IN THE SPOTLIGHT

A Model for Primary Melanoma of the CNS Implicates NRAS

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Summary: In this issue of *Cancer Discovery*, Pedersen and colleagues present the first mouse model of primary CNS melanoma, which arises when oncogenic NRAS is expressed from the endogenous *Nras* promoter in melanocytes during embryogenesis. In support of this model, two pediatric cases of *NRAS*-mutant primary melanoma of the CNS are identified. *Cancer Discov; 3(4); 382–3. ©2013 AACR.*

See related article by Pedersen et al., p. 458 (6).

Melanoma can be subdivided into categories based on body location, and some characteristic presentations are exceedingly rare. NRAS is the second most commonly mutated gene in cutaneous melanoma, the most prevalent form of the disease. After *BRAF*, which harbors an activating mutation in 40% to 50% of cutaneous melanomas, *NRAS* is mutated in approximately 20% of tumors (1, 2). Although a mouse model of melanoma driven by expression of $BRAF^{V600E}$ in the absence of other mutations has been developed, current NRAS-driven models rely on concomitant mutations in tumor suppressor genes (3–5). In this issue of *Cancer Discovery*, Pedersen and colleagues (6) show that melanocytic expression of activated NRAS results in melanoma of a quite unexpected type. Here, they present the first model for pediatric primary melanoma of the central nervous system (CNS), a rare but deadly disease.

Primary melanoma of the CNS originates from melanocytes of the leptomeninges. Patients can present with intracranial hypertension, neurologic deficits, subarachnoid hemorrhage, and seizures (7). Primary melanoma of the CNS in children occurs primarily in patients with neurocutaneous melanosis (NCM), a rare nonhereditary syndrome characterized by giant or multiple congenital melanocytic nevi (CMN; ref. 7). Although clinical data are limited, primary melanoma of the CNS in children has a poor prognosis. One study identified 5 children over the course of 13 years with primary melanoma of the leptomeninges, all of whom died within 8 months of initial presentation (8). By expressing oncogenic NRAS in mouse melanocytes during embryonic development, Pedersen and colleagues (6) were able to recapitulate the pathology of CNS melanoma, with particular relevance to pediatric cases.

To develop an NRAS-driven model of melanoma, Pedersen and colleagues (6) expressed $NRAS^{G12D}$ at physiologic levels in a spatially and temporally controlled manner. They did this by inserting a *loxP*-STOP-*loxP* cassette followed by $NRAS^{G12D}$ ($Nras^{LSL\text{-}G12D}$) into the endogenous *Nras* locus. Tamoxifen-activated Cre recombinase, expressed in melanocytes using the tyrosinase promoter, allowed for stop codon excision and expression of $NRAS^{G12D}$ at 2 months of age by painting the backs of mice with tamoxifen. For expression during embryogenesis, the authors used unmodified Cre recombinase.

Surprisingly, expression of $NRAS^{G12D}$ during embryogenesis resulted in primary melanoma of the CNS, manifesting in neurologic symptoms such as hyperreactivity and motor dysfunction at a median of 4 months of age in $Nras^{LSL\text{-}G12D}$ homozygous mice and 12.5 months of age in heterozygous mice, with a corresponding survival time of less than 6 and 12 months, respectively. Both affected and unaffected mice showed hyperpigmentation of the leptomeninges, whereas the brains of only affected mice contained pigmented lesions capable of invading the brain parenchyma. Cells comprising these lesions were highly mitotic and stained positive for melanocytic markers.

Induction of $NRAS^{G12D}$ expression at 2 months of age, on the other hand, did not result in melanoma. Regardless of the timing of oncogene induction, mice developed hyperpigmentation of the skin and benign paucicellular nevi.

Importantly, clinical evidence supports the validity of this genetic model. *NRAS* mutations have been found in primary CNS melanomas, though at a much lower frequency than *GNAQ* and *GNA11* mutations (9). The authors identified 2 children with primary melanoma of the CNS whose tumors harbored activating mutations in *NRAS* while lacking mutations in other genes commonly mutated in CNS melanoma. Interestingly, most CMN, which correlate with increased risk of leptomeningeal melanoma, also harbor mutations in *NRAS* (10). This finding implies that an early somatic mutation may be responsible for both of these phenotypes in children with NCM.

Finally, the authors showed the applicability of their model to therapeutic evaluation. Tumor cells showed constitutive extracellular signal–regulated kinase (ERK) activation and responded to MAP–ERK kinase (MEK) inhibitors. The growth of tumor allografts into syngeneic mice was delayed by the MEK inhibitor PD184352.

Many NRAS-driven models of melanoma in mice have been described, but the model presented in this issue of *Cancer Discovery* is unique in several ways: Oncogenic NRAS is driven by the endogenous *Nras* promoter, and no additional mutations must be engineered or induced by carcinogen treatment for the disease to be apparent. Why are melanocytes of the leptomeniges more susceptible to transformation by oncogenic NRAS in this model? This question remains to be explored. Perhaps

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the modulation of NRAS levels during development plays a role in tumorigenesis. Identification of cooperating mutations and analysis of pathway activation downstream of NRAS may provide clues to the mechanism of tissue specificity.

In summary, Pedersen and colleagues (6) present the first mouse model for pediatric primary melanoma of the CNS, resulting from expression of oncogenic NRAS in melanocytes during embryonic development. Because it is a rare disease, clinical data about primary melanoma of the CNS in children are very limited. Development of an animal model is a critical step toward better understanding and treating this disease.

Disclosure of Potential Conflicts of Interest

L.I. Zon is a founder and stockholder of Fate, Inc. and a scientific advisor for Stemgent. No potential conflicts of interest were disclosed by the other author.

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