The role of phospholipase C delta in fibronectin matrix assembly

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Fibronectin (FN), an extracellular matrix glycoprotein, is one of the major regulatory molecules in wound healing and tissue fibrosis, and is upregulated in some types of tumor tissues. Fibronectin matrix is assembled by fibroblasts, and its assembly requires active reorganization of actin cytoskeleton in fibroblasts but details have not been clarified. Phosphatidylinositol 4,5-bisphosphate (PIP2) metabolic pathway is known to involve in actin cytoskeleton dynamics. In this study, we examined the role of phospholipase C (PLC) an enzyme metabolizing PIP2 in modulation of characteristics of fibroblasts including FN matrix assembly. FN matrix was increased in fibroblasts treated with PLC inhibitor or embryonic fibroblasts (MEF) derived from PLC δ family deficient (KO) mice when compared with controls, suggesting that PLC activity negatively regulates FN matrix assembly. FN matrix assembly requires the interaction of FN molecule with α5β1 integrin on the cell surface of fibroblasts. Adhesion of fibroblasts treated with PLC inhibitor and KO MEF to α5β1 integrin-binding domain of FN increased when compared with controls, suggesting that PLC controls FN matrix assembly at the level of the interaction of FN molecule with the integrin. Moreover, scratch assay showed that KO MEF motility was lower than WT MEF. This suggested that genetic deletion of PLC δ family resulted in upregulation of surface level or activity of the integrin, thereby strong adhesion or increased FN matrix caused of reduced motility of fibroblasts. These data suggested that inhibition of PLC activity or genetic deletion of PLC δ family altered characteristics of fibroblasts, an important player in tumor microenvironments, and the technique to modulate PLC activity may lead to develop the tools for treatment of various diseases such as cancer and fibrosis.