IL-6 induces epithelial-to-mesenchymal transition in MCF-7 cells via SRc-FAK signaling

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Background: The difficulties in breast cancer treatment are attributable to highly metastatic ability of breast cancer cells. The aberrant activation of epithelial-to-mesenchymal transition (EMT) contributes and enhances tumor metastasis. Growing evidence demonstrates that serum interleukin-6 (IL-6) level increases with tumor grade of breast cancer. In addition, recent study indicates that IL-6 induces EMT in breast cancer cells with an epithelial phenotype. However, the mechanisms underlying IL-6-induced EMT in breast cancer remain incompletely understood.

Methods: In this study, MCF-7 breast cancer cell with an epithelial phenotype was used to explore the signaling mechanisms involved in IL-6-induced EMT.

Results: IL-6 induced EMT in MCF-7 cells, as evidenced by induction of the mesenchymal markers twist, snail, slug and repression of the epithelial marker E-cadherin. IL-6 is also capable of increasing cell motility in MCF-7 cells. These actions were associated with Src, FAK, ERK and p38 mitogen-activated protein kinase (MAPK) activation, as well as the phosphorylation of STAT3, p65 and C/EBPβ. Src-FAK signaling blockade reduced IL-6's enhancing effects in inducing ERK, p38MAPK, STAT3 p65 and C/EBPβ phosphorylation and subsequent EMT. In addition, inhibitors of ERK or p38MAPK reduced IL-6-induced p65 and C/EBPβ phosphorylation and EMT. STAT3 knockdown by STAT3 siRNA also suppressed IL-6-induced EMT. Furthermore, IL-6 caused increases in STAT3, p65 and C/EBPβ binding to the twist promoter region in MCF-7 cells.

Conclusions: These results indicated that IL-6 may activate Src-FAK-STAT3 signaling cascade, leading to EMT and subsequent breast cancer metastasis. ERK and/or p38MAPK signaling and transcription factors p65 and C/EBPβ may also contribute to IL-6-induced EMT in MCF-7 cells.