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Leptomeningeal dissemination: a sinister pattern of medulloblastoma growth.

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Leptomeningeal dissemination (LMD) is the defining pattern of metastasis for medulloblastoma. Although LMD is responsible for virtually 100% of medulloblastoma deaths, it remains the least well-understood part of medulloblastoma pathogenesis. The fact that medulloblastomas rarely metastasize outside the CNS but rather spread almost exclusively to the spinal and intracranial leptomeninges has fostered the long-held belief that medulloblastoma cells spread directly through the CSF, not the bloodstream. In this paper the authors discuss selected molecules for which experimental evidence explains how the effects of each molecule on cell physiology contribute mechanistically to LMD. A model of medulloblastoma LMD is described, analogous to the invasion-metastasis cascade of hematogenous metastasis of carcinomas. The LMD cascade is based on the molecular themes that 1) transcription factors launch cell programs that mediate cell motility and invasiveness and maintain tumor cells in a stem-like state; 2) disseminating medulloblastoma cells escape multiple death threats by subverting apoptosis; and 3) inflammatory chemokine signaling promotes LMD by creating an oncogenic microenvironment. The authors also review recent experimental evidence that challenges the belief that CSF spread is the sole mechanism of LMD and reveal an alternative scheme in which medulloblastoma cells can enter the bloodstream and subsequently home to the leptomeninges.

KEYWORDS: EMT = epithelial-to-mesenchymal transition; HGF = hepatocyte growth factor; LMD = leptomeningeal dissemination; MT1-MMP = membrane type-1 matrix metalloproteinase; PI3K = phosphatidylinositol-3 kinase; Tsp-1 = thrombospondin-1; VEGF = vascular endothelial growth factor; hematogenous metastasis; leptomeningeal dissemination; medulloblastoma; oncology

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