

The ALT Phenotype in Breast Carcinoma is Associated with HER-2 Overexpression

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Background: The majority of human carcinomas possess unlimited replicative capacity in part due to telomerase, an enzyme that maintains chromosomal telomere length. However, approximately 10-15% of human cancers do not show evidence of telomerase activity, and maintain telomere lengths by a recombination-based mechanism termed alternative lengthening of telomeres (ALT). The ALT pathway leads to marked heterogeneity in telomere lengths within individual cells, and is also distinguished by the presence of so-called ALT-associated promyelocytic leukemia (PML) protein nuclear bodies (APB) that contain large amounts of extra-chromosomal telomeric DNA, PML protein and other proteins involved in telomere-binding, DNA replication, and recombination. The ALT phenotype is commonly identified in adult sarcomas and testicular germ cell tumors, but is very rare in carcinomas. The frequency of the ALT phenotype in molecular subclasses of breast carcinoma has not been systematically evaluated.

Design: Tissue microarrays (TMAs) were created from 71 invasive ductal carcinomas (IDCs) of the breast which had been previously characterized for ER, PR, HER-2, EGFR, and CK5/6 expression. The cases included four distinct groups of IDCs having surrogate IHC profiles corresponding to categories defined by gene expression profiling {17 Luminal A (ER+, HER-2-), 7 Luminal B (ER and/or PR+, HER-2+), 14 HER-2+ (ER-, PR-, HER-2+), 21 basal-like carcinomas (BLC) (ER-, PR-, HER-2-, CK5/6 and/or EGFR+), and 12 unclassifiable triple negative carcinomas (TNC) (ER-, PR-, HER-2-, CK5/6-, EGFR-)}. Using a previously described fluorescence *in situ* method (Am J Pathol 2002;160:1259-66), telomere lengths in the IDCs were assessed.

Results: The ALT phenotype was identified in 3 of 21 HER-2 positive cases (Luminal B and HER-2+), but in none of the 17 Luminal A cases, 21 BLC cases, or 12 TNC cases (**p=0.023**).

Conclusions: In IDC, the ALT phenotype occurs preferentially in a subset of cancers with HER-2 overexpression. This association suggests that the ALT phenotype, which reflects DNA sequence amplification via recombination, may be correlated with HER-2 amplification through a common underlying mechanism. Since cancers utilizing the ALT pathway are predicted to be resistant to therapies based on telomerase inhibition, these results may have therapeutic consequences. As the presence of the ALT phenotype has prognostic significance in some cancers (e.g. Cancer Res 2006;66:8918-24), its prognostic implications in IDC of the breast should be further studied.