Perinatal or Adult \textit{Nf1} Inactivation using Tamoxifen-inducible PlpCre Each Cause Neurofibroma Formation

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Perinatal or Adult Nf1 Inactivation using Tamoxifen-inducible PlpCre Each Cause Neurofibroma Formation

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OBJECTIVES

Neurofibromas are tumors initiated by biallelic mutation of the NF1 tumor suppressor gene in the Schwann cell lineage. One idea within the field suggests that Nf1 loss must occur within progenitor cells present within a critical window during Schwann cell development in order for neurofibromas to form. To test this hypothesis and to examine whether myelinating Schwann cells can serve as aneurofibroma cell of origin, Nf1 loss was induced at perinatal or adult timepoints using a tamoxifen-inducible Plp-CreERT driver.

RESULTS

Perinatal loss of Nf1 resulted in small neurofibromas late in life, while adult loss caused large neurofibromas and morbidity beginning 4 months after onset of Nf1 loss. PLP-CreERT recombination (EGFP+ cells) occurred in: satellite cells, S100?+ myelinating Schwann cells, and p75+ cells. Plp-CreERT nerves and neurofibromas contained cells with Remak bundle disruption; however, no recombination within GFAP+ non-myelinating Schwann cells was identified. Extramedullary lympho-hematopoietic expansion that contained EGFP+/Sca-1+ stromal cells amongst EGFP-negative lympho-hematopoietic cells was also observed.
CONCLUSIONS/SIGNIFICANCE

Neurofibroma formation is not restricted to loss of Nf1 in embryonic life, but can be triggered by Nf1 loss throughout life. Although all neurofibroma models and human samples have Remak bundle disruption (leading to the assumption that Nf1 loss within the non-myelinating Schwann cell may be vital for tumor formation), there was no EGFP+ recombination within GFAP+ non-myelinating Schwann cells, eliminating the GFAP+ non-myelinating Schwann cell as the cell of origin for neurofibroma formation.

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