PLGF/NRP1 SIGNALING IS CRITICAL FOR MEDULLOBLASTOMA GROWTH

Children with medulloblastoma, the most common malignant pediatric brain tumor, are generally treated with surgery followed by chemotherapy and radiation, a combination of treatments that increases survival rates but also induces significant toxicity and adverse effects on cognition. Therapies targeting key oncogenic drivers such as sonic hedgehog (SHH) have been unsuccessful, underscoring the importance of identifying alternative actionable pathways. Snuderl and colleagues found that the expression of placental growth factor (PGF, also known as PlGF), a member of the VEGF family, was upregulated across all subtypes of pediatric medulloblastoma compared with normal cerebellar tissue, suggesting a role for PlGF in tumorigenesis. In support of this idea, treatment with anti-PlGF blocking antibodies induced tumor regression, reduced spinal cord metastasis, and prolonged survival in mice bearing distinct subtypes of medulloblastoma tumors. Elevated PGF expression in tumor cells was required for initial tumor growth and also to stimulate production of PlGF by cerebellar stromal cells, which was mediated by paracrine signaling induced by tumor-cell–secreted SHH ligands and provided the main source of PlGF expression. PlGF/NRP1 signaling may disrupt tumor–stroma interactions and provide therapeutic benefit in children with this disease.


MEKI MEDIATES PTEN RECRUITMENT TO THE PLASMA MEMBRANE

Much effort has been directed toward development of inhibitors of the RAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal–regulated kinase (ERK) pathway, a major downstream effector of oncogenic RAS signaling that is deregulated in cancer. A better understanding of interactions between the RAF/MEK/ERK pathway and other RAS effector pathways in cancer could provide insight into how feedback mechanisms contribute to drug resistance. Given previous evidence of cross-talk between the RAF/MEK/ERK and phosphatidylinositol-3 kinase (PI3K)/AKT pathways, Zmajkovicova and colleagues evaluated the effect of MEKI loss on AKT activation in mouse embryonic fibroblasts and found that AKT phosphorylation was markedly increased in MEKI-deficient cells. MEKI loss also led to a significant reduction in membrane-associated levels of the tumor suppressor PTEN, which dephosphorylates phosphatidylinositol 3,4,5 triphosphate to prevent AKT membrane recruitment and subsequent activation. Furthermore, conditional deletion of Mek1 in vivo caused phenotypes such as myeloproliferation and a lupus-like autoimmune disorder that were similar to those seen in Pten-deficient mice and constitutively active Akt transgenic mice. MEKI did not directly bind PTEN but was required for recruitment of membrane-associated guanylate kinase, WW and PDZ domain containing 1 (MAGI1), a scaffolding protein that directly binds PTEN, and formation of a MEKI–MAGI1–PTEN ternary complex at the plasma membrane. Importantly, negative feedback phosphorylation of MEKI by ERK, its downstream target, was required for formation of the MEKI–MAGI1–PTEN complex, providing a potential mechanistic explanation for why PI3K pathway activation is frequently observed in cells treated with MEK inhibitors and support for combined inhibition of these pathways to prevent release of negative feedback mechanisms in cancer cells.
