Correspondence

Stem Cell INVESTIGATION

Schwann cells: an emerging player in tissue regeneration

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The neural crest is a transient developmental structure which gives rise to a host of diverse cellular lineages as well as bona fide multipotent stem that persist into late development (1) and potentially thereafter. One of these neural crest derivatives, Schwann cells, function primarily as physical and trophic support for nerve axons; however, recent work has highlighted their remarkable phenotypic and functional plasticity in a variety to cellular contexts (2). In this regard, our recent work (3) has contributed to the growing Schwann cell "resume" and provides further support for non-canonical functions of Schwann cells in tissue repair and homeostasis. Herein, I will further discuss commentary supplied by Kaucha and colleagues (4) and Montoro and colleagues (5) regarding our recent investigation of the role of de-differentiated Schwann cells, termed Schwann cell precursors (SCPs) in digit regeneration (3).

Mammalian digit regeneration is a highly-coordinated process involving the expansion of lineage restricted progenitors which supply the necessary cellular constituents to rebuild the digit following amputation (6). Crucial to the success of digit regeneration is the formation and adequate expansion of a regenerative structure comprised of mesenchymal cells known as the "blastema". Through a process of differentiation and positional recognition, the blastema cells ultimately give rise to the post-amputation digit. Specifically, our work highlights the necessity of trophic support by SCPs to sufficiently expand the mesenchymal blastemal during reconstitution of the digit following amputation of the distal phalanx (3). However, these findings also underscore the need for further clarity of the many uncertainties discussed in the aforementioned commentaries (4,5).

One feature that sets true regeneration apart from tissue repair is the appropriate patterning of the regenerated structure following injury. Paramount to uncovering the positional cues responsible for this is a more complete and detailed examination of the cellular and molecular components of the digit regenerative environment. Seemingly, SCPs do not aid in this process. While exogenous transplantation of SCPs or treatment with their effector molecules [oncostatin M (OSM) and platelet derived growth factor-AA (PDGF-AA)] resulted in an overall rescue of digit regeneration following denervation, patterning deficiencies were still evident. As pointed out by Montoro and colleagues (5), delineating the factors responsible for accurate positional identity within the blastema would greatly enhance our knowledge of digit regeneration.

In this regard, gaining a greater understanding of the cellular composition of the blastema may help aid in this discovery. While it is now appreciated that trans-differentiation or lineage switching is likely not a driving force of digit regeneration (6), the blastema has remained an enigma in many regards. For example, does the blastema contain numerous heterogeneous populations of mesenchymal cells? Do self-renewing mesenchymal stem cells (MSCs) reside within the blastema and contribute to digit regeneration? Which blastema cells types respond to signals emanating from SCPs or interact with the nail-bed stem cells, the activity of which are crucial for digit

regeneration (7). We will likely have to wait for a more careful examination of reporter mouse strains or detailed single cell analysis before these questions can be answered.

As discussed by Kaucha and colleagues (4), there is accumulating evidence supporting the necessity of adequate innervations to promote tissue repair, limb regeneration and stem cell homeostasis. Additionally, recent work suggests that Schwann cells, at least in part, may mediate these effects. Based on this, and the fact that Schwann cells are located in most all tissues, it is attractive to surmise that Schwann cells may play a broad role in tissue repair and regeneration. This idea is also supported by our own work which demonstrates the necessity for SCPs in the repair of skin following wounding (8). A potential wide-spread regenerative role for Schwann cells begs the question of whether all Schwann cells are functionally equivalent or do specialized sub-populations exist in specific niches. Indeed, we have identified that the Schwann cells which reside at the terminal nerve endings within the digit and bulge region of the hair follicle appear to express high levels of the stem cell gene Sox2 (8), the expression of which is necessary for both skin repair and digit regeneration (3). Further inquiry will be necessary to delineate the function, if any, of SCPs in the repair of additional tissues or the role of heterogeneity within the Schwann cell pool.

Importantly, from a translational standpoint, uncovering the complexities of digit regeneration is an attractive starting point to develop regenerative medicine strategies. While it remains to be discovered if SCPs hold potential for therapeutic application outside the nervous system, future studies targeting their utility as a mechanism to enhance endogenous repair are warranted.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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