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RETAINED PTEN EXPRESSION PREFERENTIALLY IDENTIFIES MISMATCH REPAIR-PROFICIENT BREAST CANCERS

N. Fusco*[1, 2], L. Runza[1], G. Ercoli[1], D. Gambini[3], C. Blundo[4], L. Despini[4], M. Giroda[4], S. Bosari[1, 2]

[1]Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Division of Pathology, Milan, Italy, [2]University of Milan, Department of Pathophysiology and Organ Transplantation, Milan, Italy, [3]Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Division of Oncology, Milan, Italy, [4]Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Breast Surgery Unit, Milan, Italy

Introduction/ Background

Loss of phosphatase and tensin homolog (PTEN) expression and alterations in mismatch repair (MMR) genes are regarded as early oncogenic events in breast cancer. It has recently been hypothesized that the polyadenosine tract in PTEN might be a target for mutation in MMR-deficient endometrial tumors. However, the frequency and significance of MMR alterations in breast cancer is debated, and their relationship with PTEN status has not been investigated in the breast.

Aims

In this study, we sought to explore the relationships between PTEN expression and MMR alterations and to define whether PTEN immunohistochemistry is a predictor of MMR status in breast cancer.

Methods

309 cases, including 261 invasive ductal carcinomas, no special type, 32 invasive lobular carcinomas, and 16 invasive ductal carcinomas, mixed types, carefully characterized from clinical and pathological standpoints, were reviewed and used to construct 11 tissue microarrays (TMAs). For each case, a mean of 4.5 tumor tissue cores (range 3 to 6 cores) was sampled, incorporating distinct topographic areas of the tumor, as well as matched non-neoplastic breast tissue, and, when present, associated in situ carcinoma. Taken together, 1381 spots were generated. Each TMA was subjected to immunohistochemical analysis of PTEN and the DNA MMR proteins MLH1, MSH2, MSH6 and PMS2. In order to allow a quick navigation within each TMA, and to minimize human-related biases, each stained slide was digitalized and blindly analyzed by two pathologists using a dedicated software able to segment TMA cores. The pattern of expression was therefore annotated manually on a digital database using a specific add-on module.

Results

According to clinicopathologic surrogate definition of intrinsic subtypes, PTEN protein loss was more frequent in luminal A-like and triple negative groups compared to luminal B-like carcinomas, as recently observed in other studies. MMR status in Luminal B-like tumors did not differ significantly between PTEN-retained and PTEN-loss groups, regardless HER2 amplification. In particular, retained PTEN expression was a predictor of MMR proficiency in approximately 35% of cases for this group. However, in luminal A-like and triple negative breast cancer groups, retained positive expression of MMR proteins was observed in 100% of cases showing PTEN wild-type immunohistochemical expression.

Discussion: The present study is the first to investigate PTEN protein loss in a large set of breast carcinomas based on DNA MMR status by immunohistochemistry. Our findings broaden the understanding of the biology underpinning breast cancer, suggesting that MMR alterations are likely to be independent of PTEN status in the majority of luminal B-like breast cancers and that, in a way akin to endometrial carcinoma, MMR deficiency could play a part in the development of PTEN alterations in luminal A-like and triple negative breast cancers. The

integration of traditional pathology with cutting-edge digital tools allowed a rapid quantification of immunohistochemistry and effective data organization in this wide cohort multi-variable study.

Conclusion: PTEN immunohistochemistry is a useful adjunct in the clinical evaluation of breast cancer patients, being able to capture all MMR-proficient luminal A-like and triple negative tumors.