Abstract

Glioblastoma multiforme (GBM) is aggressive and incurable disease, and is frequently accompanied by augmented platelet-derived growth factor (PDGF) signaling. Overexpression of PDGF-B ligand characterized specific subclass of GBM, but the significance of the ligand remained to be elucidated. For this end, we implanted glioma cell line transfected with PDGF-BB-overexpressing vector (GL261-PDGF-BB) or with control vector (GL261-vector) into *wildtype* mouse brain, and examined the effect of glioma-derived PDGF on the tumor microenvironment. The volume of GL261-PDGF-BB rapidly increased than that of GL261-vector. A recruitment of many PDGF receptor (PDGFR)-α and Olig2-positive oligodendrocyte precursor cells (OPCs) and frequent hemorrhages were observed in GL261-PDGF-BB but not in GL261-vector glioma. Then, we implanted GL261-PDGF-BB into the mouse brain with/without *Pdgfra*-gene inactivation, corresponding to PDGFRα-KO and Flox mice, respectively. The recruitment of OPCs was largely suppressed in PDGFRα-KO than in Flox mice, whereas the volume of GL261-PDGF-BB was comparable between the two genotypes. Frequent hemorrhage, increased IgG-leakage and angiogenesis with intimate spatial correlation with recruited OPCs were observed in Flox mice. In contrast, these vascular phenotypes were largely suppressed in PDGFRα-KO mice. Increased MMP9 in recruited OPCs and decreased claudin-5 in vasculature may underlie the vascular phenotype. Glioma-derived PDGF-B signal was implicated in the induction of cancer stroma characteristically seen in high-grade glioma, and could be the therapeutic target to improve cancer microenvironment.

Keywords: glioma, microenvironment, PDGFRα, extracellular matrix, angiogenesis