TUMOUR SUPPRESSORS

Where to begin?

Neurofibromatosis type 1 is an inherited tumour predisposition syndrome in which patients develop numerous neurofibromas, some of which progress to malignant disease. The complexity of the disease has made it difficult to pin down the cells from which these tumours arise, but three papers published recently in *Cancer Cell* shed light on the possible culprit.

It has long been debated whether neurofibromas arise from neural crest stem cells (NCSCs) or more differentiated Schwann cells (a form of glial cell). Sean Morrison and colleagues found that cultured NCSCs from the peripheral nervous system (PNS) of embryonic day 13 (E13) *Nf1*-null mouse embryos formed increased numbers of multipotent neurospheres *in vitro*. The neurospheres were also larger, owing to greater proliferation rates, indicating that NF1 probably functions to negatively regulate NCSC self-renewal. Similar results were found by Nancy Ratner and colleagues when they ablated *Nf1* expression using a Cre–Lox approach in cultured PNS cells from E12.5 embryos. Additionally, they found that deletion of *Nf1* in E8.5 neural tube-derived neural crest cells did not induce colony formation, nor did deletion in Schwann cells that had been differentiated *in vitro*, indicating that the timing of NF1 loss could be crucial.

Morrison and colleagues went on to show that NCSCs from *Wnt–Cre*;*Nf1*-null embryos, which die at birth, can differentiate normally and do not persist post-natally in regions of the PNS where plexiform neurofibromas form, and that *Nf1*-null NCSCs do not form tumours when injected into mice. So, given that the NCSCs are not responsible, from what cells do neurofibromas arise? Both Morrison and colleagues and Yaun Zhu and colleagues selectively deleted *Nf1* in early migrating and multipotent neural crest cells. Neurofibromas that formed in these adult mice contained non-myelinating Schwann cells that had increased rates of proliferation.

Through careful, detailed analyses of peripheral nerves in these mice, Zhu and colleagues found that loss of *Nf1* disrupted the ordered association of non-myelinating Schwann cells with axons in regions known as Remak bundles. Over time the number of non-myelinating Schwann cells increased, and the data of Zhu and co-workers indicate that these cells are responsible for early-stage neurofibroma development. Moreover, these authors continued to track the non-myelinated Schwann cells and showed that as neurofibromas develop these cells continue to increase in number at the expense of myelinated axons, the degeneration of which seems to recruit mast cells into the developing neurofibromas.

Ratner and colleagues used a different promoter, desert hedgehog (*Dhh*), to selectively delete *Nf1* at E12.5 in developing glial cells but not neural crest cells. These mice also developed plexiform (and dermal) neurofibromas; Remak bundles in these mice were also abnormal and had mast cells present.

So it seems that *Nf1*-null NCSCs are not the cause of neurofibromas, instead biallelic loss of *Nf1* affects more differentiated glial cells.

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ORIGINAL RESEARCH PAPERS Joseph, N. M. *et al.* The loss of NF1 transiently promotes self-renewal but not tumourigenesis by neural crest stem cells. *Cancer Cell* **13**, 129–140 (2008) | Zheng, H. *et al.* Induction of abnormal proliferation by nonmyelinating Schwann cells triggers neurofibroma progression. *Cancer Cell* **13**, 117–128 (2008) | Wu, J. *et al.* Plexiform and dermal neurofibromas and pigmentation are caused by NF1 loss in desert hedgehog-expressing cells. *Cancer Cell* **13**, 105–116 (2008)