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PDGFRα signaling strength confers sensitivity to vinblastine in glioblastoma

The PDGF Receptor alpha is overexpressed and activated in a substantial number of Glioblastoma (GBM) tumors. Although the activation of PDGFRα in GBM is chronic in nature, our knowledge of PDGFR signaling pathways is largely derived from acute stimulation studies, which are less representative of the clinical setting. In order to decipher the identity and clinical significance of sustained PDGFRα signaling during tumorigenesis and to reveal therapeutic vulnerabilities, we created a novel genetically engineered conditional mouse model based on genomic events that are observed in patients, that is the overexpression of PDGFRα and its chronic activation by PDGF-A ligand in the context of loss of function of the p53 tumor suppressor gene. To broaden its clinical relevance, we created our model system with a titratable expression of PDGF-A, which is specific for PDGFRα homodimers. De novo intracranial PDGF-A;PDGFRα tumors arise in these mice with full penetrance and short latency and display histological and molecular features that are consistent with Proneural GBMs. Tumor growth in animals was intimately related to the levels of PDGF-A ligand expression, suggesting differences in cellular signaling in tumors with low and high levels of activated receptors. Indeed, global phospho- (pTyr, pSer/pThr) and total proteomic analyses on cells derived from PDGFRα-positive GBMs revealed that the strength and utilization of specific signaling pathways are dependent on the levels of PDGFRα activation. Further investigation of these pathways unveiled a role for the microtubule binding protein Stathmin 1 (STMN1) in the vulnerability of these GBM cells to the microtubule-disrupting drug vinblastine. Our results open the possibility that GBM patients whose tumors express active PDGFRα could benefit from treatments with vinca alkaloid type of therapeutic agents. Our observations also argue strongly for the development of inhibitors of STMN1 function for the treatment of PDGFRα positive GBMs.

Biography

Alain Charest, MSc, PhD is an Associate Professor in the Department of Medicine at Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA. Dr. Charest received his postgraduate degrees at McGill University, Montreal, Canada. The focus of the Charest laboratory is on leveraging clinically relevant genetically engineered mouse models of primary malignant brain cancer to study central aspects of gliomagenesis and molecular responses to therapeutic interventions. Recent work from the Charest lab involves studies on how PDGFRa signaling strength confers sensitivity to chemotherapeutic agents in Glioblastoma Multiforme.

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