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Cancer Science & Pediatrics 2019: PI3K/AKT-signalling pathway and immune-escape in triple negative breast cancer - J C Hahne - Germany Catholic Clinical Centre Mainz Germany

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Breast cancer accounts for 23% of all new tumour cases and it is the most common cancer among women worldwide. A high percentage (15-25% of all breast cancer cases) is characterized as triple-negative breast cancer (TNBC). Although TNBCs are sensitive to chemotherapy, survival of patients with these tumours is poor. Lack of effective therapies, younger age at onset and early metastatic spread have contributed to the poor prognosis and outcomes associated with TNBC. The phosphatidylinositol 3-kinase (PI3K)/ AKT-pathway plays a critical role in malignant transformation of tumours and their subsequent growth, proliferation and metastasis as well as in activation of pathways that result in immune-escape mechanisms. Therefore, the PI3K/AKT pathway is considered an attractive candidate for therapeutic interventions. A modified FATAL assay was used as an in-vitro system to investigate the interaction between TNBC cell lines and natural killer (NK)-cells. Furthermore, the ability of PI3K/AKT inhibition with AEZS-126 to selectively target TNBC cell proliferation and survival was explored. In parallel, we analyzed mechanisms of cytotoxicity related to PI3K/AKT inhibition.

Breast cancer is the cancer with the highest prevalence in women and is the number-one cause of cancer mortality worldwide. Cell transduction is a fundamental process in the development and progression of cancer. Modifications in various cell signaling pathways promote tumour cell proliferation, progression, and survival. The PI3K/Akt/mTOR pathway is an example of that, and it is involved in growth, proliferation, survival, motility, metabolism, and immune response regulation. Activation of this pathway is one of the main causes of cancer cell resistance to antitumor therapies. This makes PI3K/Akt/mTOR signaling a crucial object of study for understanding the development and progression of this disease.

Thus, this pathway may have a role as a potential therapeutic target, as well as prognostic and diagnostic value, in patients with breast cancer. Despite the existence of selective PI3K/Akt/mTOR pathway inhibitors and current clinical trials, the cellular mechanisms are not yet known. The present review aims to understand the current state of this important disease and the paths that must be forged. Breast cancer is the most prevalent cancer type in women as well as the leading cause of cancer mortality in this population worldwide, with a peak incidence between 45 and 65 years of age .Although it is not common, breast cancer can also occur in men, with a frequency of 1 in 100 diagnosed cases, representing less than 1% of all cancers in men.

Among the most important risk factors associated with breast cancer are ageing, family history, nulliparity, hormonal factors, such as early menarche or late menopause, and other factors related to lifestyle, such as alcohol consumption, obesity, and physical inactivity.

Breast cancer can be hereditary or sporadic. The most frequent mutations associated with hereditary cancer include those that affect DNA damage repair (DDR) genes, the most important of which are mutations in the BRCA1, BRCA2, and TP53 genes Sporadic cancer represents approximately 85% of all cases of breast cancer and is associated with some of the risk factors mentioned above; however, it has also been associated with exposure to carcinogens, such as air pollutants, electromagnetic radiation, and DDR gene expression dysregulation.

According to their presentation, ductal carcinoma in situ is the most diagnosed breast cancer type, followed by lobular carcinoma in situ. Breast cancer, in turn, is divided into different subtypes based on the presence or absence of the estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor. Thus, we can distinguish between a luminal subtype, being ER/PR+, an Her2+ subtype, which has this receptor overexpressed, and a triple negative or basal-like subtype (TNBC). Following this classification, the luminal subtypes can be divided into luminal A, characterized by ER/PR+, HER2–, and low Ki67 expression, and luminal B, characterized by ER/PR+, HER2+, and high Ki67 expression. Subtype Her2+ is ER/PR negative, and the triple negative indicates a lack of all these receptors.

Cell signal transduction is a fundamental process in the development and progression of cancer. Hanahan and Weinberg noted that tumour cells exhibit a set of characteristics or hallmarks, including uncontrolled proliferation, genomic instability, and apoptosis evasion. To this end, modifications to various cell signaling pathways promote tumour cell proliferation, progression, and survival. These alterations are due to mutations in oncogenes that overexpress certain proteins, mutated proteins that present uncontrolled activity, or inactivation of tumour suppressor genes that favor these processes.

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