Tumor Formation in Response to Loss of the Chromatin Remodeler Chd5 in Zebrafish

Taylor R. Sabato, Erin L. Sorlien, and Dr. Joseph P. Ogas
Department of Biochemistry, Purdue University

ABSTRACT

Chromodomain helicase DNA binding protein 5 (CHD5) has been identified as a tumor suppressor in humans. Deletion or mutation of CHD5 has been observed in numerous cancers, including neuroblastoma and melanoma. We hypothesize that chd5 is also a tumor suppressor in zebrafish, a powerful model system to study tumorigenesis. Many genes involved in tumorigenesis are conserved in zebrafish, and they develop fully penetrant tumor phenotypes. We have created chd5 knock-out zebrafish using CRISPR/Cas9 and are monitoring them for tumor development. In addition to the chd5 knock-outs, we are undertaking a double-mutant approach by coupling loss of chd5 with other genes known to be important for tumor formation. Specifically, we are using a mutant form of the oncogene BRAFV600E and a mutant version of the tumor suppressor tp53. BRAFV600E is a kinase that promotes cell division. Tp53 is tumor suppressor gene that initiates apoptosis when severe DNA damage occurs. Expression of gain-of-function BRAFV600E gene creates nevi in zebrafish, similar to the production of moles in humans, but is not sufficient to promote melanoma formation. Tp53 when mutated results in nerve sheath tumors in zebrafish at 8.5 months. When BRAFV600E mutant is combined with mutant tp53, the fish develop melanomas beginning at 4 months. We have crossed our chd5 knock-out alleles with BRAFV600E and tp53 to create various mutant lines, and we are examining the resulting progeny for tumor development, specifically melanoma. Establishment of a chd5-dependent tumor model using zebrafish will enable novel studies of the function of CHD5 in human cancers.

KEYWORDS

Chromodomain helicase DNA-binding protein, zebrafish, melanoma, CRISPR-Cas9