Functional Interaction of Estrogen Receptor Beta and Argonaute 2 in Transcriptional Modulation of Gene Expression in Breast Cancer Cells
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Estrogen Receptors (ER) are ligand-inducible transcription factors that regulate the expression of target genes, with ERβ inhibiting estrogen-mediated cell proliferation by enhancing expression of growth-inhibitory genes and counteracting ERα actions in breast cancer (BC). Thus, the presence of ERβ represents a positive prognostic value and understanding its role in carcinogenesis may help in prognosis and cancer therapy.

Experimental evidences show ligand-independent ERβ actions, since, in hormone-deprived human BC cells, unliganded ERβ strongly modulates gene expression profiles. ERβ may exert these functions by recruiting different co-regulators onto specific DNA sequences. To identify molecules associated with unliganded ERβ in BC cell nuclei, Tandem Affinity Purification (TAP) coupled to mass spectrometry (MS) was applied. Among 306 proteins identified, resulting to be associated with ERβ, particular interest has been given to protein Argonaute 2 (AGO2), involved in transcriptional gene silencing induced by microRNAs. Gene Ontology analysis performed with all ERβ-associated proteins revealed that nuclear AGO2, together with several molecular partners of ERβ, are mainly involved in transcriptional repression. ERβ/AGO2 interaction and the nuclear co-recruitment of other known AGO2 interacting proteins were also confirmed by co-immunoprecipitation in MCF-7 cells expressing tagged ERβ. AGO2 silencing determined significant changes in the expression of unliganded ERβ regulated genes. Chromatin ImmunoPrecipitation followed by massively parallel sequencing (ChIP-Seq) allowed the identification of ERβ- and AGO-binding sites within BC cells genome, indicating a functional role of ERβ/AGO2 complex in hormone-independent gene regulation in BC.

RESEARCH SUPPORTED BY: AIRC (Grant IG-13176), MIUR (FIRB RBFR12W5V5_003) University of Salerno (FARB 2012-2013), EU COST (Action BM1006 ‘SeqAhead’), CNR InterOmics Flagship Project, a ‘Vladimir Ashkenazy’ AIRC fellowship (to M. Ravo) and a FIRC ‘Mario e Valeria Rindi’ fellowship (to G. Nassa).*A.S. is a PhD student of the Research Doctorate “Sciences and Biomedical Technologies”, University of Roma Tre, Roma (RM), Italy; +G.B. is a PhD student of the Research Doctorate ‘System Biology’ of University of Salerno, Baronissi (SA), Italy.