Estrogen receptor pathway activity in endometrial carcinomas and its relation to tumor grade and disease related mortality

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Background

Immunohistochemical (IHC) loss of expression of the estrogen (ER) and progesterone receptor (PR) from endometrial carcinomas (EC) is associated with high tumor grade, and with recurrent disease. However, receptor expression does not always mean the ER pathway is active.

The activity of signal transduction pathways (including the ER pathway) can be assessed with a new method. A pathway activity score from the mRNA levels of the target genes of the pathway-specific transcription factor is calculated using a computational Bayesian model.

The objectives of this study were to compare ER pathway activity to ER/PR IHC results with respect to endometrial carcinoma grade and disease related mortality.

Methods

Datasets
- Affymetrix dataset of fresh frozen (FF) tissue (GSE56026)
- Formalin fixed, paraffin embedded tissue (FFPE) from endometrial carcinomas treated at the Radboud university medical center

Cases
- Grade 1 endometrioid EC (Affymetrix n=28, FFPE n=36)
- Grade 2 endometrioid EC (Affymetrix n=75, FFPE n=32)
- Grade 3 endometrioid EC (Affymetrix n=41, FFPE n=12)
- Serous EC (Affymetrix n=10, FFPE n=15)

Analysis
- ER pathway activity analysis using Affymetrix microarray (FF tissue) or qPCR (FFPE tissue)- based ER pathway model (Figure 1)
- IHC: 4µm FFPE sections stained for ER (1:80 diluted SP1 RM-9101-S antibody) or PR (1:500 diluted PgR636 antibody) expression

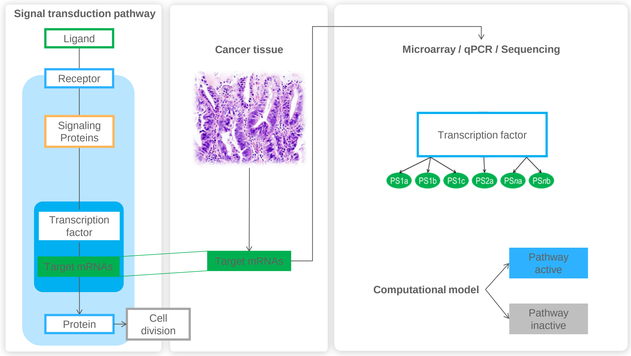

Figure 1. Input for the measurement are Affymetrix HG-U133Plus2.0 microarray data or qPCR. The Bayesian network model has three types of nodes: a transcription complex, target genes and probesets. The model describes (i) how expression of target genes depends on activation of the respective transcription complex, and (ii) how probeset intensities depend in on the expression of the target genes.

Models can be used to quantitatively measure pathway activity in an individual test sample by entering mRNA measurements, and inferring backwards in the model the probability (or log2odds) that the active transcription complex must have been present.

Results

Affymetrix
- Inverse relation between pathway activity and tumor grade, with significant differences between grade 1-2 EC, and grade 3 and serous EC (Figure 2)

FFPE tissue
- Inverse relation between pathway activity and tumor grade (Figure 2), with a significant difference between grade 1-2 EC, and grade 3 and serous EC (p=0.03)
- Univariate analysis: ER/PR IHC, and ER pathway activity (Figure 2) associated with disease related mortality
- Multivariate analysis: only advanced stage and ER pathway activity associated with disease related mortality

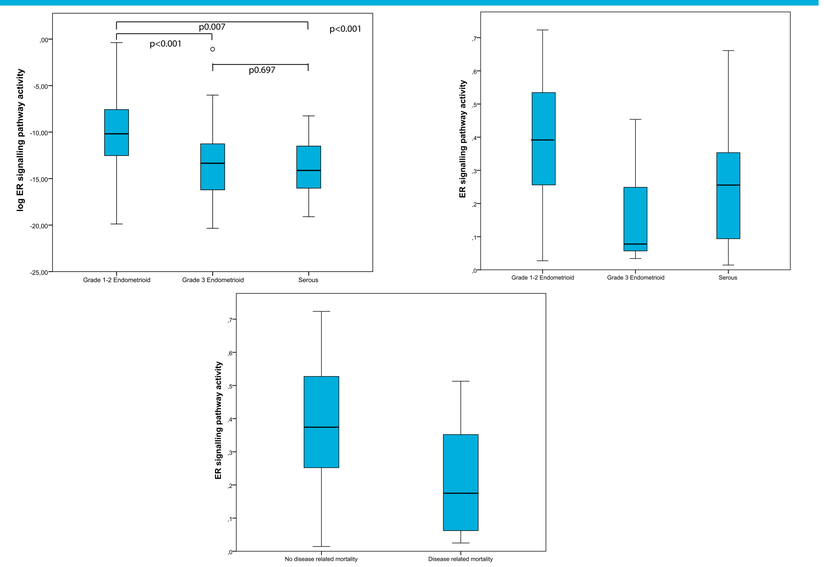

Figure 2. Relation between grade and pathway activity as shown using Affymetrix data (top left), and using qPCR data (top right), as well as the relation between pathway activity and disease related mortality using qPCR data (bottom)

Conclusion

There is an inverse relationship between ER pathway activity and endometrial carcinoma grade

Presence of the ER and/or PR receptor does not mean the ER pathway is active

ER pathway activity, measured by either Affymetrix microarrays or qPCR, is a stronger predictor of disease related mortality than the presence of the ER and/or PR receptor, as measured by immunohistochemistry

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