Abstract

Oligodendrocyte progenitor cell (OPC) migration is critical for effective myelination of the central nervous system (CNS). White matter dysfunction is an important feature of many CNS disorders including multiple sclerosis (MS) and vascular dementia. Within injured areas of CNS, myelin loss and oligodendrocyte death though trigger endogenous attempts at regeneration, is nevertheless ineffective. However, during disease progression, remyelination failure may eventually occur due to impaired survival/proliferation, migration/recruitment, and differentiation of OPCs. Different studies indicates that oligodendrocytes behaviors are very complex and regulated by a number of extracellular cues that work supportively to ensure that OPCs arrive in the correct place at the correct time in the white matter tracts. Not only during normal myelination but also during remyelination, the growth factors (GFs) and extracellular matrix (ECM) protein affect the OPC migration. Studies have also shown altered levels of GFs and ECM in the demyelinating lesions. *Understanding the regulatory mechanisms of migration of OPC is crucial to being able to dissect out the subsequent processes that culminate in myelination.* Data from the current study, confirmed that 1ng/ml PDGF-A (physiological concentration) require extracellular matrix (ECM) - fibronectin (FN) synergy for the activation of ERK signaling pathway which is involved in the sustained migration of OPCs *in vitro*. The present study also demonstrates that upon the interaction of integrin's with FN, pERK1/2 is targeted to the cell periphery which also indicates the importance of FN on which the PDGF-A acts as a fuel for the pERK1/2 distribution. PDGF-A and FN collectively increased the pERK1/2-F-actin interaction and enhanced the filopodia formation prior to OPC migration. However, the higher concentration of PDGF-A (10ng/ml) didn't require FN engagement to enhance the OPC migration. Further, data from the present study clarified that PDGFRα activation by higher concentration (10ng/ml) causes αvβ1 and αvβ3 integrin switching, lipid raft microenvironment formation and cytoskeletal rearrangement.

Abstract

"Role of PDGFRα- Integrin Interactions in Oligodendrocyte Progenitor Migration"

Another cell model system used in the present study was C6 glioma, wherein, the PDGFRα and integrin interactions in ECM detached condition, i.e., anoikis resistance was studied extensively. Glioma is the most common brain tumor with very poor prognosis despite recent progress in chemotherapy and immunotherapy. Expression of the cognate ligand, PDGF A-chain, is dramatically increased from low or undetectable levels in low grade (I and II) to high levels in high grade (III and IV) tumors, suggesting a role in tumor progression. Integrins, the receptors of ECM are upregulated in gliomas. Moreover, lipid rafts are found elevated in the cancers and are sensitive to raft depletion. Data from the present study confirmed that PDGFRα activation is essential for integrin switching from αvβ1 to αvβ3; and the actin cytoskeleton and lipid raft interaction is important for the PDGFRα and αvβ3 interactions during anoikis resistance. In conclusion, the data from the current study suggests, firstly, that modifying expression level of integrins on oligodendrocyte precursors may increase the migratory capacity of these cells and secondly, therapeutic strategy may be developed for transplanting genetically modified oligodendrocyte precursors to repair widespread lesions in demyelinating disorders like Multiple sclerosis. In addition, the elucidation of the mechanism underlying the unregulated PDGFRα activation and lipid raft mediated regulation of glioma anoikis resistance will provide new insights into the mechanism of invasion/metastasis and also provide new targets for cancer prevention and therapy.