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

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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 (CAV1+) 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 Ki67 over-expression associated with CAV1+ (all p-values <0.001), whereas HER2 expression and amplification were significantly higher in CAV1- TNBC, whereas, CK5/6, CK14, CK17, Ki67, TLE3, PTEN, CASP8, TOP2A, ERCC1, and TOP2A expression by IHC were observed in CAV1+ patients and TOP2A expression as well as expression of other growth factor 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.

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

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Conclusions
CAV1 identifies a subtype of TNBC which exhibits high levels of growth factor receptors (EGFR and PDGFRα), resulting in higher rates of mitogenesis, as demonstrated by higher levels of Ki67 (92% vs. 84%, p=0.001) and TLE3 (56% vs. 26%, p=0.001). In addition, EGFR and PDGFRα is an additional potential target that segregates with CAV1 positive TNBC. Kinase inhibitors of PDGFRα and EGFR should be investigated.

It appears that CAV1 facilitates an oncogenic role in breast cancer, as evidenced by the 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