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A functional link between ER and the Breast Cancer SNP rs7716600

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Abstract

Cancer is a genetic disease characterized by uncontrolled cell growth due to genomic and epigenetics alterations, which may have an effect on susceptibility to cancer. Genome Wide Association Studies have revealed multitude of breast cancer-associated Single Nucleotide Polymorphism (SNPs). The majority of these SNPs are located in non-coding regions of the genome. Yet, how these SNPs influence directly the function of Estrogen Receptor in breast cancer patients is poorly known. In this work, we hypothesized that changes in the chromatin status, in the binding of transcription factors and in gene expression might be regulated by natural genetic variants, which ultimately might affect breast cancer development.

We performed Quantitative Train Locus (eQTL) studies on breast adenocarcinoma and normal breast samples. The analysis of the data revealed that the locus rs7716600 at 5p12 region is linked to breast cancer susceptibility. Importantly, the analysis of the data also showed that the different locus variants are associated with the expression of the Mitochondrial Ribosomal Protein S30 (MRPS30) and it is exclusively linked with ER-positive breast tumours. Further genomic analyses in breast cancer cells have revealed that the expression variant allele AA is associated with the methylation of the promoter, which correlates with a significant reduction of the expression of the gene. To gain insight into the mechanism of action, we performed functional experiments with MCF-7 breast cancer cell line, which is positive for the expression of ER and holds the variant allele AA. The results showed that MRPS30 expression is down regulated upon estrogen treatment and its expression is associated with the binding of ERand with the repressor CTCF. Importantly, the binding of these critical factors occurs at the promoter and close to the SNP associated region, which suggests that CTCF might generating a chromatin repressive loop and might be explaining the repressive expression of the gene.

Altogether, these data suggest that genetic variants of the locus 5p12 can affect ER-positive breast cancer development, which is expressed in the 70% of the breast tumors. In the future, the analysis of 5p12 locus variant may become an important clinical biomarker for breast cancer susceptibility and strongly impact breast cancer prevention.

Biography

Antoni Hurtado obtained his undergraduate degree in Biology in 1998 and his masters in 2000 in Barcelona (Spain). Later on in 2001 he started his PhD at Vall-Hebron research Institute (Barcelona, Spain). Finally, in 2007 he moved to Cambridge Research Institute-CRUK (Cambridge, United Kingdom) to start his post-doctoral stage in Cambridge, where he made an important contribution to understand the molecular mechanism of tamoxifen resistance. His work has given new insight into how ER transcriptional activity is modulated by cooperative transcription factors in breast cancer: FoxA1, that orchestrates ER binding on the chromatin, and PAX2, that dictates the transcriptional activity of ER induced by tamoxifen. The scientific quality and innovation of such works have been recognized in several international meetings and by the company BiogenIdec, which awarded him with the prize: the best Spanish Young Investigator of 2009 in Oncology research. From August of 2011 he holds a group leader position at NCMM-EMBL Nordic partnership institute in Oslo.