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Characteristics of the Receptor and Molecular Genetic Features of Tumor Cells from Primary Cultures of the Luminal a Subtype of Breast Cancer

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Abstract : The majority of breast cancer (BC) cases are estrogen receptor (ER) positive, and the most common among surrogate molecular biological subtypes is Luminal A. Despite ongoing treatment, drug resistance occurs in a significant proportion of patients, leading to disease recurrence. To determine the sensitivity of a particular tumor to therapy, it is necessary to create an in vitro model, which could then serve as a basis for the selection of personalized therapy for breast cancer. The aim is to evaluate the molecular genetic profile of tumor cells from primary cultures of the Luminal A subtype of breast cancer as a potential model for assessing resistance to therapy. Materials and methods: Primary cell cultures were obtained from a surgical sample in patients with Luminal A subtype of breast cancer when the following inclusion criteria were met: absence of previous therapy and availability of voluntary informed consent. The subtype was determined using the IHC method. Growth was maintained in a serum-free Mammocult™ environment (STEMCELL, Canada). The culture was passed after 7-10 days (p1-p5), and flow cytometry was performed on a Beckman Coulter cytometer (USA) at each passage. Antibodies to estrogen (Alexa Fluor® 647, SP1, Abcam, Canada) to HER2 (24D2, Brilliant Violet 421™, Biolegend, USA) were used for evaluation, and at least 5,000 events were analyzed.). NGS testing was performed on the same cells (Prep&Seq™ U-panel BCEv1, 63 genes). Results: Luminal A subtype includes cases with a Ki-67 threshold of less than 10% of tumor cell nuclei, no HER2 expression (level 0 to 1 points), lack of amplification of the HER2 gene, and high estrogen and/or progesterone levels. The median for RE expression was 66.5% (IQR 7.1) from p1 to p5, and this index didn´t change significantly throughout culture ($p<0.001$). The presence of Her2 oncoprotein was detected in 5.0% across all passages (IQR 5.2). The data obtained are consistent with the characteristics of the Luminal A subtype. NGS testing detected mutations in genes associated with breast cancer: BARD1, BRCA2, BRIP1, CASP8, CCNE1, CDH1, KEAP1, MSH3, NF1, PALB2, RAD51D, RECQL5, TP53 ZNF217, as well as in genes associated with the Luminal A subtype: PIK3CA, MAP3KI, ESR1. At all passages are detected in the MAP3K1 gene, 7 mutations (3 missenses, 3 synonymous, 1 in-frame) except p2 and p5. A mutation in 1 exon (synonymous) is added at p2 and p5, while no changes are detected in the other genes. Conclusion: Primary cell cultures during the five passages can preserve the expression of RE and the composition of mutations in genes and can be used as an in vitro model. The combination of mutation in ESR1 and MAP3K gene is a potential factor of acquired resistance to therapy in patients with Luminal A breast cancer.

Keywords : breast cancer, Luminal A subtype, primary cell culture, HER2 receptors, estrogen receptors, MAP3K1 gene, ESR1 gene
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