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Translational Control of Estrogen Receptor Alpha Expression

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Estrogen Receptor Alpha (ERα) expression in breast tumors is a favorable prognostic factor. ER mRNA is transcribed from two promoters, variable relative use occurs in breast tumors. The proximal (prox) ER promoter transcribes a complete exon one whereas the distal promoter is 2kb upstream in the genome and splices into nt164 of the prox form. The 5' region of ER prox promoter transcript contains a 20 amino acid residue upstream open reading frame (uORF) terminating 50 bases upstream of the main ER translational start which is shared by both transcripts. We analyzed expression from ER-Green Fluorescent Protein (GFP) fusion constructs of prox-ER upstream sequences and the first 18 ER codons. Using flow-cytometry and western blotting we showed that prox_uORF elimination increases GFP levels. We hypothesize the lack of correlation between ER-protein and prox-transcript levels in breast tumors is due to inhibitory translational control by the prox-peptide. Replacing the C-terminal (Phe) codon with termination codons further inhibited expression of GFP fusion proteins. The super inhibitory effect of the Phe to stop mutations is related to the peptide of the ORF as inhibition was reversed by eliminating the prox_uORF translational start codon. Effects were similar in each of several ER positive and negative cell lines. Our goals are to understand the control of ER expression, to determine consequences of alternate promoter and possibly develop strategies to manipulate ER expression based on alternate promoter features as an preventive or therapeutic treatment.