Docket #: S97-107

Transgenic Mice Carrying a Reporter Gene for the Hedgehog Signaling Pathway

The patched gene is a component of the so-called Hedgehog signaling pathway that is known to be involved in the commonest human cancer, basal cell carcinoma, and in brain cancer. In this pathway, a secreted signaling protein called Hedgehog binds to a receptor called Patched on receiving cells. Patched is employed in many events in normal development including formation of the neurons that are depleted in Parkinson's disease, formation of normal limbs and musculature, signaling in gut development, chondrogenesis, and proper development of the brain. When Hedgehog binds to its receptor, the transcription of “target” genes is induced. Target genes include powerful Wnt and TGFß regulators of development and cell growth, and are the output from the Hedgehog pathway. One of the genes whose transcription is induced is patched itself, the receptor gene, perhaps to soak up excess Hedgehog and limit the duration of the signaling. Whatever the reason, high-level transcription of patched is an indicator of the receipt of Hedgehog signal in every tissue that has been checked in humans, mice, chickens, fish and files. Therefore having a way to readily detect patched transcription in various cell types provides a powerful assay for Hedgehog signaling.

Transgenic mice were constructed containing an E. coli lacZ gene inserted into the patched gene. Homozygous embryos are normal, so the insertion did little or no damage to the gene. The homozygotes have also been determined to be fully viable. The exact structure of the gene carrying the insertion is not known, but the insert clearly interrupts the gene internally. ßgalactosidase produced under the control of the inserted gene is found in most or all of the places the patched gene is normally transcribed. Thus the lacZ gene is properly regulated by control elements that flank the patched gene. To our knowledge, no other mice have been constructed with any of these properties

Applications of these mice include establishing standard in vivo and in vitro assays for Hedgehog activity, creating cell lines from a variety of differentiating tissues and testing response to Hedgehog, and screening chemical and biological substances for their activity as agonists or antagonists of the pathway.

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