The Role of Deptor in Breast Cancer Metastasis

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Mammary tumorigenesis converts Transforming Growth Factor-ß (TGF-ß) from a tumor suppressor in normal tissue into a tumor promoter in the later stages of breast cancer by inducing epithelial-mesenchymal transition (EMT) programs that drive metastasis. How TGF-ß acquires tumor-promoting characteristics during metastasis remains unknown, as does the role of Deptor, the endogenous inhibitor of mTOR. It is known that Deptor exhibits decreased expression during metastatic progression. As such, the objective of this study was to determine (i) whether TGF-ß regulated Deptor expression in breast cancer cells, and if so, through which downstream effectors, and (ii) how aberrant Deptor expression impacts the growth of breast cancer cells. Our analyses suggest that Smad3 activation was required for TGF-ß mediated downregulation of Deptor and that decreased Deptor expression is a characteristic of EMT. Functionally, downregulation of Deptor expression in metastatic (4T07) cancer cells inhibited their growth in vitro and in vivo. Lastly, forced expression of Deptor in cells that originally did not contain Deptor (MDA-MB-231) induced enhanced pulmonary outgrowth in vivo. Collectively, this study explains the dichotomous roles Deptor plays in regulating the growth and survival of breast cancer cells during the metastatic cascade.

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