中文題目：在壓力超負荷所引起的心臟纖維化和舒張功能異常，浸潤巨噬細胞分泌的半乳糖凝集素-3 扮演關鍵角色

英文題目：The infiltrating macrophage-secreted galectin-3 plays essential role in pressure overload-induced cardiac fibrosis and diastolic dysfunction

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Background: Cardiac fibrosis is the major pathophysiological process, contributing to the development of diastolic heart failure. We examine the role of circulating macrophage-derived galectin-3 (gal-3) in cardiac fibrosis and diastolic dysfunction in response to transverse aortic constriction (TAC) and elucidate the underlying molecular mechanism.

Method: Wild-type (WT) and gal-3 knock-out (KO) mice were subjected to TAC for two weeks. Immunohistochemistry were used for assessment of myocardial macrophage infiltration, and gal-3 and CTGF (connective tissue growth factor) expression; Picrosirius and Masson stains for myocardial fibrosis; MTT and Brdu incorporation assays for cell proliferation; Flow-cytometry analysis for cell differentiation; Co-immunoprecipitation and confocal microscopy for lectin-carbohydrate interaction and co-localization respectively; Cardiac ECHO for estimation of left ventricular (LV) function.

Result: WT mice after TAC showed significant increase of myocardial macrophage infiltration, gal-3 and CTGF expression, fibroblast proliferation/differentiation, interstitial fibrosis, and impaired LV diastolic function, compared with sham-operated animals ($n=10$, $p<0.01$). Macrophage depletion or gal-3 Knock-out which ameliorated macrophage recruitment markedly suppressed myocardial fibrosis and diastolic dysfunction, and vice versa. In in-vitro, co-immunoprecipitation and confocal microscopy confirmed gal-3-EGFR interaction and co-localization on cell membrane respectively. Flow-cytometry revealed that Gal-3 interacts with cell surface EGFR depending on carbohydrate-binding property. Treatment with recombinant gal-3 increased EGFR and downstream ERK phosphorylation, and CTGF expression in cultured cardiac fibroblasts or their gal-3 knock-down cells.

Moreover, using MTT and Brdu incorporation assays, either direct addition of recombinant gal-3 or co-culture with macrophages significantly promoted cardiac fibroblast proliferation via CTGF expression. Furthermore, pretreatment with Gal-3 or CTGF neutralizing antibody significantly inhibited exogenous gal-3-induced cardiac fibroblast proliferation in culture.

Conclusion: Pressure-overload promotes myocardial macrophage infiltration and the infiltrating macrophage -secreted gal-3 cross-links with its cell surface glycoconjugate, EGFR, resulting in its autophosphorylation, activation of subsequent mitogenic ERK signaling, myocardial CTGF expression, fibroblast proliferation/differentiation and myocardial fibrosis ultimately leading to diastolic dysfunction. Our findings provide molecular basis for gal-3 as a potential therapeutic target in diastolic heart failure.