San Antonio Breast Cancer Symposium - December 7-10, 2021

Evaluation of the Activity of Key Actionable Oncogenic Driving Pathways in Triple Negative Breast Cancer Using OncoSignal™; a Novel Molecular Assay Based on Transcriptional Profile Analysis

Genevra Magliocco[1], Eveline den Biezen[2], Diedrick Keizer[2], Martijn Akse[2], Martijn van Zelst[2], Dianne van Strijp[2], Saskia Vermeer[2], Anja van de Stolpe[2], and Anthony Magliocco[3].

[1]Boston University School of Medicine, Boston, MA; [2]Philips Molecular Pathway Diagnostics, Eindhoven, Netherlands; [3]Protean BioDiagnostics Inc, Orlando, FL

INTRODUCTION

Triple negative breast cancer (TNBC), defined by the absence of expression of estrogen receptor (ER), progesterone receptor, and HER2, is a heterogenous subgroup of breast cancer which currently accounts for a significant proportion of the mortality from the disease. Consequently, there is an urgent need to identify more effective therapy for women with this type of breast cancer. We have recently developed a novel assay, OncoSignal™ which is capable of precisely measuring the activity of seven key signaling pathways through utilizing measurements of mRNA. The assay quantitatively determines the specific activity of ER, androgen receptor, PI3K, MAPK, HedgeHog, Notch, and TGFβ signal pathways via measurement and analysis of mRNA expression from transcriptional targets of these pathways. This approach overcomes some of the limitations of NGS and other methods which analyze only partial components of a complex signaling pathway, producing significant risk of false positive and negative results, and resulting in potentially inaccurate diagnosis and treatment selection. In this study we evaluated oncogenic pathway activation in 88 cases of TNBC using the OncoSignal™ assay.

MATERIALS & METHODS

Samples and pathway scores for TNBC tumors were calculated using a publicly available Affymetrix dataset GSE76275. This study included 88 cases of TNBC obtained at Baylor College of Medicine. OncoSignal™ pathway activity scores (PAS) were calculated from the transcriptional profile for each case. In addition, 10 samples of benign breast tissue were available for analysis of PAS and used as controls for this evaluation. The mean pathway activity scores and ranges were calculated from the benign tissues. The PAS results for each of the 7 oncogenic pathways from the TNBC cases were compared with PAS results from benign tissues.

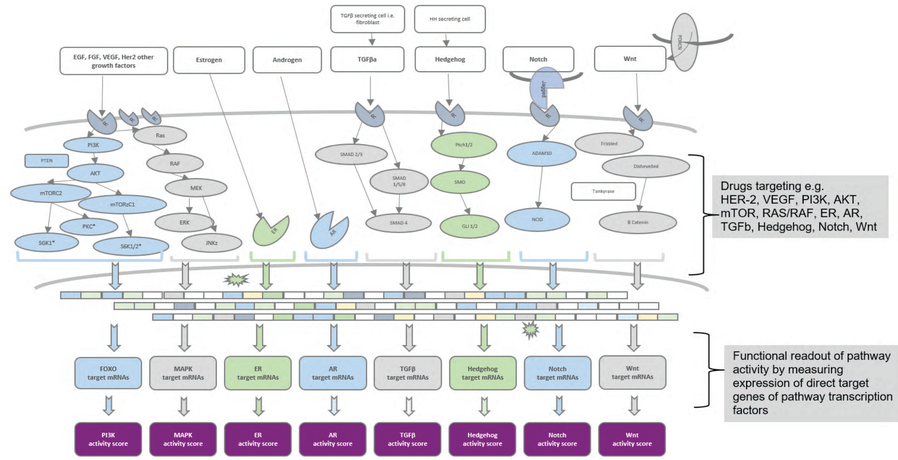
RESULTS

The OncoSignal™ PAS were significantly higher in TNBC compared to benign tissues for MAPK, PI3K, and HH pathways Figs 2 and 3. The PAS of ER and TGFβ pathways were significantly lower in TNBC compared to the benign tissue. MAPK, AR, ER, PI3K, and HH were elevated in 86%, 17%, 8%, 95%, and 94% of TNBC cases respectively. TGFβ pathway, for which oncogenic versus tumor suppressive functionality is contextually determined, showed reduced PAS in 85% of TNBC cases compared to benign tissue controls.

OBJECTIVES

To evaluate the activation status of 7 key targetable oncogenic signal pathways in triple negative breast cancer.

Figure 1 (Below): Major signaling pathways that can be measured by OncoSignal Method.



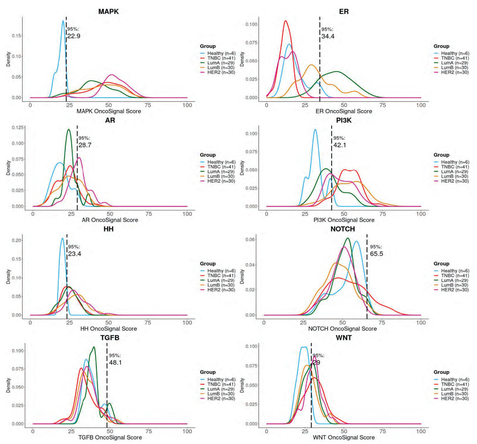


Figure 2 (Left): The distribution of pathway activity per pathway per subtype. The dotted line represents the threshold that was set to determine aberrant pathway activity. Six benign samples were obtained from mammary plastic surgery. The tumors contained between 50–90% cancerous cells 10% was used as the cut-off for ER and PR positive cells. 30% staining of membrane for HER2-positivity, 35 LA (ER+, PR+, HER2–); 40 LB (ER+, PR+, HER2+/–); 33 HER2 (ER–, PR–, HER2+) and 46 TNBC (ER–, PR-, HER2–).

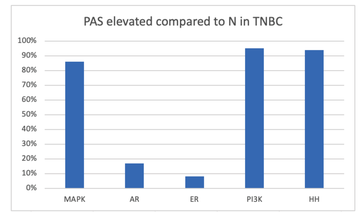


Figure 3 (Above): The % of cases showing increased pathway activation per pathway in TNBC.

CONCLUSIONS

OncoSignal™ analysis identifies enhanced targetable oncogenic pathway activity in a majority of TNBC breast cancers. Of interest, 7 of 88 cases (8%) classified as TNBC using IHC methods showed evidence of estrogen receptor signal pathway activation, and 15 (17%) showed elevated AR PAS. PI3K and MAPK had high PAS in over 85% of TNBC cases. Results suggest loss of tumor suppressive function of the TGFβ pathway. We conclude that OncoSignal™ analysis may help identify TNBC tumors with targetable signal transformation pathways.

REFERENCES

1. van de Stolpe A, Verhaegh W, Blay J-Y, et al. RNA Based Approaches to Profile Oncogenic Pathways From Low Quantity Samples to Drive Precision Oncology Strategies. Front Genet. 2021;11:598118. doi:10.3389/fgene.2020.598118

2. Kim Y-A, Cho D-Y, Przytycka TM. Understanding Genotype-Phenotype Effects in Cancer via Network Approaches. Karchin R, ed. PLOS Comput Biol. 2016;12(3):e1004747. doi:10.1371/journal.pcbi.1004747

3. Verhaegh W, van Ooijen H, Inda MA, et al. Selection of Personalized Patient Therapy through the Use of Knowledge-Based Computational Models That Identify Tumor-Driving Signal Transduction Pathways. Cancer Res. 2014;74(11):2936-2945. doi:10.1158/0008-5472.CAN-13-2515

4. Verhaegh W, van de Stolpe A. Knowledge-based computational models. Oncotarget. 2014;5(14):5196-5197. doi:10.18632/oncotarget.2276

5. van Ooijen H, Hornsveld M, Dam-de Veen C, et al. Assessment of Functional Phosphatidylinositol 3-Kinase Pathway Activity in Cancer Tissue Using Forkhead Box-O Target Gene Expression in a Knowledge-Based Computational Model. Am J Pathol. 2018;188(9):1956-1972. doi:10.1016/j.ajpath.2018.05.020

6. Santen RJ, Song RX, McPherson R, et al. The role of mitogen-activated protein (MAP) kinase in breast cancer. J Steroid Biochem Mol Biol. 2002;80(2):239-256. doi:10.1016/S0960-0760(01)00189-3

7. van de Stolpe A, Holtzer L, van Ooijen H, Inda MA de, Verhaegh W. Enabling precision medicine by unravelling disease pathophysiology: quantifying signal transduction pathway activity across cell and tissue types. Sci Rep. 2019;9(1):1603. doi:10.1038/s41598-018-38179-x

CONTACT

Anthony Magliocco

email: magliocco@proteanbiodx.com
phone: (813) 817 - 2042