Endocrine resistance in breast cancer

Current therapeutic strategies for treating estrogen receptor (ER) positive breast cancer involve either reduction of circulating estrogen (in premenopausal women by ovariectomy or chemical ovarian blockade with LHRH analogues such as goserelin or in postmenopausal women with aromatase inhibitors such as anastrazole and letrozole and application of selective estrogen receptor modulators such as tamoxifen, raloxifene and fulvestrant for pharmacological receptor blockade. The success of these interventions is limited by the variable but persistent onset of acquired resistance as well as intrinsic refractiveness due to loss or non-functionality of the target ER. Cellular models of endocrine insensitivity have indicated multiple mechanisms including alternative growth factor mediated signaling independently as well as by constitutive receptor activation by phosphorylation or through epigenetic mechanisms. Drugs targeting single downstream mediators such as tyrosine kinases, m-TOR, PI3K, ERK etc that are effective in vitro have met with limited success in vivo, most likely due to tumor heterogeneity. Loss of cellular adhesion and polarity and increased tumor migratory potential is now attributed to trans-differentiation of epithelial cancer cells into a more motile mesenchymal-like phenotype (EMT) and we have shown this to be linked to ER loss. Reversal of this transition by ectopic expression of key components demonstrates potential to restore epithelial morphology and anti-estrogen sensitivity. The small non-coding micro RNAs recently recognized as critical gene regulators, exhibit differential expression in tamoxifen sensitive vs. resistant cell lines and offers an entirely new more universal mechanism to combat resistance by reversing the aggressive metastatic phenotype by EMT reversal.

Biography

Yunus A Luqmani has graduated from Chelsea College, University of London and he has obtained his PhD in Neurochemistry from Imperial College followed by Postdoctoral Research at Max Planck Institute for Biophysical-chemistry, Gottingen. After further appointments at various London Institutes including Queen Elizabeth College, Ludwig Institute for Cancer Research at Royal Marsden Hospital, St George’s and Charing Cross Hospitals, he was appointed as an Associate Professor at Kuwait University in 1994. He is currently a Professor and Chairman of the Department of Pharmaceutical Chemistry in Faculty of Pharmacy at Kuwait University. His research studies focus on identifying cellular processes that are implicated in resistance to endocrine therapy of breast cancer.

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