Generation of a Mouse Model for Schwannomatosis

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TECHNICAL ABSTRACT

Background: Schwannomatosis shares many features of the neurofibromatoses (NF); however, its cause is largely unknown and currently there is no medical treatment for this disease. Schwannomatosis is characterized by the onset of multiple intracranial, spinal, or peripheral schwannomas, but without vestibular schwannomas, which is diagnostic of NF2. Earlier studies have identified NF2 gene mutations in multiple schwannomas removed from schwannomatosis patients; however, each of these associated tumors carries a different mutation, which is in contrast to a common constitutional mutation found in multiple schwannomas removed from NF2 patients. Recent molecular genetic studies have revealed the involvement of an additional tumor suppressor gene in schwannomatosis, and a four-hit hypothesis involving inactivation of both the INI1/SNF5 and NF2 genes in the formation of schwannomatosis-associated tumors has been suggested.

Objective/Hypothesis: The objective of this study is to generate a mouse model for schwannomatosis. We hypothesize that simultaneous inactivation of both the Snf5 and Nf2 genes in specific tissues including Schwann cells will lead to multiple schwannoma formation in mice.

Specific Aims: (1) Production of transgenic mice carrying the NF2 promoter-driven Cre gene (NF2Cre). Mice with Nf2 inactivation in Schwann

cells using the P0Cre display some characteristics of NF2 including schwannomas; however, the tumor was seen only in a small fraction of P0Cre;Nf2flox2/flox2 mice at old ages. Also, meningiomas, which is a frequent manifestation of human NF2 and may also have Snf5 mutation, were not found in these mice, suggesting that meningioma progenitor cells may not be permissive to the P0 promoter. To generate a schwannomatosis mouse model, we plan to generate transgenic mice carrying the NF2Cre. We have shown that the NF2 promoter directs transgene expression to various NF2-affected tissues including acoustic ganglion, trigeminal ganglion, spinal ganglia, the ependymal cell-containing tela choroidea, and retinal pigmented epithelium.

(2) Generation of triple compound NF2Cre;Nf2flox2/flox2;Snf5flox/flox mice for simultaneously inactivating Snf5 and Nf2 in NF2-affected tissues. SNF5, a subunit of the SWI/SNF ATP-dependent chromatin-remodeling complex, is a tumor suppressor that regulates cell cycle, growth, and differentiation. Specific inactivating mutations in SNF5 have been identified in malignant rhabdoid tumors (MRTs). In mice, homozygous deletion of Snf5 results in embryonic lethality prior to implantation, while heterozygous mice were born normal; however, beginning as early as 5 weeks of age, heterozygous mice developed tumors consistent with MRTs. Occasionally, some Snf5+/- heterozygous mice also have schwannoma. Thus, simultaneous inactivation of both Snf5 and Nf2 in Schwann cells may result in efficient schwannoma formation.

Study Design: At least three lines of transgenic NF2Cre mice will be produced. The NF2Cre mice will be mated with the Rosa26loxP reporter mice, whose ROSA26 beta-gal expressing locus is induced upon Cre expression. We will choose one of the NF2Cre mouse lines that show robust Cre expression in various NF2-affected tissues for subsequent mating. We have obtained the Snf5flox/flox mice from our collaborator

Charlie W.M. Roberts at Harvard Medical School and the P0Cre and Nf2flox2/flox2 mice from Marco Giovannini of The House Ear Institute. Through sequential mating, we will generate compound NF2Cre;Nf2flox2/flox2;Snf5flox/flox mice. Similar to the P0Cre;Nf2flox2/flox2 mice, we anticipate that the NF2Cre;Nf2flox2/flox2;Snf5flox/flox mice will display the schwannoma phenotype. However, because of the use of NF2 promoter, inactivation of both Nf2 and Snf5 will occur in various NF2-affected tissues and this likely will result in more severe abnormalities such as multiple tumor formation. As an alternative, we can use other Schwann cell-specific promoter-driven Cre, such as P0Cre, or the inducible CreER system to generate the gene knockout. We will closely watch the NF2Cre;Nf2flox2/flox2;Snf5flox/flox mice for any abnormalities including tumor formation. Any tumors or abnormal tissues will be excised and used in immunohistochemical analysis for tumor type, proliferation index, and protein expression.

Innovation: The proposed conditional knockout approach should allow us to simultaneously inactivate both Snf5 and Nf2 in various NF2-affected tissues. We will also monitor any tumor formation by small-animal magnetic resonance imaging. Once the model is developed, we will make it available to others at appropriate administrative costs or on a collaborative basis. We also plan to deposit the animal to the Mouse Models of Human Cancers Consortium and the Jackson Laboratory.

Impact: If successful, this mouse model will be the first animal model for schwannomatosis. The availability of such a model will allow us not only to better understand the synergistic role of Snf5 and Nf2 in schwannomatosis-associated tumorigenesis, but also to perform preclinical drug testing, ultimately leading to a cure of this devastating disease.

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