Caveolin-1: A marker for Basal-like Breast Cancers

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Abstract

Introduction: Caveolin-1 (Cav1) is associated with basal-like triple-negative (ER-, PR-, HER2-) breast cancers (TNBC). Its biological contribution to this subtype has not been fully explored and controversy persists regarding the molecular role of Cav1 in carcinogenesis.

Experimental Procedures: Thirty-four TNBC (17 Cav1+/17 Cav1-) patients molecularly-profiled with a commercial assay (Caris Life Sciences, AZ) were evaluated retrospectively. Cav1 status was determined by immunohistochemistry (caveolin-1 polyclonal, ≥+15%) The majority of specimens (28/34) used for profiling were from primary breast sites and contained ≥50% neoplastic cells. The transcripts were profiled using Illumina’s HumanRef-12 microarray (Illumina, San Diego, CA). Data were normalized using miArray normalization procedure. Differential expression analysis was performed using the ‘limma’ and ‘edgeR’ functions from R’s limma package.

Pathway analysis was carried out using R’s pathway impact analysis (SPIA) package with 69 cancer, immunity, and cell signaling related KEGG pathways.

Results: Using a cutoff of two-fold and an absolute value of 0.05, we identified 954 genes differentially expressed between Cav1+/- TNBC patients. Included in these 33 genes which were found to be up-regulated by over five-fold and 3 genes down-regulated by 0.05-fold. Additionally, genes of note are those involved in cell signaling, cell adhesion, tumor invasion and metastasis, including up-regulation of FGF8, PI3K, FGFR3, integrins (ITGA10, ITGB1, ITGB2), cell adhesion molecules (LAMB3, COL3A1) and molecules which facilitate tumor invasion (LAMB3, MMP1, MMP2, MMP3). In addition, genes found to be down-regulated in Cav1+ patients and notable for their roles in promoting epithelial-mesenchymal transition (EMT) included Claudin-1 (CLD3) and CDH11 (Ncad) (Max1). We also detected an approximately two-fold down-regulation of CIN2KDA in Cav1+ patients. Using SPIA pathway analysis, 12 pathways were found to be differentially activated in Cav1+ vs. Cav1- TNBC. The most differentially activated pathways were the focal adhesion pathway (p=0.51E-18), PI3K-Akt signaling pathway (p=2.01E-6) and TGF-β and MAPK signaling pathways (p=0.005, 0.014, respectively).

Conclusions: Differential gene expression patterns and pathway analyses provide evidence for distinct protein expression profiles for biological consequences of Cav1+/-TNBC. Caveolin-1 TNBC patients exhibit up-regulation of genes important for cell communication, extracellular matrix remodeling and tumor invasion, and down-regulation of genes that may facilitate EMT and loss of cell cycle control. The focal adhesion pathway, as well as TGF-β, PI3K and MAPK signaling pathways, were identified as differentially activated by over five-fold in Cav1+ vs. Cav1- TNBC. Cav1+/- TNBC together, these data support the role of Cav1 in identifying a subtype of TNBC that may have a greater risk for invasion and metastasis. The correlation of this subtype with prognosis and drug response should be investigated in future studies.

References