Does Hormone Expression by IHC predict ER Pathway Activity? An Analysis in A Metastatic Breast Cancer Patient Cohort.

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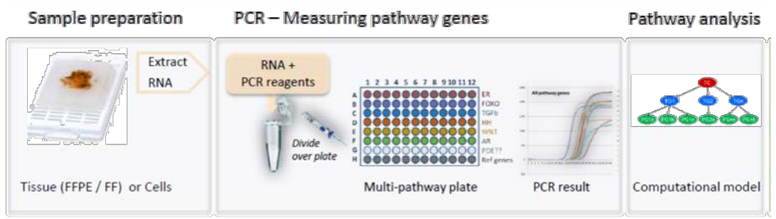
Abstract

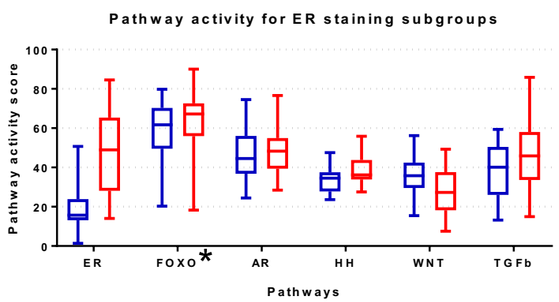
Background: Immunohistochemistry (IHC) staining for ER and progesterone (PR) receptors in breast cancer tissue is the current standard for testing for eligibility for hormone targeted therapies[1]. However, these markers are imperfect predictors of response, and ER/PR expression can be heterogeneous, especially in the metastatic setting. Within an adjuvant tamoxifen-treated ER positive patient group functional ER pathway activity was associated with improved patient outcome[2]. This study investigated how ER/PR staining correlates with ER pathway activity in a cohort of metastatic breast cancers.

Methods: Cases of metastatic breast cancer with variable reported ER expression by IHC were selected from the Stanford Pathology Database. Cases were scored by a breast pathologist for percent cellularity of sample, percent and intensity of ER and PR staining, and a qualitative rating of heterogeneity of staining. Digital slides were annotated for areas of cellularity to perform ER pathway activity analysis. Functional ER pathway activity was measured in a quantitative manner using a biologically validated method, based on Bayesian computational model inference of functional pathway activity from RT-qPCR measurements of mRNA levels of target genes of the pathway transcription factor, providing an ER Pathway Activity Score (PAS)[2].

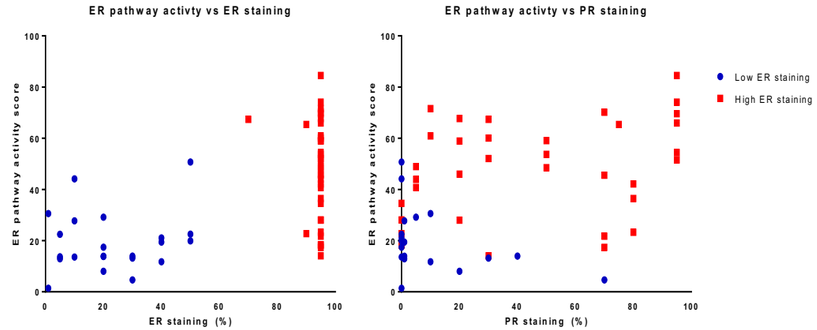
Results: A total of 64 samples were tested for ER/PR expression as well as for ER pathway analysis. Annotated tumor areas of 57 samples were used for measurement of ER PAS. 61.4% were ER expression high (defined as ≥50% ER IHC positive, mean 94.0%) and 38.6% were ER low (defined as <50% ER IHC positive, mean 23.0%). ER high cases had higher mean ER PAS when compared to ER low cases (ER high, mean PAS 47.6, SD 19.2; versus ER low, mean PAS 19.4, SD 11.7; unpaired one-tailed 2-sample t-test p<0.001). Importantly, there was a wide variation in ER PAS even in cases with high ER expression levels. PR levels did not correlate with ER PAS. Three cases had clustered areas with different ER expression levels within the tissue slide (heterogeneous cases), resulting in 7 separately analyzed areas; ER pathway activity was separately analyzed in these areas. ER PAS was remarkably similar across areas with variable ER staining, e.g. within one tissue slide, areas with 20% and 90% ER expression had nearly the same ER PAS.

ER Pathway Activation Score

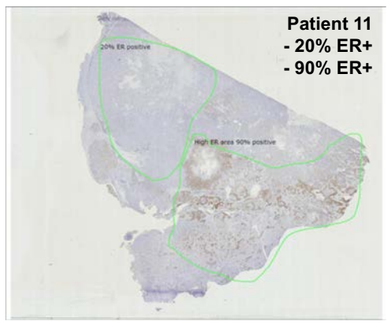


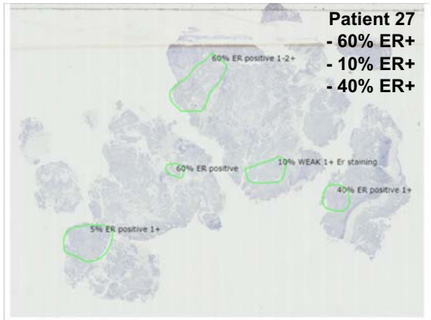


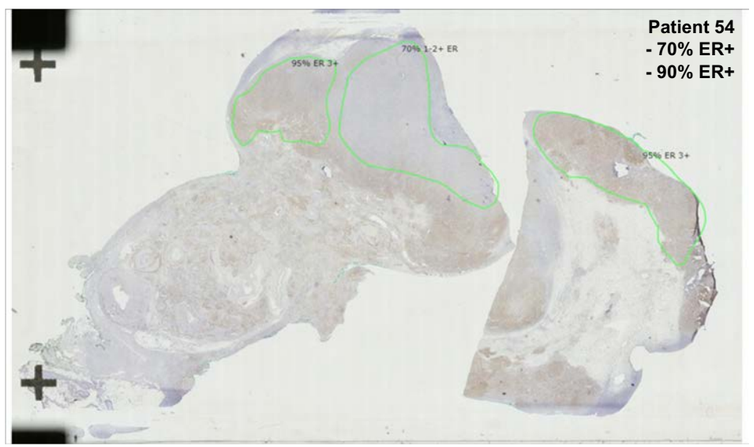
ER IHC vs. ER Pathway Activity



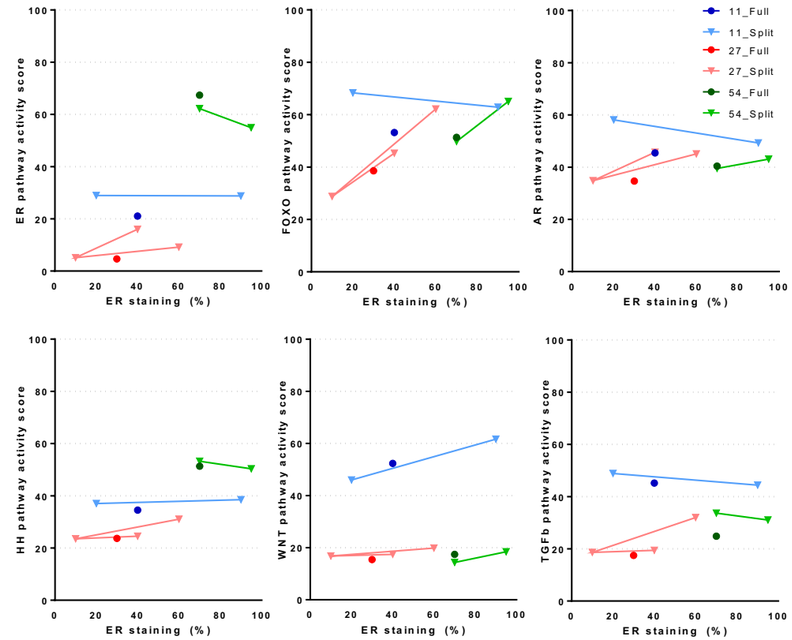
ER IHC Heterogeneity







ER IHC Heterogeneity vs. Pathway Activity



Conclusions

- Grouping cases into high vs low ER IHC staining reveals expected differences in ER PAS and confirms earlier results suggesting that ER IHC staining is necessary for ER activity[2]
- ER IHC levels may be an imperfect predictor of actual ER pathway activity on an individual case basis
- Preliminary results on cases with regional heterogeneity for levels of ER IHC expression suggest that ER PAS is more homogenous than IHC levels
- Clinical studies examining value of ER PAS to predict response to hormonal therapies are ongoing. Initial results are promising for using ER PAS to predict response to hormonal therapy[2] & publication in prep

References

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Disclosures

Anja van de Stolpe, Anne van Brussel, and Henk van Ooijen are employees of Philips.

The remaining authors declare no competing financial interests.