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Session A. Breast cancer

A30 Genetic and epigenetic factors affect RET gene expression in breast cancer cell lines and influence survival in patients

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Background: The RET proto-oncogene encodes for a transmembrane tyrosine kinase receptor whose signalling pathway is activated by the binding with one of its ligands and coreceptors. Aberrant RET signaling is oncogenic, as demonstrated by its involvement in different human cancers. In recent years, a large body of evidence has demonstrated that RET is overexpressed in a subset of breast cancer (BC). In particular, in Estrogen Receptor-positive (ER+) breast tumors, overexpression of RET resulted to be involved in endocrine resistance.

Materials and methods: We investigated the molecular mechanisms (either genomic, transcriptional or post transcriptional) which underlie RET overexpression, and its possible modulation in BC, in two ER+ cell lines, MCF7 and T47D, known to express high e low levels of RET mRNA. Looking for genetic variants responsible of variable RET expression, we have also carried out a pilot association study in 93 ER+ BC patients.

Results: We noticed that RETexpression is similarly modulated by estrogens in MCF7 and T47D while treatments with TNF, IL-8 and deacetylase inhibitors differently affect RET expression in BC cell lines. After sequencing ER-responding regions and a known enhancer in intron 1 at RET locus, we identified two single nucleotide variants rs12247450 and rs2435357, whose genotype is different between MCF7 and T47D, possibly accounting for the opposite RET expression pattern. In particular, SNP rs2435357 is associated with reduced expression of the gene. T47D cells carry the genotype associated with lower expression and this data can explain both the reduced expression of the RET gene and the different response to Sodium Butyrate. We carried out a pilot study genotyping for rs2435357 a cohort of 93 ER + early BC patients. We observed a statistically significant increased OS in patients with one of the variant alleles (CT or TT) in comparison to those carrying the CC wild type allele. The association was confirmed in multivariate analysis, where nodal status, grading, HER2 status and Ki67 were adjusted for (HR = 0.243, 95%; CI = 0.088-0.675; P = 0,007).

Conclusions: Our data are consistent with the observation that RET overexpression is associated to poor prognosis in ER+ BC and strongly candidate this SNP as prognostic factor. These findings might deepen into the role played by RET in breast tumorigenesis and stand RET as a potential candidate molecular target for BC treatment.