Title: RECK attenuates CAF-mediated promotion of epithelial-mesenchymal transition in breast cancer

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Abastact: Cancer associated fibroblasts (CAFs) play pivotal roles in modulating behaviors of tumor cells through various mechanisms. Here we analyzed a pair of fibroblastic cells derived from stromal tissue of breast cancer (BC-CAFs) or corresponding normal mammary microenvironment (NMFs). We found that the reversion-inducing cysteine-rich protein with Kazal motif (RECK) was highly expressed only in NMFs. Conditioned media derived from BC-CAFs enhanced epithelial-mesenchymal transition (EMT) in breast cancer cells significantly stronger than NMFs. Similarly, BC-CAFs induced EMT in co-injected breast cancer cells when xenografted into immune-compromised mice. These activities of BC-CAFs were significantly suppressed by RECK overexpression. BC-CAFs exhibited higher rate of active/latent TGF-β1 and active/pro-MMP-2. Induction of RECK in BC-CAFs significantly antagonized EMT induction with diminished activation of TGF-β1 and pro-MMP-2. Inversely, depletion of RECK in NMFs promoted EMT with enhancement of TGF-β1 and pro-MMP2 activation. BC-CAFs express higher level of histone deacetylase 1/2 (HDAC-1/2). Multiple HDAC inhibitors induced RECK in BC-CAFs with concomitant decrease in TGF-β 1and pro-MMP2 activation and ability to induce EMT. BC-CAFs exhibited higher histone acetylation in the promoter of RECK. These findings suggest that RECK ectopic expression in BC-CAFs suppresses TGF-β1 maturation by inhibiting pro-MMP-2 activation thereby attenuates EMT and that RECK promoter deacetylation occurs in fibroblasts associated with developing breast cancer. HDAC inhibitors may exhibit therapeutic efficacy in breast cancer by inducing RECK in BC-CAFs.

Keywords: Breast cancer (BC) Cancer-associated fibroblasts (CAFs) Reversion-inducing cysteine-rich protein with Kazal motifs

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