ELP1-associated medulloblastoma

Immunohistochemistry as a tool to identify ELP1-associated medulloblastoma [1].

Large-scale germline sequencing studies in unselected cohorts of pediatric neuro-oncology patients have demonstrated novel candidate tumor predisposition genes (ELP1 alterations in sonic hedgehog medulloblastoma) [2] [3].

Cancer genomics has revealed many genes and core molecular processes that contribute to human malignancies, but the genetic and molecular bases of many rare cancers remain unclear. Genetic predisposition accounts for 5 to 10% of cancer diagnoses in children, and genetic events that cooperate with known somatic driver events are poorly understood. Pathogenic germline variants in established cancer predisposition genes have been recently identified in 5% of patients with the malignant brain tumor medulloblastoma. By analyzing all protein-coding genes, Waszak et al. identified and replicate rare germline loss-of-function variants across ELP1 in 14% of pediatric patients with the medulloblastoma subgroup Sonic Hedgehog (MBSHH). ELP1 was the most common medulloblastoma predisposition gene and increased the prevalence of genetic predisposition to 40% among pediatric patients with MBSHH. Parent-offspring and pedigree analyses identified two families with a history of pediatric medulloblastoma. ELP1-associated medulloblastomas were restricted to the molecular SHHα subtype4 and characterized by universal biallelic inactivation of ELP1 owing to somatic loss of chromosome arm 9q. Most ELP1-associated medulloblastomas also exhibited somatic alterations in PTCH1, which suggests that germline ELP1 loss-of-function variants predispose individuals to tumor development in combination with constitutive activation of SHH signaling. ELP1 is the largest subunit of the evolutionarily conserved Elongator complex, which catalyzes translational elongation through tRNA modifications at the wobble (U34) position. Tumors from patients with ELP1-associated MBSHH were characterized by a destabilized Elongator complex, loss of Elongator-dependent tRNA modifications, codon-dependent translational reprogramming, and induction of the unfolded protein response, consistent with loss of protein homeostasis due to Elongator deficiency in model systems7-9. Thus, genetic predisposition to proteome instability may be a determinant in the pathogenesis of pediatric brain cancers. These results support the investigation of the role of protein homeostasis in other cancer types and the potential for therapeutic interference [4]

1)
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