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ABSTRACTS

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Characterisation of a new mechanism of ATR/Chk1 regulation in breast cancer: role of mTORC2

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mTOR is a serine–threonine kinase belonging to the PIKK family and acts as a central node to integrate signalling from growth and stress factors to regulate cell growth. Other members of the PIKK family are ATM, ATR and DNA-PKcs, which all have established roles in the DNA damage response. mTOR is the catalytic component of functionally distinct complexes mTORC1 and mTORC2. Recent data show that mTORC2 complex also has tyrosine kinase activity. Dysregulation of mTOR signalling occurs in numerous cancers, particularly in breast cancer, leading to the use of mTORC1 inhibitors such as the rapamycin analogue (rapalog), everolimus, for advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane. There are many ongoing clinical trials of rapalogs in combination therapy including DNA-damaging agents to treat breast cancer as well as mTOR kinase inhibitors that target both mTORC1 and mTORC2 complexes. Using breast cancer cell lines and biochemical methods, we have recently demonstrated that there is significant crosstalk between the nutrient and stress sensing mTOR pathway and the DNA damage response activation of ATR/Chk1. We recently demonstrated that DNA damage-induced cell cycle arrest at S and G2/M phase is dependent on mTOR. Specifically, mTORC2 was required for the activation of Chk1, a key cell cycle regulator, at the level of Chk1 protein production. Furthermore, in a panel of breast cancer cell lines, with varying degrees of chemoresistance, an mTOR kinase inhibitor was able to overcome resistance to DNA-damaging agents by potentially destabilising cell cycle arrest and thereby enhancing DNA damage-induced cell death. These data suggest that mTORC2-Chk1 signalling is a survival pathway in breast cancer which has important implications for breast cancer combination therapy.