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EDITORIAL

Help for Sick Kids: New Insights Into Hepatoblastoma

Hepatoblastoma is the most common type of malignant pediatric liver cancer, which affects children in their first 3 years of life. A substantial number of patients with hepatoblastoma experience metastasis and are faced with aggressive tumors that are characterized by multiple nodules at diagnosis, vascular invasion, chemoresistance, and relapse.[1] These cases are unresectable and have a high mortality rate. Understanding of molecular basis for aggressive hepatoblastoma is required for the development of novel therapeutic approaches. In contrast to hepatocellular carcinoma, hepatoblastoma is characterized by mutations mainly in 2 genes CTNNB1 (β-catenin) and NFE2L2/NRF2.[2,3] Additional mutations are observed in the TERT promoter and in ARID1A, which is chromatin remodeling gene. Although only 5%–10% of hepatoblastoma patients harbor mutations in NFE2L2/NRF2, these mutations are linked to aggressive hepatoblastoma. Although the role of β-catenin mutations in hepatoblastoma has been partially elucidated,[4,5] the mechanistic contribution of mutations of NFE2L2/NRF2 to hepatoblastoma has remained unknown until today.

To elucidate the role of NFE2L2/NRF2 mutations in the development of pediatric liver cancer, Prochownik's group determined the effects of patient-derived NFE2L2/NRF2 mutants in the contest of β-catenin and YAP activation in transgenic mice.[6] These combinations reproduce the mutations that are typically observed in hepatoblastoma patients with chemoresistant, relapsed, and aggressive forms of the pediatric liver cancer. Remarkably, both patient-derived NFE2L2/NRF2 mutants significantly shortened survival of the mice in this setting, demonstrating a critical contribution of NFE2L2/NRF2 mutations to the aggressiveness of hepatoblastoma. Importantly, mutant expressing tumors contained extensive areas of necrosis and innumerable fluid-filled cysts showing that specific pathologic features of aggressive hepatoblastoma are mediated by NFE2L2/NRF2 mutations. The authors did not stop here, but through transcriptomic analysis and functional follow-up identified the serine protease inhibitor serpin E1 to be responsible for extensive necrosis associated with NFE2L2/NRF2 mutations. Finally Wang et al[6] analyzed RNA-Seq data from 194 hepatoblastoma cases and found copy number variations and missense mutations in almost half of them, emphasizing the important role of NFE2L2/NRF2 mutations in aggressive hepatoblastoma. Thus, this elegant work showed the critical role of NFE2L2/NRF2 mutations in development of aggressive features of pediatric liver cancer including low survival rate, fast progression of tumors, and promotion of the widespread necrosis.

The study by Wang et al[6] provides a strong rationale for addressing mechanisms that contribute to the aggressiveness of hepatoblastoma. Particularly, 1 of the critical questions relates to the high levels of mutant β-catenin and NFE2L2/NRF2 proteins in patients with aggressive hepatoblastoma. What are the mechanisms that increase transcription of these key genes? In this regard, a previous report identified short chromosomal regions, called aggressive liver cancer domains, which are located within the β-catenin and NFE2L2/NRF2 genes. These regions are activated in aggressive hepatoblastoma by PARP1-dependent opening of chromatin leading to an increase of transcription of the mutant β-catenin and NFE2L2/NFR2 genes.[7] This finding suggests PARP1 inhibition as a potential treatment for hepatoblastoma. The second question is related to post-translational modifications, which, similar to genetic mutations, might stabilize oncogenic forms of β-catenin and NFE2L2/NRF2. Several studies performed on fresh specimens support such a scenario.[7,8] An interesting example of an oncogenic modification of β-catenin has been described for fibrolamellar hepatocellular carcinoma, where a mutant protein kinase phosphorylates β-catenin at Ser675 and thus stabilizes the protein and promotes transformation.[9] In summary, a full understanding of hepatoblastoma requires the analysis of the combinatory effects of genetic mutations, increased transcription of oncogenes, and stabilizing post-translational modifications.

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