A gene profile that identifies molecular subtypes of breast cancer is highly enriched in genes having Estrogen Receptor binding sites

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Background

Classification of breast cancer into molecular subtypes may be important for the proper selection of therapy, as tumors with seemingly similar biology can have strikingly different clinical outcomes. We have previously developed an 80-gene molecular subtyping profile (BluePrint) for the classification of breast cancer into three molecular subtypes: triple-negative ("Basal-type"); hormone receptor-positive ("Luminal-type") and ERBB2-positive ("ERBB2-type"). In this study, we sought to determine if Luminal-type tumors are characterized by active ER signaling.

Methods

ERα ChIP-seq data from proliferating MCF-7 breast cancer cells was used from a publically available dataset [Ross-Innes, 2010]. The transcription start sites of the 58 genes in the gene set that identifies the Luminal-type subgroup were determined. The presence of Estrogen Receptor binding sites was analyzed within a window of -/+ 20 kb from the transcription start site. The sequence track was visualized using the UCSC genome browser (http://genome.ucsc.edu/). Peak intensity was determined from the tag count.

Results

We found that 32 of the 58 Luminal profile genes have ERα binding sites adjacent to their promoters (55%), whereas only ~28% of all RefSeq genes (~24,000) have ERα binding sites in their promoters. This result indicates that the genes associated with Luminal-type breast cancer are significantly enriched for those that have ERα binding sites adjacent to their promoters (p= 1.2e-5).

Interaction network between the Luminal genes and the Estrogen Receptor

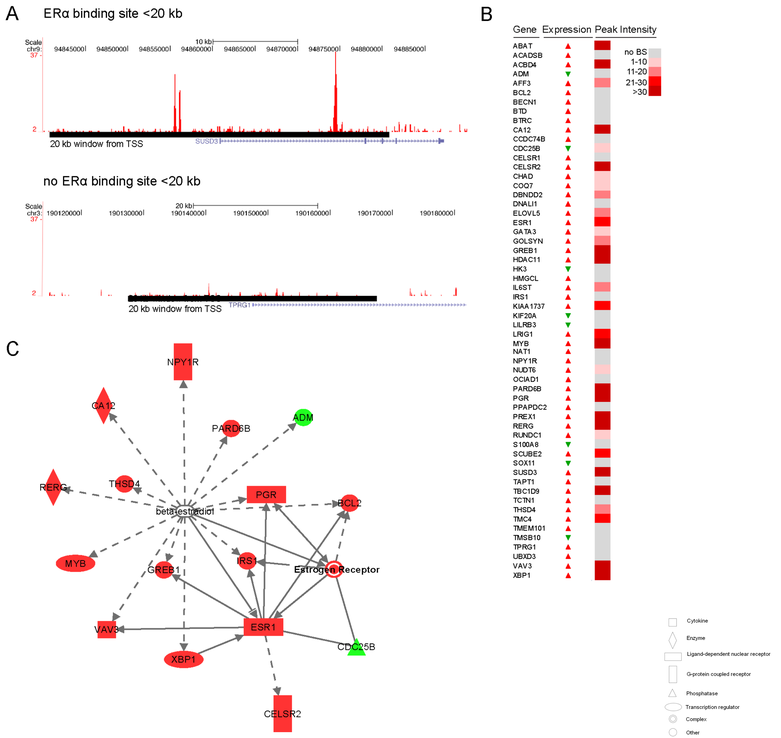

Figure legends

Luminal signature genes show enrichment for Estrogen Receptor binding sites close to their transcription start sites. Estrogen Receptor ChIP-seq analyses were performed from a publicly available dataset of proliferating MCF7 breast cancer cells, and the Estrogen Receptor binding site occupancy was determined within a 20kb distance from the transcription start site of a gene from the luminal signature.

Figure A: Example of the presence (top panel) or absence (bottom panel) of an Estrogen Receptor binding site within a 20kb distance from the transcription start site.

Figure B: Estrogen Receptor binding site presence was determined for all genes in the Luminal signature and visualized in a heatmap.

Figure C: Interaction network between the Luminal genes and Estrogen Receptor. Seventeen of the Luminal genes are proven to have interactions with ER. A dashed line indicates an indirect interaction and a solid line indicates direct interactions. Red/Green indicates that the gene is up/down-regulated in the Luminal-type subgroup. The shape of the gene indicates the type of the protein encoded by this gene.

Conclusions

- Luminal-type associated genes are enriched for ER binding sites proximal to the transcription start site, suggesting that these genes are direct targets of ER.

- Classification of breast tumors as "Luminal" by BluePrint most likely describes breast cancers that depend of ER signaling.

- This data suggests that Luminal-type breast cancer are likely to response to endocrine therapy.