PROCOAGULANT TISSUE FACTOR EXPRESSION IS LINKED TO DISTINCT SUBTYPES IN Glioblastoma AND PLAYS A ROLE IN TUMOR DORMANCY

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BACKGROUND: The coagulation system bridges the immediate (hemostatic) and late (inflammation, angiogenesis) tissue responses to disruption of tissue homeostasis. Tissue factor (TF) is the central regulator of these pathways. Glioblastoma (GBM) is associated with a highly procoagulant phenotype, and in some cases with high levels of TF. Here, we interrogate the link between these features and GBM progression. METHODS: We mined human GBM databases for expression of coagulation factors and performed xenograft experiments with GBM cell lines engineered to express either TF or EGFRvIII oncogene. RESULTS: Expression of coagulation factors (coagulome) is subtype-specific in GBM and TF expression correlates with the classical subtype. Inhibition of TF modulates EGFRvIII-driven growth of GBM xenografts. GBM-related human cells undergo tumor dormancy in a manner influenced by tissue factor (TF) expression. Thus, indolent, TF-deficient subline of human glioma, U373, forms viable, but permanently dormant deposits at the injection site. Expression of TF in these cells leads to a stepwise transition to latent and overt tumor growth phases, and this process that is associated with recruitment of vascular (CD105+) and myeloid (CD11b+ and F4/80+) elements. Importantly, the microenvironment orchestrated by TF expression facilitates permanent secondary changes in the phenotype, gene expression profile, DNA copy number and DNA methylation state of tumor cells that escaped from dormancy. CONCLUSIONS: We postulate that there is a degree of specificity in activation of the coagulation system by GBM subtypes driven by defined oncogenic pathways. Thus, TF is regulated by EGFR-dependent transformation. Conversely, we also suggest that procoagulant events in the tissue microenvironment (niche) may affect the fate of occult tumor cells, including biological and genetic progression to a full blown GBM-like malignancy. SECONDARY CATEGORY: Preclinical Experimental Therapeutics.