound healing

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Abstract

Dermal wound healing is the process of repairing and remodeling skin following injury. Delayed or aberrant cutaneous healing pose a challenge for the health-care system. The lack of detailed understanding of cellular and molecular mechanisms involved in this process hamper the development of effective targeted treatments. In a recent study, Parfejevs and colleagues, by using state-of-the-art technologies, including *in vivo* sophisticated Cre/loxP techniques in combination with a mouse model of excisional cutaneous wounding, reveal that Schwann cells induce adult dermal wound healing. Strikingly, genetic ablation of Schwann cells delays wound contraction and closure, decreases myofibroblast formation, and impairs skin re-epithelization after injury. From a drug development perspective, Schwann cells are a new cellular candidate to be activated to accelerate skin healing. Here, we summarize and evaluate recent advances in the understanding of Schwann cells roles in the skin microenvironment.

Keywords

Schwann cells; skin; wound; healing; microenvironment

INTRODUCTION

Skin, cutis, is the largest organ of the human organism. It serves as the main boundary between the surroundings and the internal tissues (1). The skin maintains favorable visceral physiologic conditions by providing an equilibrium between liquid intake and loss,

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regulating the concentration of electrolytes, as well as controlling heat loss (2). The cutaneous tissue also shields internal organs from external harm provoked by diversified physical, chemical, and infectious agents (3). Wounds in the skin induced by burns, traumas, and chronic disorders are a major public health problem affecting millions, and resulting in the impairment of life quality, and in prolonged hospitalization period, which culminate in considerable health costs (4, 5).

Skin wound healing is a complicated and dynamic biological process with the aim of restoring the cutaneous' barrier role. It comprises distinct yet overlapping well-coordinated and highly regulated sequence of events, which include clot formation, inflammation, tissue remodeling, new tissue formation, and revascularization (6, 7). Cutaneous repair occurs with an intricate cascade of interactions between cells present in the skin microenvironment, extracellular matrix proteins, and growth factors (8). A wide range of strategies have been developed for accelerating wound closure in skin lesions based on what we know so far about cutaneous healing (9). Deciphering the details of cellular and molecular mechanisms involved in dermal restoration is central in skin research. Discovering key cells and the underlying mechanisms participating in wound healing will create novel therapeutic strategies for skin repair. In particular, how stromal cells associated with the peripheral nervous system, Schwann cells, contribute to the skin recovery after lesion is not entirely clear. These cells are defined by their intimate relationship with peripheral axons throughout life (10, 11).

Now, in a recent article in *Nature Communications*, Parfejevs and colleagues reveal that Schwann cells contribute to adult dermal wound healing (12). The authors examined the role of Schwann cells in the injured skin by using elegant state-of-the-art techniques, including *in vivo* sophisticated Cre/loxP techniques in combination with a mouse model of excisional cutaneous wounding. *In vivo* lineage-tracing technologies to track specifically Schwann cells (Plp-CreER/tdTomato and Dhh-Cre/tdTomato mice) demonstrated that, after dermal lesion, endogenous Schwann cells disseminated from the disrupted peripheral nerves into the granulation tissue of the wounded skin, de-differentiated, and proliferated (12) (Figure 1). Strikingly, specific genetic ablation of Schwann cells, by using Plp-CreER/Sox10 floxed mice, delayed wound contraction and closure, decreased myofibroblasts formation, and impaired re-epithelization in the affected skin. Interestingly, conditional activation and expansion of Schwann cells, by Pten inactivation, triggered TGFβ signaling, and enhanced myofibroblasts generation. Additionally, by co-cultures of Schwann cells with fibroblasts, Parfejevs and colleagues suggested that Schwann cells promote differentiation into myofibroblasts via paracrine activation of transforming growth factor β (TGFβ) signaling. Although this work identifies a novel role for cutaneous Schwann cells, which could be used as a therapeutic target to improve dermal wound healing, some major questions still remain unanswered. For example, since TGFβ signaling is one of the main molecules orchestrating the wound healing process, it remains to be evaluated whether Schwann cells and/or their secreted molecules activate TGF-β signaling *in vivo*. Moreover, which myofibroblasts precursors are activated in the skin healing microenvironment, since Schwann cells do not differentiate into myofibroblasts? Or in which cell types important for the post-cutaneous injury scenario are Schwann cells differentiating?

Here, we discuss the findings from this study, and evaluate recent advances and unresolved questions in our understanding of the role of Schwann cells in the cutaneous microenvironment.

PERSPECTIVES / FUTURE DIRECTIONS ORIGIN OF MYOFIBROBLASTS IN THE SKIN HEALING

Dermal wound closure is accompanied by skin contraction and the creation of scar tissue, that is defined by vigorous fibrous tissue deposition, which in excess may lead to cutaneous debilitating pathologies (13). The lack of detailed knowledge about the biological mechanisms involved in dermal fibrosis limits the success of clinical applications. The key cell producing fibrous tissue through extracellular matrix deposition is the myofibroblast (14). Understanding which cells generate cutaneous myofibroblasts is essential, as gaining control of those cells will allow the arrestment, or even the reversion of fibrosis production (15). This has been the focus of extensive basic research with the goal to improve the design of targeted anti-fibrotic therapies. Although the biological processes underlying fibrosis formation in the skin are not fully understood, multiple cell types have been suggested as the generators of myofibroblasts, including resident fibroblasts (16), epithelial cells (17), circulating progenitor cells (18), pericytes (19–23), and endothelial cells (24, 25). Parfejevs and colleagues demonstrated that Schwann cells do not differentiate into myofibroblasts in the adult skin during healing (12). However, since cell-to-cell communications may play positive roles during fibrous tissue deposition, it will be interesting to investigate which cells capable of originating myofibroblasts are activated during skin healing by Schwann cells to form matrix-producing cells, and how.

SCHWANN CELLS DERIVED SIGNALS IMPORTANT AFTER CUTANEOUS INJURY

Schwann cells release multiple bioactive molecules able to regulate behavior, proliferation and migration of other cellular populations (26–28). Therefore, Schwann cells may induce a reparative and regenerative milieu in the skin after lesion.

TGFβ signaling is one of the main pathways orchestrating wound healing, resulting in the secretion of extracellular matrix components (29). Parfejevs and colleagues show that *in vivo* genetically induced expansion of injury-activated Schwann cells induce myofibroblast appearance in the dermal wound via TGFβ signaling (12). The authors demonstrated that *in vitro* activated Schwann cells co-cultured with dermal fibroblasts also induced myofibroblast differentiation via TGFβ signaling (12). Nevertheless, it remains to be evaluated whether Schwann cells activates TGFβ signaling in dermal fibroblasts also *in vivo*. Also, it remains unsolved whether TGFβ itself is directly provided by injury-activated Schwann cells, and which molecules secreted by Schwann cells are important for this pathway activation. Schwann cells may produce activated TGFβ in other tissues (28), however whether they produce this molecule in the lesioned skin *in vivo* is still unknown. Additionally, whether Schwann cell-derived TGFβ is important for wound closure remains to be studied. TGFβ has not been yet conditionally deleted from cutaneous Schwann cells or from other possible

sources in the skin, so there is no direct evidence that Schwann cells are the main/only functionally important source of TGFβ for myofibroblast differentiation. Transgenic mouse models have been widely applied to explore the roles of different cell populations within tissues-microenvironments. The ability, not only to ablate cells, but also to delete single genes in specific cell types in adult mice has allowed us to answer specific questions regarding the roles of distinct cell populations in the regulation of several physiologic and pathologic processes. The exact molecular mechanisms involved in cutaneous myofibroblast differentiation *in vivo* are yet unclear, and will need to be revealed in future works. The crossing of TGFβ floxed mice (30) with Schwann cell-specific inducible CreER drivers, such as PlpCreER, will allow us to specifically delete TGFβ in Schwann cells *in vivo*. In addition to studies in transgenic mice, transcriptomic and single Schwann cell analysis represent fundamental tools that will help us understand the role of Schwann cells in the skin microenvironment.

Platelet-derived growth factor β (PDGFβ) / Platelet-derived growth factor receptor β (PDGFRβ) signaling regulates events critical to fibrous tissue deposition. Activation of this pathway stimulates matrix-producing cells activation, migration, and proliferation (31). Parfejevs and colleagues exhibit that Schwann cells upregulate the expression of PDGFβ after dermal lesion (12). Interestingly, several stromal cells present in the skin microenvironment, important in wound healing progress, express the cell-surface tyrosine kinase receptor, PDGFRβ, such as pericytes (32–45), vascular smooth muscle cells (46, 47), and tissue-resident fibroblasts (48). Therefore, PDGFβ/PDGFRβ signaling may play crucial role in the communication between these important cell types during dermal healing. Future studies should explore the role of this pathway after injury in the skin. Importantly, inhibitors of this pathway, including sunitinib and imatinib have been proposed as anti-cancer drugs (49–51), and are Food and Drug Administration (FDA) approved (52).

SCHWANN CELLS PLASTICITY IN THE SKIN

Schwann cells were until recently considered cells committed exclusively to the glial fate. Surprisingly, recent elegant studies indicated that, in specific conditions, Schwann cells may also behave as stem cells forming other cell populations as well. Schwann cells have the ability to differentiate into melanocytes (53), chromaffin cells (11, 54), odontoblasts (55), endoneural fibroblasts (56), parasympathetic (57, 58) and enteric neurons (59). Due to this multipotency, Schwann cells could be potential targets for tissue repair and regenerative medicine. Although Parfejevs and colleagues determined that Schwann cells do not form myofibroblasts during skin healing (12), it remains to be studied whether dermal Schwann cells have the ability to differentiate into other cell types important post-cutaneous injury. Genetic fate-tracing mouse models should be explored further for assessing Schwann cell plasticity *in vivo* in the skin.

The decisions of stem cells to continue quiescent, self-renew or differentiate are dependent on the interaction of these cells with other cells in their surrounding niches (60–68). Recently, multiple cell types have been identified as potential niche-supporting cells for stem cells in the skin (69). Nevertheless, how the composition of the cutaneous stem cell niche is affected during skin healing remains poorly understood. Schwann cells have been shown to

be essential components of the stem cell niche in the bone marrow (28, 70–76). Whether Schwann cells maintain dermal stem cells as well remains unknown. Interestingly, a recent study has revealed that osteoactivin is essential to activate mesenchymal stem cells in the skin, accelerating healing (77, 78). Future studies should explore whether dermal Schwann cells upregulate osteoactivin after lesion, and whether they contribute to endogenous activation of mesenchymal stem cells.

THE SKIN MICROENVIRONMENT

The skin involves an intricate microenvironment which contains, in addition to Schwann cells, several other types of stromal cells, immune cells (79, 80), innervations (11, 81), and extracellular matrix proteins. This complex mixture of cells cooperate to perform the necessary roles for the skin functioning, and the interplay between the distinct cellular components will define the dermal outcomes in distinct pathophysiological circumstances. Deciphering the individual and combinatorial signals that influence skin healing will help develop effective therapeutic interventions. Thus, what is the cross-talk between distinct Schwann cells involved in skin healing and other skin microenvironment cells remains to be examined. For instance, future studies are required to evaluate the importance of Schwann cell' interactions with immune cells in skin healing. Further insights into the cellular and molecular processes involved in wound healing will have important implications for our understanding of skin homeostasis and disease.

SCHWANN CELLS' HETEROGENEITY

Schwann cells are heterogeneous. They have been shown to be subdivided into subpopulations (10). Parfejevs and colleagues, in their study, consider Schwann cells as a homogeneous cell population (12). Schwann cells line nerve projections, protecting them and facilitating their survival. The skin is a richly innervated organ, with a variety of nerve fibers, including sensory and autonomic axons, influencing a multitude of physiological and pathophysiological cutaneous functions (82). It remains to be studied whether Schwann cells that support distinct types of nerve fibers also present differences in their behavior during dermal healing. The heterogeneity of Schwann cells in the skin should be defined in future studies. Therefore, it still needs to be evaluated whether cutaneous Schwann cells correspond to a homogeneous cell population or not. Are Schwann cells associate with sensory nerves the same cells as the ones attached to sympathetic fibers? Future research shall examine whether particular Schwann cell phenotypes relate to a precise behaviors after cutaneous lesion. The presence of dermal Schwann cells not expressing Plp, as well as their role in skin microenvironment, should be explored in future studies. Additionally, Schwann cells are subdivided in myelinating, associated with motor neurons, and non-myelinating Schwann cells. Future studies will need to reveal whether both myelinating, from sciatic nerves, and non-myelinating Schwann cells migrate to the wound *in vivo* after dermal injury. Also, it will be interesting to explore whether a subset of Schwann cells that participate in wound healing migrate from outside the skin.

CLINICAL RELEVANCE

Millions suffer with non-healing wounds around the world (83). Various disorders are characterized by poor skin healing, including skin atrophy, deformity, neuropathy, anaemia, microvascular disease, local factors, or the toxic effects of drugs used in therapy. Parfejevs and colleagues demonstrated that Schwann cells' activation improved dermal wound healing (12). It will be interesting to explore whether Schwann cells could be also used as a cell therapy for skin healing. These results suggest that Schwann cell transplantation may improve wound closure. Moreover, wound restoration is important in multiple organs, and the healing process varies among distinct tissues. As Schwann cells are present in multiple tissues, are Schwann cells important for healing in other organs as well?

Although skin healing mouse model aims to recreate features of human wound after lesion, wound healing in mice may differ from the one in humans (84). Considering the peculiarity of each specie is essential to interpret the data correctly. Albeit the use of human patients have several limitations, such as ethical issues, logistical problems, and patient variability with regards to the extent and duration of the lesion, the combined use of different tools will reduce the limitations of each technique. Therefore, future analyses of human skin Schwann cells should reveal the translatability of this important Schwann cells novel role.

CONCLUSION

The study by Parfejevs and colleagues reveals a new important role of Schwann cells in the skin. Nevertheless, our understanding of dermal Schwann cell biology still remains limited, and future studies should shed light on the complexity and interactions of different cellular components of the cutaneous microenvironment during wound healing. A great challenge for the future will be to translate the research from mouse models into human patients. How human Schwann cells contribute to different stages of dermal wound healing remains to be determined. Improving the availability of human tissue samples will be essential to reach this goal.

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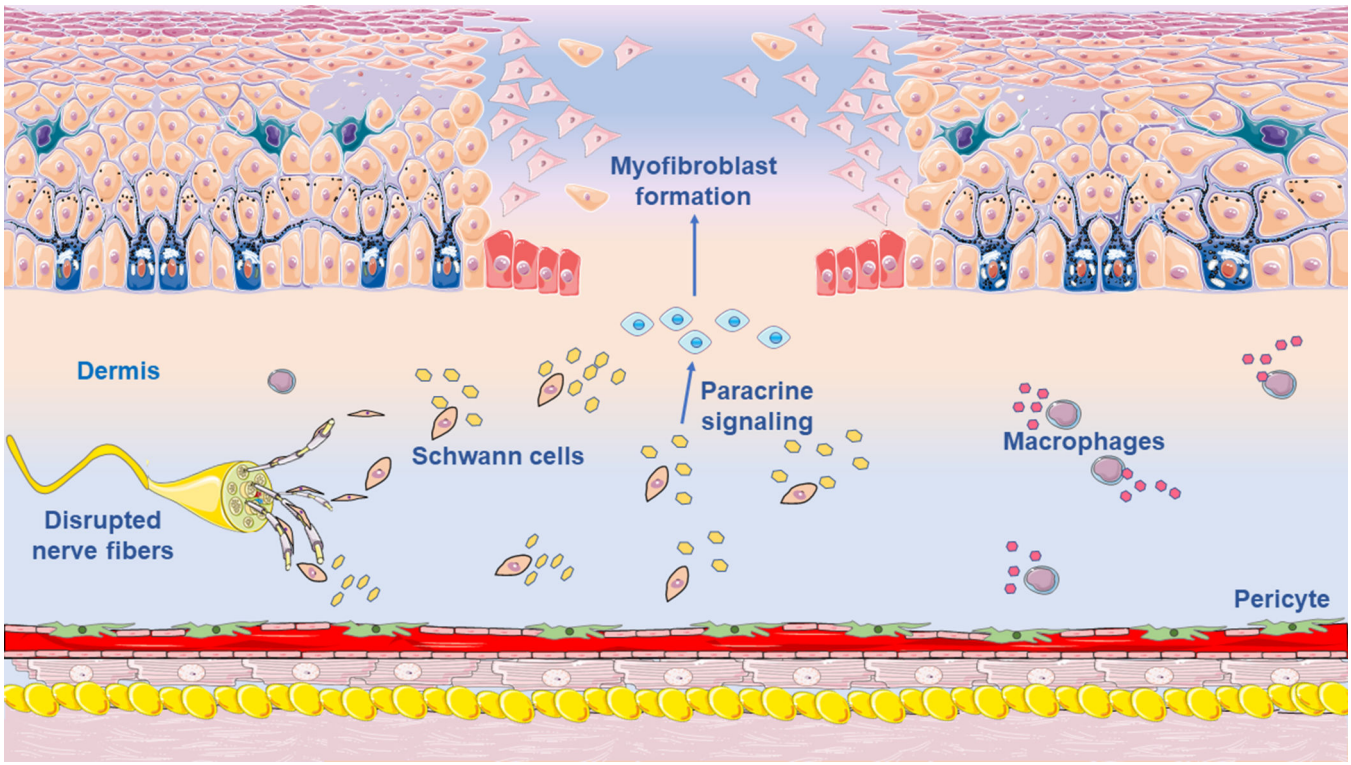

Figure 1. Skin lesion activates Schwann cells to induce wound healing.

Cutaneous healing involves the cell-to-cell cross-talk between several cell types. Deciphering the cellular and molecular mechanisms that drive the wound closure is a central question in regenerative medicine. Parfejevs and colleagues now show that Schwann cells from the disrupted dermal peripheral nerves contribute to myofibroblasts formation, wound contraction, and re-epithelization of the injured skin (12). Future studies may reveal the complexity of the dermal microenvironment important for wound healing in much greater detail.