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Identifying role of N-myristoyltransferase in the mTOR signalling cascade of ER-α positive breast cancer cells (MCF-7)

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Breast cancer is the most common malignancy in women from the western world. Estrogen receptor (ER) is a key regulatory in the malignancy of breast cancer. The status of the ER-α of breast tumours is used for predicting response to endocrine therapy. ER-α can be post-translationally modified multiple ways including but not limited to phosphorylation, acylation and, ubiquitination. ER- α can be phosphorylated on multiple amino acid residues throughout the whole protein and within all major structural domains: the N-terminal A/B domain, the DNA-binding or C domain, the hinge or D domain and, the ligand-binding domain or E domain. When phosphorylation occurs in the N-terminal domain it is associated with good endocrine therapy outcome, while phosphorylation that occurs in the C-terminal domain leads to poor prognosis. For example, phosphorylation of the ER-α at S^{118}, S^{167}, and S^{236} predict better prognosis whereas, T^{311}, Y^{537}, and S^{559} predict poor outcome. This has lead to a phosphorylation score called P7 score that more precisely predicts prognosis. Independent studies suggest ER- α phosphorylated at $serine^{118}$ leads to good endocrine therapy prognosis while phosphorylation at $tyrosine^{537}$ leads to poor outcome. N- myristoyltransferase (NMT) is an enzyme that modifies proteins by covalently attaching a myristic acid to their N-terminal end. The non-receptor tyrosine kinase pp60cSrc phosphorylates ER- α at $tyrosine^{537}$ leading to poor prognosis. Myristoylation of pp60cSrc is essential for its activation. The mTOR pathway member Akt/PKB regulates NMT1 activity thus establishing a crosstalk between mTOR pathway and NMT mediated signalling pathways. Therefore, we investigated mTOR-NMT-cSrc mediated regulation of ER-α in ER-α positive MCF-7 cells by inhibiting mTOR and ER-α. Results suggest increased expression of NMT1 upon down-regulating mTORC1 activity and further activation of NMT mediated signalling pathway such as activation of c-Src. Understanding of ER-α activation mechanism would lead to identification of panel of surrogate markers, which would aid in designing treatment protocols for better endocrine therapy outcomes.

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