

P053 The role of the PI3K/Akt cascade in the development of hormone refractory prostate cancer.

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Cell line studies demonstrate that the PI3K/Akt pathway is up-regulated in hormone refractory prostate cancer (HRPC) and Akt expression in prostate tumours has been linked with biochemical recurrence. The current study therefore aims to establish if up-regulation of the PI3K/Akt cascade is one possible route to the development of clinical HRPC.

Fluorescent in situ hybridisation and immunohistochemistry were employed to investigate the role of the key members of the PI3K/Akt cascade in the development of HRPC using matched hormone sensitive and insensitive tumours from prostate cancer patients. Amplification of key genes in this pathway were not observed in the current study, however an increase in PI3K protein expression was independently linked to time to biochemical relapse ($p=0.014$). An increase in expression of phosphorylated Akt⁴⁷³ or phosphorylated androgen receptor (AR) at the Akt consensus site (serine 210) was linked to shorter disease specific survival ($p=0.0019$ and $p=0.0015$, respectively). In addition, phosphorylated Akt⁴⁷³ and phosphorylated AR²¹⁰ ($p<0.001$ c.c. 0.711) correlated in the HRPC tumours suggesting activation of this pathway. These results provide evidence using clinical specimens, that the PI3K/Akt pathway is up regulated during development of HRPC, resulting in phosphorylation of the AR, which may sensitise AR to circulating adrenal hormones, therefore providing a mechanism for development of HRPC in the clinical setting.