Insights: Publications

P2RY14 cAMP signaling regulates Schwann cell precursor self-renewal, proliferation, and nerve tumor initiation in a mouse model of neurofibromatosis

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Neurofibromatosis type 1 (NF1) is characterized by nerve tumors called neurofibromas in which Schwann cells (SCs) show deregulated RAS signaling. NF1 is also implicated in regulation of cAMP. We identified the G-protein-coupled receptor (GPCR) P2ry14 in human neurofibromas neurofibroma-derived SC precursors (SCPs), mature SCs, and mouse SCPs. Mouse Nf1-/- SCP self-renewal was reduced by genetic or pharmacological inhibition of P2ry14. In a mouse model of NF1 genetic deletion of P2ry14 rescued low cAMP signaling, increased mouse survival, delayed neuro-fibroma initiation, and improved SC Remak bundles. P2ry14 signals via Gi to increase intracellular cAMP, implicating P2ry14 as a key upstream regulator of cAMP. We found that elevation of cAMP by either blocking the degradation of cAMP or by using a P2ry14 inhibitor diminished NF1-/- SCP self-renewal in vitro and neurofibroma SC proliferation in in vivo. These studies identify P2ry14 as a critical regulator of SCP self-renewal, SC proliferation, and neurofibroma initiation.

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