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P-Akt as a biomarker of a subset of triple negative breast cancer patients potentially sensitive to the pp2a activator, FTY720

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Introduction: The most commonly used biomarkers to predict the response of breast cancer patients to therapy are oestrogen receptor (ER), progesterone receptor (PgR), and HER2. Patients positive for these biomarkers are eligible for specific therapies including anti-oestrogen therapy for ER and PgR positive patients, and trastuzumab, a monoclonal antibody, in the case of HER2 positive patients. Patients who are negative for all three biomarkers, the so-called triple negatives, however, derive little benefit from such therapies and are associated with a worse prognosis. The PI3K/Akt pathway has been found to be activated in triple negative breast cancer cases, providing a possible target for therapy. Patients having an elevated activation of the PI3K/Akt pathway could benefit from therapies targeting this pathway. Possibilities include using inhibitors of the PI3K/Akt pathway, or drugs which activate phosphatases involved in the pathway such as FTY720 which activates the phosphatase PP2A.

Aim: The purpose of this study was to investigate the incidence of increased Akt activation in triple negative breast cancers in Malta by immunohistochemical staining, and the effect of FTY720 on the activation of Akt in two human breast cancer cell lines.

Methodology: A serine-473 Akt1 antibody (p-Akt (S473)) was used to investigate the activation of Akt in triple negative breast cancer cases in the Maltese population. Scoring of stained sections was performed on the basis of intensity. Furthermore, the effect of FTY720, a pharmacological activator of the phosphatase PP2A which negatively regulates Akt activity, on the activity of Akt in two human breast cancer cell lines: MCF-7 and HCC1937, was investigated. This was tested under conditions of starvation, and also Akt stimulation by IGF-1 using In-Cell Western blotting. HCC1937 was of particular interest since it is also negative for ER, PgR, and HER2, and is known to have enhanced Akt activity.

Results: 27% of triple negative breast cancer patients had an elevated level of p-Akt (S473). FTY720 at a concentration of 1μM, which did not affect cell viability, was shown to suppress Akt activation in MCF-7 and HCC1937 cells subjected to IGF-1, an activator of Akt.

Conclusion: The subset of triple negative having elevated Akt activation (27%) would be eligible for treatment using therapies which target the PI3K/Akt pathway, such as kinase inhibitors or phosphatase activators. The *in vitro* experiment using FTY720 suggests that it is a potential drug for use in adjuvant therapy in breast cancer cases having a high p-Akt (S473).