【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Agricultural sciences)

Title of Project : Integrative studies on the dynamism of mesenchymal cells during tissue restoration / regeneration

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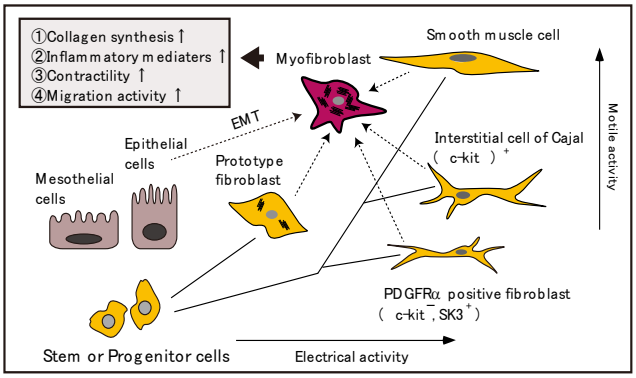
Research Area : Agriculture
Keyword : Tissue restoration/regeneration, myofibroblasts, mesenchymal cells, motility

【Purpose and Background of the Research】

Fibrosis in parenchyma organs (such as liver, heart, lung, kidney and gastrointestinal tracts) is a mortal disease if not properly treated. At present, few drugs are effective in treating fibrosis, and relatively few studies have been conducted on the mechanism of fibrosis comparing with other chronic diseases such as cancer. Major works on fibrosis have focused on the immune and collagen expression mainly noticing the effect of tissue growth factor β (TGFβ).

The purpose of this study is to know if the control of motility function of myofibroblasts, which play critical roles in fibrogenic responses, is benefit for suppressing this disease. For this purpose, we will clarify the mechanism of contractile and migratory functions of these cells in relation to their activation processes.



【Research Methods】

This study covers the cells that are capable to trans-differentiate into active myofibroblasts in gastrointestinal tracts, liver, lung and kidney. We will conduct this research project mainly focusing on signal transduction system for motile functions. Followings are the details of each specific programs with a list of interested molecules.

(1) Mechanism of trans-differentiation (transcriptional system) (SRF/Myocardin, CPI-17, MYPT-1, RhoA, MLCK, SM22 etc.)
(2) Signal transduction for cell motility functions (CPI-17, MYPT-1, RhoA, MLCK etc.)
(3) Epithelial-mesenchymal transition (EMT) and endothelium-mesenchymal transduction (End-MT) as a source of myofibroblast (cadherin, cytokeratin etc.)
(4) Extracellular matrix produced by mesenchymal cells (tenascin-c, collagens etc.)
(5) Mechanism of cell shape change (possible involvement of water permeable channels) (aquaporin, CPI-17, MYPT-1 etc.)
(6) Change of interstitial cell of Cajal in inflammation (c-kit, contractile proteins etc.)
(7) Change of PDGFRα positive fibroblast like cells in inflammation (PDGFRα, SK3 etc.)
(8) Clinical approach for the above mentioned programs (all molecules listed above)

【Expected Research Achievements and Scientific Significance】

Most drug discovery programs for fibrosis have targeted the suppression of inflammation and the reduction of collagen synthesis. Anti-fibrogenic strategy targeting the motility function of mesenchymal cells will provide novel insight into the therapeutic intervention.

【Publications Relevant to the Project】

・Iwanaga K, Okada M, Murata T, Hori M, Ozaki H (2012) Prostaglandin E2 promotes wound-induced migration of intestinal subepithelial myofibroblasts via EP2, EP3, and EP4 prostanoid receptor activation. **J Pharmacol Exp Ther** 340(3):604-611.
・Iizuka M, Murata M, Hori M, Ozaki H (2011) Increased contractility of hepatic stellate cells in cirrhosis is mediated by enhanced Ca^{2+}-dependent and Ca^{2+}-sensitization pathways. **Am J Physiolol** 300, G1010-G1021.

【Term of Project】 FY2013-2016

【Budget Allocation】 151,000 Thousand Yen

【Homepage Address and Other Contact Information】

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