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Molecular Determinants of Medulloblastoma Metastasis and Leptomeningeal Dissemination

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Abstract

Medulloblastoma is the most common malignant brain cancer in pediatrics consisting of four molecular subgroups, namely wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4. One of the biggest challenges in the clinical management of this disease is the leptomeningeal dissemination (LMD) of tumor cells with high morbidity and mortality. Many molecular regulators to date have been identified to participate in medulloblastoma metastasis. In the SHH subgroup, the co-upregulation of CXCR4 and PDGFR, as well as the activation of c-MET, show significant promigratory effects on medulloblastoma cells. Amplification or overexpression of genes on the long arm of chromosome 17, such as *LASP1* and *WIP1*, facilitates tumor invasion in both Group 3 and Group 4 medulloblastomas. PRUNE1, NOTCH1, and MYC interactor JPO2 are more specific genetic drivers of metastatic Group 3 tumors. The RAS/MAPK and PI3K/AKT pathways are two crucial signal transduction pathways that may work as the convergent downstream mechanism of various metastatic drivers. Extracellular signals and cellular components in the tumor microenvironment also play a vital role in promoting the spread and colonization of medulloblastoma cells. For instance, the stromal granule cells and astrocytes support tumor growth and dissemination by secreting PlGF and CCL2, respectively. Importantly, the genetic divergence has been determined between the matched primary and metastatic medulloblastoma samples. However, the difficulty of obtaining metastatic medulloblastoma tissue hinders more profound studies of LMD. Therefore, identifying and analyzing the subclone with the metastatic propensity in the primary tumor is essential for future investigation.