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*“Hedgehog pathway activation in juvenile pilocytic astrocytoma”*



Pilocytic astrocytoma is commonly viewed as a benign lesion with an excellent 10-year survival rate. However, disease onset is most prevalent in the first two decades of life, current therapeutic modalities are often limited by tumor location and size and late recurrences are not uncommon. Thus, as many children are left with residual or recurrent disease, the short and long-term morbidity and mortality rates of this indolent disease can be quite significant. Our hope is that a better understanding of the biology of sporadic pilocytic astrocytoma will guide the development of new therapies to decrease morbidity and improve survival from this malignancy.

A recent advancement in our understanding of malignancies has been the identification of a rather small population of cancer cells that are critical for maintaining the growth of the entire tumor. These have been termed cancer stem cells and they appear to be resistant to conventional chemotherapy and radiation treatments. However, another major advancement has been the recognition that some of the same signaling pathways that regulate the growth of stem cells during embryonic development also regulate cancer stem cells. One of these developmental pathways is called the Hedgehog signaling pathway. In malignancies of the skin, lung and intestine for example, it has been demonstrated that Hedgehog signaling is required for their growth. In our previous work, we identified compounds that inhibit Hedgehog signaling and determined that the Hedgehog pathway is activated in stem cells in specific subtypes of adult astrocytoma. We have recently collected a panel of pediatric brain tumors for Hedgehog pathway analysis. A striking finding is that juvenile pilocytic astrocytomas contain markedly elevated levels of the Hedgehog receptor and that within tumors the receptor is expressed in stem-like cells. These preliminary results suggest that the Hedgehog pathway may be activated in juvenile pilocytic astrocytoma cancer stem cells. Thus the inhibition of Hedgehog signaling in juvenile pilocytic astrocytoma may target a critical tumor cell population in a pathway-specific manner. With support from The Childhood Brain Tumor Foundation, we seek to determine if the Hedgehog pathway is activated in juvenile pilocytic astrocytoma and whether delivery of Hedgehog inhibitors will halt the growth of this tumor. If successful, these preclinical findings will constitute an important component for developing a novel therapeutic strategy for juvenile pilocytic astrocytoma.