Melanocyte Production: Dark Side of the Schwann Cell

We have long known that late-migrating neural crest cells generate melanocytes. A recent study, however, has found that many melanocytes are generated via a different route and are derived from Schwann cell precursors.

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Melanocytes are melanin-producing pigment cells and constitute a considerable fraction of the cells in the adult skin. These cells are important as they provide protection from sunlight, as well as being involved in generating the distinctive pigment patterns of different species of vertebrates, which play important ecological roles. It is known that melanocytes arise from neural crest cells — a transient embryonic progenitor population that migrates from the dorsal aspect of the newly formed neural tube during early development [1]. These cells generate a wide range of differentiated cell types and it has been shown that melanocytes are produced specifically by the late migrating population [2]. It is believed that, after leaving the neural tube, the melanocyte precursors migrate widely throughout the body, and intermingle with the dermis and eventually the epidermis. It would have been fair to say that, although many molecular details needed resolving, we felt we were in the position of understanding the basics of melanocyte production. A recent paper [3], however, presents some startling new evidence for the existence of a hitherto undiscovered mode of melanocyte generation. The new data suggest that melanocytes are not exclusively produced by late migrating neural crest cells, but rather that a substantial number arise from Schwann cell precursors associated with extending nerves.

Fate-mapping studies have defined the derivatives of the neural crest and shown that melanocytes are generated by this precursor population [1]. Furthermore, it has also been shown that there is correlation between the timing and path of migration of neural crest cells and the differentiated cell types that they will produce. Thus, the early migrating neural crest cells move ventrally and give rise to sensory and sympathetic neurons as well as glia, including the Schwann cells that associate with the peripheral nerves. Contrastingly, the late migrating crest cells travel between the somites and the ectoderm exclusively producing melanoblasts, the precursors to the melanocytes [4,5] (Figure 1A). Yet, as Adameyko *et al.* [3] noted, a number of aspects relating to the eventual migration of melanoblasts within the dermis remained unclear and this prompted them to closely scrutinise the process of melanogenesis.

To characterise the migration of melanoblasts into the skin, Adameyko *et al.* [3] analysed the expression of microphthalmia-associated transcription factor (MITF), a key regulator of melanogenesis [6], in neural crest cells. As expected, they found that MITF expression is associated with neural crest cells lying lateral to the neural tube, between the somites and the ectoderm; however, they also found a distinct population of MITF+ cells associated with the developing spinal nerves. These cells also express *Sox10*, a gene associated with both melanoblasts and Schwann cell precursors [7]. The authors found that, as development progresses, the MITF+ cells located close to the dorsal neural tube decrease in number, while the MITF+ cells found close to the nerve greatly increase in number. In particular, MITF expressing cells were found in the vicinity of nerve fibres projecting towards the skin (Figure 1B).

These results suggested that Schwann cell precursors associated with extending nerves could be a source of melanocytes. To test this hypothesis, Adameyko *et al.* [3] conducted ablation experiments in chick embryos. They found that, if they removed both the dorsal late migrating crest population and the extending spinal nerves, there was a dramatic loss of pigment cells on the experimental side; however, if they only ablated the dorsal late migrating crest population, but left in place the spinal nerve with associated Schwann cell precursors projecting to the limb, many melanocytes were still present in the limb. To confirm the inference that melanocytes can be generated by

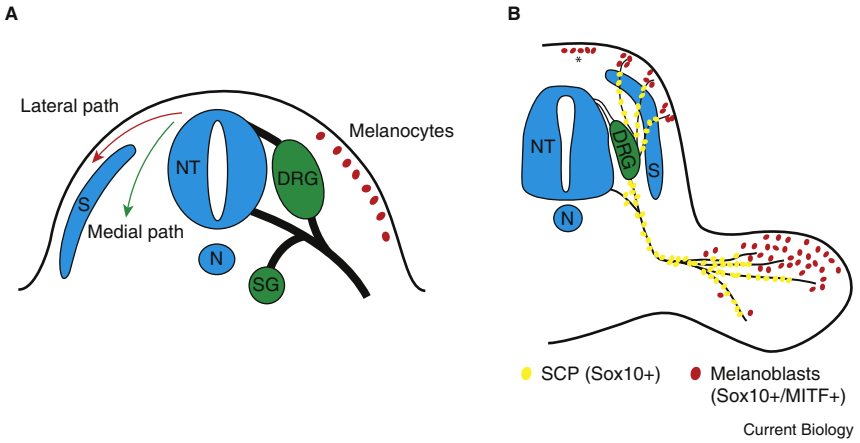

Figure 1. Melanocyte production.

(A) Previous view of melanocyte production. The paths of migration, medial and lateral of the neural crest are shown on the left side, while the derivatives generated by neural crest following either path are shown on the right. The early migrating neural crest cells take the medial path (green) alongside the neural tube (NT), and they will form the neurons of the dorsal root ganglia (DRG) and the sympathetic ganglia (SG). The late migrating neural crest cells will follow the lateral path (red) between the ectoderm and the somites (S) and they will form the melanocytes (red). N, notochord. (B) Melanocytes are also produced by Schwann cell precursors (Schwann cell precursors). The melanoblasts (Sox10+/MITF+) (red) generated by the late migrating neural crest cells can be found dorsally and are indicated with an asterisk (*). Schwann cell precursors (yellow) express *Sox10* and they are found associated with the spinal nerve. Melanoblasts (Sox10+/MITF+) (red) can also be seen to be in the vicinity of the nerve endings, extending into the limbs and towards the skin overlying the somites (S).

schwann-cell precursors, the authors also used *Cre*-based fate mapping in mice. The promoter of the gene for proteolipid protein is selectively active in Schwann cell precursors and Schwannn cells [8], and they used this element to drive expression of a tamoxifen-inducible Cre recombinase. These mice were then crossed to a yellow fluorescent protein (YFP) reporter line. Tamoxifen treatment of these mice results in permanent expression of YFP in Schwann cell precursors and all cells derived from them. They found that, after such treatment, many Schwann cells expressed YFP, as expected, but crucially, they also found that many of the melanocytes associated with hair follicles also expressed YFP. This is strong evidence that melanocytes indeed originate from Schwann cell precursors.

If Schwann cell precursors can generate both Schwann cells and meclanocytes, the question arises as to how this fate choice is controlled. Adameyko *et al.* [3] had noted that the MITF-expressing *Sox10*+ cells were also found in the proximity of the nerve fibres but not in direct contact with these axons. This would seem to suggest that the axons may play a role in directing the fate of Schwann cell precursors. To test this, they axotomised the nerves. They found that loss of the axons resulted in a great increase in the number of MITF+ cells on the operated side. Thus, it would seem that signals from the nerve maintain cells as Schwann cell precursors but in the absence of those signals some Schwann cell precursors will differentiate as melanocytes. Significantly, it was also found that in the adult, mature Schwann cells also retain the ability to differentiate into melanocytes. Some time after transection of the sciatic nerve, melanocytes derived from Schwann cells could be found in the vicinity of the nerve fragment.

Adameyko *et al.* [3] were further able to identify some of the signals emanating from the nerve that could play a role in regulating this fate choice. Neuregulin (NRG1) is a neuronally-derived signal that promotes Schwann cell development [9]. Mice lacking the ErbB3 receptor tyrosine kinase have compromised NRG1 signalling [8], and, although there is an overall reduction in Schwann cell precursors in these animals, there is also a significant increase in MITF+ cells. Furthermore, addition of NRG1 to cell cultures reduced the number of MITF+ cells. However, the addition of other factors to these cultures, such as the growth factors IGF1 and PDGF, which are produced by Schwann cells, could promote an increase in the number of MITF+ cells. Thus, it seems that there are opposing signals that will act to control the balance between Schwann cell and melanocyte differentiation.

This new study [3] is significant as it gives us profound new insights into the origin of melanocytes and more generally neural crest cells. It overturns our previous view that melanocytes were exclusively generated by a distinct population of neural crest cells; those that migrate last, and that these cells were committed to a melanogenic fate just after delamination from the neural tube. Rather it would seem that the process of melanocyte differentiation is more complex and plastic. This study also highlights the importance of Schwann cell precursors as the source of both glial cells and melanocytes. As the authors note, this may help explain the association between alteration in skin pigmentation and neurological disorders, such as is observed in patients with neurofibromatosis type 1.

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Evolution: Exposing the Buried Costs of Reproduction

Investigating the cost of reproduction and terminal reproductive investment is difficult in most species as individuals can respond plastically to most brood manipulations. Experiments in a burying beetle provide new insight into the allocation of resources towards current and future reproductive events.

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Anybody who has carried a baby to term, helped a child through a bout of gastroenteritis, paid fees for daycare or sat through a school concert can tell you that reproduction is costly. The costliness of reproduction is the central assumption of life-history theory, yet these costs can be incredibly tricky to measure and thus to understand. Reproductive costs are manifested as trade-offs between offspring number and quality, and between current and future reproductive effort, so parents should optimize their investment in reproduction in relation to their age, the resources they have available to invest in reproduction, the environmental conditions they