What is the role of aneuploidy in embryonal tumors? Cytogenomic analysis of hepatoblastomas

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Abstract/Resumo

Cytogenetic alterations leading to changes in chromosome copy number (aneuploidy) are hallmarks of cancer cells. However, their roles in tumor initiation and progression are unclear. Hepatoblastoma (HB) is an uncommon embryonal liver tumor accounting for approximately 80% of childhood hepatic cancer and is mostly diagnosed in children under the age of 18 months. Currently, there are no validated prognostic or therapeutic biomarkers for HB patients. Most HBs are sporadic cases, although its incidence is elevated in certain genetic syndromes with known constitutive genetic mutations, including Beckwith–Wiedemann and familial adenomatous polyposis. To explore the cytogenomic profile of HBs, we investigated a cohort of 10 hepatoblastomas by comparative genomic hybridization based on microarrays (array-CGH 180K platform) aiming to identify relevant chromosome regions and genes. Additionally, we have characterized the copy number profile of two different commercial HB cell lines as well as two hepatocellular carcinoma lineages. The array-CGH analysis revealed quite stable genomes in this kind of embryonal tumor. Four HBs presented with no detectable chromosomal imbalances, whereas four of them exhibited mainly whole-chromosome and arm aneuploidies, with a prevalence of gains affecting 1q and the entire chromosomes 2 and 8. Few focal alterations could be delimited, including a 2q24.3 amplification in two tumors sharing a minimum common region of 5.3 Mb that harbors 20 genes; a complex rearrangement of non-contiguous deletions at 3p26.1-p25.2; and a large 55 Mb segment deleted at 4q31-4q25. Interestingly, two HBs presented a higher load of chromosomal rearrangements compared to the HB group. The characterization of the liver tumor cell lines highlighted the quiet chromosomal landscape of the embryonal liver tumors compared to their adult counterpart, hepatocellular carcinomas, which carry several cytogenetic changes in a complex genome. Our data suggested that aneuploidy possibly plays a limited role in HB tumorigenesis, rather linked to the process of acquisition of entire chromosomes than to the amplification of oncogenes and tumor suppressors losses.

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