Brain neoplasms and coagulation.

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Abstract

Brain vasculature is uniquely programmed to protect central nervous system tissues and respond to their metabolic demands. These functions are subverted during the development of primary and metastatic brain tumors, resulting in vascular perturbations that are thought to contribute to progression and comorbidities of the underlying disease, including thrombosis and hemorrhage. Chronic activation of the coagulation system is particularly obvious in glioblastoma multiforme (GBM), where intratumoral vasoocclusive thrombosis may contribute to hypoxia, pseudopalisading necrosis, and angiogenesis. GBM is also associated with spontaneous or iatrogenic bleeding, and the emission of circulating procoagulants implicated in the unusually high risk of peripheral venous thromboembolism. Tissue factor (TF) expression is elevated in several types of brain tumors, including adult and pediatric GBM, as is the production of TF-containing microparticles (TF-MPs). Both TF expression and its vesicular emission are regulated by tumor microenvironment (e.g., hypoxia), in concert with activated oncogenic and growth factor pathways (RAS, EGFR, MET), as well as the loss of tumor suppressor gene activity (PTEN). Discovery of distinct oncogenic networks led to recognition of unique molecular subtypes within brain tumors, of which GBM (proneural, neural, classical, and mesenchymal), and medulloblastoma (SHH, WNT, group 3, and group 4) exhibit subtype-specific composition of the tumor coagulome. It remains to be established whether mechanisms of thrombosis and biological effects of coagulation in brain tumors are also subtype specific. In this regard, TF pathway represents a paradigm, and its impact on tumor dormancy, inflammation, angiogenesis, formation of cancer stem cell niches, and dissemination is a subject of considerable interest. However, establishing the extent to which TF and TF-MPs contribute to pathogenesis and thromboembolic disease in the context of primary and secondary brain tumors may require molecular stratification of patient populations. We suggest that a better understanding of these molecular linkages may pave the way to a more effective (targeted) therapy, prophylaxis, adjunctive use of anticoagulants, and other agents able to modulate interactions between brain tumors and the coagulation system.

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