中文題目：半乳糖凝集素-3刺激心臟纖維母細胞增生的分子機制

英文題目：The molecular mechanism of Galectin-3-stimulated cardiac fibroblast proliferation

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Background: Heart failure remains one of the most prevalent and challenging medical conditions. Cardiac fibrosis is one of the major pathophysiological processes that contribute to the development of cardiac remodeling and ultimately resulting in heart failure. Cardiac fibroblasts can proliferate and increase the deposition of the extracellular matrix proteins which leads to cardiac fibrosis and subsequent diastolic dysfunction accounting for 30% to 50% of congestive heart failure in clinical setting. It is well known that in the failing heart, aside from dynamic overload, immunologic and inflammatory processes also play an important role. Previous data revealed that cardiac macrophages are activated at an early stage in failure-prone, hypertrophied hearts and that these macrophages express galectin-3, a 26 KDa β-galactoside-binding protein. Recent epidemiological studies also revealed that serum galectin-3 level is elevated in patients with acute heart failure and is a novel prognostic biomarker of adverse outcomes. Galectin-3 has been shown to be involved in multiple biological processes including cell proliferation, adhesion and death through interaction with its complementary glycoconjugate. However, the molecular mechanisms responsible for galectin-3-induced cardiac fibroblast proliferation remain unclear. In this study, we aim to investigate the proliferative effects of exogenously added galectin-3 on cultured cardiac fibroblasts, identify cell surface glycoproteins attached by galectin-3 and determine intracellular signaling pathways triggered by galectin-3.

Materials and Methods: Culture of cardiac fibroblasts, assessment of cell viability and proliferation by MTT assay and BrdUrd incorporation respectively, phosphorylation of EGFR and ERK1/2 by western blot analysis, interaction between galectin-3 and EGFR by immunoprecipitation assay , and detection of colocalization by immunocytochemistry.

Result: MTT assay revealed that the growth of cardiac fibroblasts treated with galectin-3 for 24hr significantly increased in a dose-dependent manner (1.21-fold increase vs control, $p<0.05$) and BrdUrd incorporation assay showed the 1.24-fold increase of cell proliferation compared with control ($p<0.05$). Western blot analysis showed galectin-3 treatment(1μg/ml) increased tyrosine phosphorylation of epidermal growth factor receptor(EGFR) and phosphorylation of downstream mitogenic signal molecular ERK1/2. This increase of EGFR and ERK1/2 phosphorylation occurred within 1 minute and reach peak at 10 minute after galectin-3 treatment.

Immunoprecipitation assay revealed that galectin-3 interact with EGFR on cell membrane. In addition, we demonstrated colocalization of EGFR and galectin-3 by immunocytochemistry.

Conclusion: This study showed that exogenous galectin-3 cross-link with receptor tyrosine kinase, EGFR and induced autophosphorylation of EGFR and subsequent phosphorylation and activation of downstream mitogenic ERK pathway, ultimately leading to cardiac fibroblast proliferation. Our data may provide molecular basis for galectin-3 as a potential therapeutic target in the treatment of heart failure.