ABSTRACT

Oligodendrocytes, myelin forming glial cells, are counted among the most vulnerable cells of the central nervous system due to their complex differentiation and unique metabolism or physiology. Oligodendrocyte progenitor cells (OPCs) originate from embryonic telecephalon, ganglionic eminences and sub-ventricular zone (SVZ) of the brain, from where they migrate to colonize the entire CNS. OPC migration is regulated by growth factors, chemotropic factors and chemokines. These factors include FGF2, PDGF-A, VEGF, CXCL1, Netrin and Semaphorins. PDGF-AA, is one of the potent growth factor, has been shown to regulate migration and proliferation of OPCs, thereby, serving both as motogen and mitogen. Total ablation of PDGF Receptor-α (PDGFRα) is embryonic lethal, however, the heterozygous knockout shows a significant reduction in myelination with significantly reduced numbers of OL throughout the spinal cord. Recently our group has shown that PDGF-A regulate the oligodendrocytes progenitors cells migration through activation of MAPK-ERK pathway, however, further understanding of the downstream effectors of ERK signalling involve in cytoskeleton reorganization leading to OPCs migration is not yet clear. Other protein kinases are also reported to be involved in the migration of OPCs such as Cdk5 through activation of PDGF-AA. Further, inhibition of ROCK signaling leads to maturation of OPCs into myelinating oligodendrocytes. However, role of ROCK signaling in OPCs migration has not been elucidated. Rho/ROCK signaling also has been seen to be involved in cells migration and found to regulate ERK1/2 pathway. The present study focuses on further downstream targets of PDGF-A induced ERK1/2 activation which involve in cytoskeleton dynamics during OPC migration.. The results show that PDGF-A induced OPC migration was reduced in the presence of MEK inhibitor/siRNA which confirms the involvement of ERK signaling. Further, it was found that PDGF-A induces pERK-paxillin-FAK complex formation and reorganization of actin monomers at the leading edge in OPCs .In addition, the role of ROCK signaling in regulation of PDGF induced ERK1/2 and OPCs migration was also studied. PDGF-A induced migration was reduced in the presence of ROCK inhibitor suggests ROCK signaling crucial for migration. However, inhibition of Rock signaling did not significantly reduce the pERK levels indicating separate pathways and no crosstalk between ERK and ROCK signaling.

Apart from oligodendrocytes, PDGF signaling also have been shown to play an important role in cancer progression. However, role of PDGF signaling in brain cancer such as glioma is not clear. So other parts of this study focus on the role of inhibition of PDGFR signaling in attenuation of glioma progression and underlying molecular mechanisms. The results indicated that the inhibition of PDGF signaling using PDGFR inhibitor and MEK inhibitor affects the growth, proliferation, tumorigenic potentials and migration of Rat C6 glioma cells. Also, PDGF signaling inhibition was found to modulate the actin-myosin reorganization through ROCK signaling. Pharmacological inhibition studied was further supported by overexpression and Knockdown of ERK signaling during glioma progression.