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**LMO4 Modulation on Regulation of TGFβ Signaling and its Implications in Breast Cancer Metastasis**

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**ABSTRACT**

Transforming Growth Factor β (TGFβ) is one of the main cytokines that plays essential roles in regulating epithelial-mesenchymal transition (EMT). TGFβ confer a unique characteristic in which they able to act as a tumour suppressor during the early stage of cancer development. Meanwhile, as the cancer progresses into the late stage, TGFβ switches its function and become tumour promoter. The recently uncovered regulator of TGFβ signalling which is the fourth member of LIM-only-domain protein; LMO4, has been discovered to be highly expressed in tissues with active EMT and is differentially expressed in breast carcinoma samples. To investigate the correlation between LMO4 and TGFβ signal transduction pathways, we used mouse mammary tumour cell line, 4T1 and its generated form of LMO4 knockdown. We found that knockdown of LMO4 expression in 4T1 cells enhance TGFβ Smad3 promoter activity as well as increase the phosphorylation of Smad2, suggesting that LMO4 may mediate TGFβ pathway. Furthermore, we also discovered that LMO4 modulation on TGFβ signalling enhances the EMT which consequently led to 4T1 cells differentiation in mesenchymal-like cells, increase in migratory and invasion capacity and poor cells adhesion. Surprisingly, although knockdown of LMO4 enhances TGFβ-mediated cell migration which is a part of EMT, however, the detachment and reseeding of the migrated cells which resemble the reversal process; MET, was inhibited. These results define a novel function of LMO4 as a co-repressor in TGFβ (Smad-dependent) signalling pathway and suggest its involvement during breast cancer metastasis. Moreover, these findings also suggest that knockdown of LMO4 TGFβ is not just able to enhance TGFβ-mediated EMT but may also negatively implicate MET. Identification of LMO4 as a modulator of TGFβ signalling may be useful in providing clearer molecular and cellular targets for development of anti-cancer therapeutics at different stages of cancer development.