Luteinizing hormone signaling and LH receptor biosynthesis: polymorphisms and breast cancer

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A main regulator in the production of sex steroids is luteinizing hormone (LH). LH receptor (LHR) gene variants may alter the set point of hormonal regulation of estrogen production. In the LHR gene a CTGCAG insertion at position 18 in exon 1 results in a Leu-Gln (LQ) insertion in the hydrophobic (h-) region of the signal peptide (allelic frequency 0.26). By PCR-RFLP genotyping of 266 breast carcinomas we found that women homozygous for +LQ-LHR were on average 8.3 years younger at age of diagnosis compared to homozygous -LQ-LHR women (p=0.03). Furthermore overall survival was significantly worse for +LQ carriers compared to -LQ-LHR homozygotes.
We hypothesized that the LQ insertion in the signal sequence influences targeting of the nascent protein to the ER for translocation and subsequent maturation processes.
To test this hypothesis we have studied the influence of insLQ on protein synthesis by stably transfecting HEK 293 cells with an LHR exodomain construct, either with +LQ or –LQ signal sequence.
Using reducing treatment as a sensor for folding and deglycosylation enzymes PNGaseF and Endo H to specify glycosylation status of the protein products, we concluded that part of the newly formed –LQ protein was not translocated in the ER membrane.
After comparing the + and –LQ signal peptide constructs vs. no signal peptide; no h-region and the efficient hemagglutinin signal peptide we conclude that the increased hydrophobicity of the h-region is responsible for better ER targeting of the +LQ variant. This seems to lead to higher cell surface expression for the +LQ variant as reflected by a higher Bmax. Finally altered differential maturation may be indicated by a significant increase in EC 50 for the +LQ (0.20) vs. –LQ-LHR (0.32).
In conclusion: the +LQ variant is biologically more active then its –LQ counterpart, this may contribute to breast tumorigenesis.

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