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Estrogen Receptor Regulation – Don't Forget Translation

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To The Editor: Immunohistochemical analysis of ER α in breast cancer is now routine and plays a major role in the selection of appropriate adjuvant endocrine therapy in patients with this disease¹. Nevertheless, the predictive value of such a test has been questioned due to problems associated with technical feasibility and reproducibility. A recent report in Breast Cancer Research and Treatment by Pentheroudakis et al. sought to address this issue by using the kinetic reverse-transcriptase polymerase chain reaction (kRT-PCR) technique to assess the predictive significance of ER α , PgR and microtubule-associated protein Tau at the level of mRNA expression in early breast cancer². This study was based on previous reports suggesting a satisfactory correlation of mRNA levels and protein levels as determined by IHC³⁻⁵. Despite this, after excluding chance agreement estimated by the Kappa co-efficient, their results revealed only a fair to moderate concordance between IHC and kRT-PCR determination of ER α (Kappa = 0.41) and PgR (Kappa = 0.33) expression². Also, only a trend towards significance between ER α mRNA status and benefit from hormonal therapy in patients with early breast cancer was observed².

ER exists as 2 genetically distinct isoforms, ER α and ER β and it is now becoming clear that complex regulatory mechanisms exist for both subtypes. ER α mRNAs are produced from multiple different 5'UTRs that have differential effects on translation⁶. Furthermore, expression

levels of ER α mRNAs containing specific 5'UTRs have been correlated with endocrine responsiveness in breast cancer patients⁷. Our own work on ER β demonstrates that two different ER β 5'UTRs have potent, yet differential, inhibitory effects on ER β translation and this contributes to deregulation of ER β expression in breast cancer⁸. In the case of progesterone receptor (PR), there is less direct evidence for a role for 5'UTRs in regulating protein expression. However, it is well established that the two functionally different human PR isoforms (A and B) are associated with different 5'UTRs⁹, and variant forms of these UTRs appear to exist, at least within Genbank.

In conclusion, we suggest the complex regulatory mechanisms for members of the nuclear receptor superfamily, which are beginning to be unravelled, may provide an explanation for the inconsistencies observed between mRNA and protein expression. This casts doubt on the use of transcriptional profiling for predicting pathway activities or benefit from hormonal therapy in breast cancer.

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