Abstract:

Medulloblastoma (MB) is a highly malignant embryonal tumor of the cerebellum with a preferential manifestation in children. Although the majority of MBs occur sporadically, this tumor is also associated with familial cancer syndromes including the nevoid basal cell carcinoma or Gorlin syndrome. Mutations in the tumor suppressor gene PATCHED 1 (PTCH1) have been described in both familial and sporadic cases and inactivation of one Patched 1 (Ptch1) allele in mice promotes development of MB. In order to determine candidate genes involved in tumorigenesis of MB, we have screened tumors of heterozygous Ptch1 mice for differentially expressed genes by means of cDNA microarray technology. Our data show that genes involved in cell cycle, signal transduction and metastasis are transcriptionally up-regulated in MB compared to normal cerebellum. Gene ontology analysis reveals cell cycle regulators to be the predominant functional gene class altered in MB of Ptch1 mutants, including D-type cyclins and cyclin-dependent kinase 4. We furthermore describe that overexpression of the growth arrest and DNA-damage-inducible gene Gadd45a is common in Ptch1-associated tumors and Ptch1 null embryos. These results suggest that cDNA microarray technology is a useful tool to discover genes involved in the development of MB that arise in response to a persistent activation of sonic hedgehog (Shh) signaling. This
approach may provide novel data for diagnosis, treatment and prevention of human PTCH1-related malignancies.