Caveolin-1: Oncogenic Role in Breast Cancer? Clues from Molecular Profiling

[1]Rebecca Feldman, [1]Zoran Gatalica, [1]Sandeep K. Reddy, [2]Michael Castro, [3]Jasgit C. Sachdev
[1]Caris Life Sciences, Phoenix, AZ; [2]Personalized Cancer Medicine, Honolulu, HI; [3]Scottsdale Healthcare, Paradise Valley, AZ

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Abstract

Background: Caveolin-1 (CAV1) is the structural component of caveolae, compartments within the plasma membrane that sequester signaling molecules, thus facilitating molecular "hot spots". The role of CAV1 in breast cancer is an active area of investigation. We sought to understand the clinical and pathological characteristics of CAV1 positive tumors (CAV 1+) through a retrospective analysis of molecularly-profiled breast cancer patients.

Methods: 2,728 breast cancer patients molecularly profiled with a commercial assay (Caris Life Sciences) were evaluated retrospectively for expression of various biomarkers by immunohistochemistry (IHC) and in situ hybridization. JMP statistical analysis tool was used to ascertain distributional differences.

Results: Using a threshold of 2+ and 30%, 121/2728 (4%) of patients exhibited CAV1 over-expression by IHC. To observe clinicopathologic differences in the CAV1 + and CAV1- tumors, distribution by age, metastatic disease, and triple negative histology (TNBC) were analyzed. Average age for both groups was 55. 39% vs. 54% were metastatic and 84% vs. 31% were TNBC (p=0.0001) among CAV1+ and CAV1- groups, respectively. To evaluate the potential oncogenic associations of CAV1, we evaluated the relationship between CAV1+ and various oncogenic pathways. Positive EGFR protein expression and presence of EGFR gene amplification, as well as cKIT over-expression associated with CAV1+ (all p-values <0.001), whereas HER2 expression and amplification were associated with CAV1- (p=0.001 for both). In addition, higher Ki67, p53 and TOP2A expression by IHC were observed in CAV1+ patients compared to the CAV1- subgroup (90% vs. 66%, 50% vs. 36%, 84% vs. 65% ; all p-values <0.0001). Biomarker expression differences that did not meet statistical significance: ERCC1, MGMT, PDGFRA, RRM1, SPARC, TS and TOPO1.

Conclusions: The majority of CAV1+ breast cancers are comprised of triple negative, higher proliferative tumors, with aberrant p53 expression as well as expression of other growth factor signaling proteins. This data supports the potential role of CAV1 in fostering molecular hubs for signaling and CAV-1 being a potential target for future therapeutic investigation in TNBC.

*Corresponding author: Rebecca Feldman, rfeldman@carisls.com

Background

Caveolin-1 is a membrane protein and the main structural component of caveolae, compartments within the plasma membrane that sequester signaling molecules thus facilitating molecular "hot spots". The literature has suggested two roles of caveolin-1 in breast cancer, (1) tumor suppressor function and (2)oncogene function.[1]

We sought to provide clues as to whether one role or the other is the predominant role of caveolin-1 (CAV1) in breast cancer.

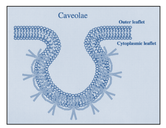

Figure 1. Structure of caveolae in lipid membrane of tumor cells.
Adapted from *www.ruf.rice.edu.*

Figure 2. Structure and assembly of caveolin-1 protein dimers.
Adapted from Lisanti, et al. 2000. J Biol Chem.

Partial List of Proteins that interact with Cav-1 CSD:
PDGFR α and β
EGFR
Insulin Receptor
TGFR β
H-Ras
eNOS
c-Src

Table 1. Partial list of proteins that interact with CSD.
Adapted from Liu, et al. 2002. J Biol Chem.

Methods

2728 breast cancer patients referred to Caris Life Sciences from 2010-2012 were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of protein expression (immunohistochemistry [IHC]), gene amplification (CISH or FISH) and sequencing (Sanger). All thresholds and antibodies used can be provided by request. For differentiating the two subgroups, CAV1+ and CAV1-, a threshold of 2+ and 30% (intensity and cell staining) was utilized and the caveolin-1 (polyclonal) antibody was used. The 2-tail Fisher's exact test was performed to test where proportions of positive results were different by subgroup (p≤0.05).

Results

Of the 2728 patients included in the study, 121 or 4%, exhibited positive CAV1 expression. 2607 patients were considered negative for CAV1.

Table 2. Features of CAV1- and CAV1+ breast cancers

	CAV1- (n=2607)	CAV1+ (n=121)
Median Age (range)	55 (23-90)	55 (28-89)
% Metastatic	1398 (54%)	47 (39%)
% TNBC*	813 (31%)	102 (84%)

* p-value for TNBC distribution in CAV1+ cases, p=0.0001

Results, contd.

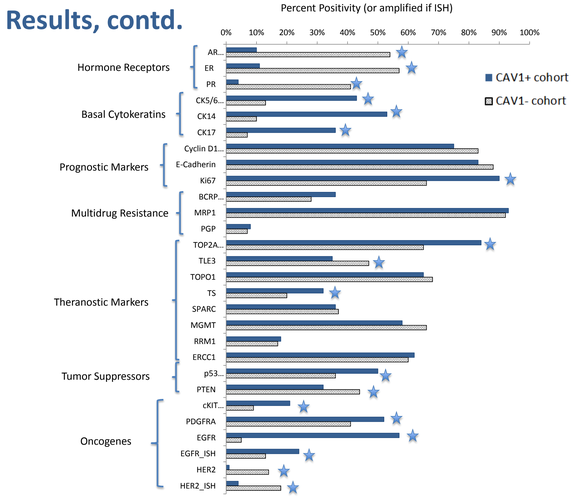

Figure 3. Biomarker differences between CAV1+ and CAV1- breast cancers. Stars indicate differential expression among CAV1+ and CAV1- breast cancers. Caveolin-1 positivity is associated with triple negative breast cancers, including basal cytokines. (All p-values <0.001.)

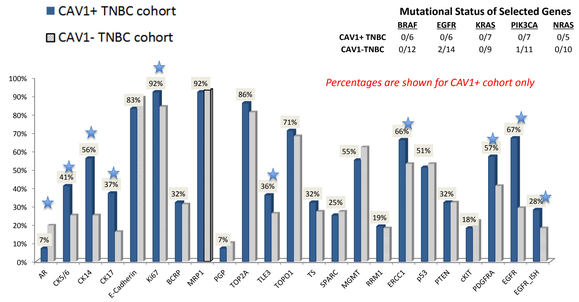

Figure 4. Biomarker differences between CAV1+ and CAV1- TNBC. Androgen Receptor was significantly higher in CAV1- TNBC, whereas, CK5/6, CK14, CK17, Ki67, TLE3, ERCC1, PDGFRA, EGFR IHC and ISH were all significantly higher in CAV1+ TNBC.

Results, contd.

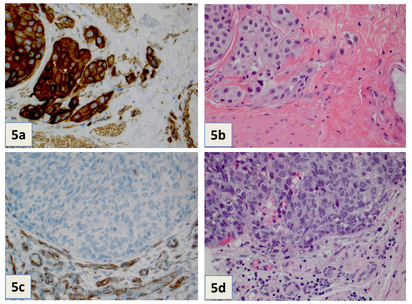

Figure 5a-5d. Representative slides showing patterns of Caveolin-1 positive (5a) and negative status (5c). Corresponding H&E are also provided (5b, 5d).

Conclusions

- CAV1 identifies a subtype of TNBC which exhibits high levels of growth factor receptors (EGFR and PDGFRA), resulting in higher rates of mitogenesis, as demonstrated by higher levels of Ki67 (92% vs. 84%, p=0.001) and TLE3 (36% vs. 26%, p=0.001).
- Higher levels of TLE3 in CAV1+ subgroup, may point to a higher proportion of CAV1+ cancers undergoing M-phase of the cell cycle, pointing to a particularly sensitive group of cancers to cell cycle perturbation, for example, through anti-tubulin agents (e.g. paclitaxel).
- In addition to EGFR, PDGFRA is an additional potential target that segregates with CAV1 positive TNBC. Kinase inhibitors of PDGFRA and EGFR should be investigated.
- It appears that CAV1 facilitates an oncogenic role in breast cancer, as evidenced by its association with high levels of growth factor receptors and higher levels of markers of proliferation and mitogenesis (Ki67, TLE3). Investigating the therapeutic role of CAV1, whether targetable itself, or its contribution to multidrug resistance, is warranted.

References

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2. Agelaki, S., C. Stournaras, et al. (2009). "Caveolin-1 regulates EGFR signaling in MCF-7 breast cancer cells and enhances gefitinib-induced tumor cell inhibition." Cancer Biol & Ther (8)15:1470-1477.
3. Abramson, V.G., J.A. Pietenpol, et al. (2014). "Subtyping of Triple-Negative Breast Cancer: Implications for Therapy." Cancer (10.1002/cncr.28914).