CANCER-ASSOCIATED PTEN MUTATIONS ALTER PTEN CELLULAR FUNCTION

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Background: The phosphatase and tensin homolog (PTEN) is a tumour suppressor that plays an important role in normal cellular function, including regulating the cell cycle arrest, apoptosis, cell adhesion, migration and differentiation. Alterations of PTEN are central to the development of various cancers and other diseases. Previous work in our laboratory demonstrated the occurrence of PTEN gene mutations in 25% of primary human colorectal tumours [1]. Interestingly, all tumours harbouring alterations of PTEN demonstrated either reduced or absent PTEN protein expression. Overall, 10 novel cancer-associated PTEN mutations were described.

Aim: This project aims to determine the effect(s) of these novel mutations on PTEN cellular function.

Methods: Wild type and mutant PTEN expression constructs were prepared and transiently transfection into various cancer cell lines (U87MG glioblastoma, MCF7 breast cancer cells and HCT116 colon cancer cells). The effect(s) of WT and mutant PTEN on cell cycle phase distribution, the rate of cell proliferation and AKT activation were assessed.

Results and Discussion: In contrast to the effects observed with WT PTEN, a number of the tested PTEN mutations were found to decrease the ability of PTEN to (a) bring about cell cycle arrest, (b) slow the rate of cell proliferation and (c) decrease the level of AKT activation. The effects observed were dependent on the cell type as individual mutations did not have the same effect in all cell lines.

References

1. Nassif NT, Lobo GP, Wu X, Henderson CJA, Morrison CD, Eng C, et al. PTEN mutations are common in sporadic microsatellite stable colorectal cancer. Oncogene. 2004;23(2):617-28.