YAP IS A CRITICAL AND NOVEL REGULATOR OF MIGRATION AND INVASION AND PREDICTS POOR OUTCOME IN Glioblastoma
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BACKGROUND: Cell migration plays a pivotal role during tissue morphogenesis and homeostasis in multi-cellular organisms. By integrating extracellular cues and intracellular signaling, migration ensures the organized spatial distribution of cells. One of the hallmarks of tumor malignancy is the ability of cells to not only locally invade its surrounding parenchyma but also distally metastasize. Tumors often display a collective sheet of migrating cells which may eventually disseminate and migrate in a single cell manner. To model this phenomenon, we studied the underlying mechanism controlling collective and single cell migration. METHODS: We studied collective and single cell migration in a nanogrooved substratum which mimics reorganized fibrous structures of extracellular matrix. We used our in vivo murine intracranial xenograft model using human GBM cells to study the role of YAP in driving invasive tumor growth. We studied if the YAP-driven cell dispersal mechanisms confer poor patient prognosis in the TCGA and REMBRANDT GBM databases. RESULTS: Using a nanogrooved substratum we observed an epithelial-to-mesenchymal transition-like (EMT-like) behavior with formation of finger-like structures with faster moving marginal cells at the sheet edge. Cells at the tip of these structures frequently lost contact with neighboring cells and disseminated from the original collective cell sheet, which was accompanied by the expression of EMT markers (vimentin and the nuclear translocation of β-catenin). Recently, Yes-associated protein (YAP), a mechanosensor and transcriptional regulator, has been implicated in potentiating migration, invasion, and metastasis; however, the underlying mechanisms remain poorly understood. We observed that YAP is activated in these finger-like projections. We explored mechanisms of YAP-mediated migration and invasion in normal cells and cancer cells where YAP is hyperactive. We found that YAP plays a pivotal role in regulation of this complex migratory and invasive behavior through a novel small Rho-GTPase-dependent signaling mechanism. As with glioblastoma (GBM), metastatic cancers often evade detection because individual cells spread from the primary bulk tumor; thus, making complete resection and treatment impossible. Congruent with our in vitro studies, our in vivo murine model demonstrates the role of YAP in driving invasive tumor growth. We show that these YAP-driven cell dispersal mechanisms confer poor patient prognosis in the TCGA and REMBRANDT GBM databases. CONCLUSIONS: Our findings provide new insights into the biology of aggressive cancers with particular prognostic relevance of this YAP-driven pro-migration and invasion cascade in glioblastoma. In addition, our studies suggest these YAP-dependent mechanisms are evolutionary conserved during development and regeneration and are co-opted by pathological diseases. SECONDARY CATEGORY: Neuropathology & Tumor Biomarkers.