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

Debra A. Mayes
Wright State University - Main Campus, debra.mayes@wright.edu

Tilat A. Rizvi

Jose A. Cancelas

Nathan T. Kolasinski

Georgianne M. Ciraolo

See next page for additional authors

Authors

Debra A. Mayes, Tilat A. Rizvi, Jose A. Cancelas, Nathan T. Kolasinski, Georgianne M. Ciraolo, Anat O. Stemmer-Rachamimov, and Nancy Ratner

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[1]Mayes DA, [1]Rizvi TA,[1,3]Cancelas JA, [1]Kolasinski N,[2]Ciraolo CM,[4]Stemmer-Rachamimov AO, and[1]Ratner N
Divisions of[1]Experimental Hematology and Cancer Biology, and[2]Pathology, Cincinnati Children?s Hospital Medical Center,[3] Hoxworth Blood Center, University of Cincinnati, Department of Pathology[4], Massachusetts General Hospital and Harvard Medical School.

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 whethermyelinating 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-CreERTnerves and neurofibromas contained cells with Remak bundle disruption; however, no recombination within GFAP+ non-myelinating Schwann cells was identified. Extramedullarylympho-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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