

P15

p53 Status in Breast Cancer and its Potential Role as a Repressor of Cdc7 Kinase

**I. Proctor** ; K. Stoeber ; G.H. Williams

University College London, London, United Kingdom

TP53 mutations are detected in 20-40% of sporadic breast cancers and in certain sub-types the frequency approaches 100%. Whilst most studies attribute p53 function to transcriptional activation, there is growing evidence that p53 can also affect cellular responses through the repression of gene expression. A proposed target of p53-mediated transcriptional repression is the kinase Cdc7. Cdc7 kinase activates the Mcm2-7 replicative helicase, an essential step in the initiation of DNA synthesis. Therefore, downregulation of Cdc7 kinase by intact p53 would be in keeping with its established role as a tumour suppressor. In this study we assess how Cdc7 protein expression correlates with p53 status and cell cycle phenotype, a recently described and highly accurate marker of proliferation status.

**Methods:** Archival tissue from 173 patients with breast cancer was immunostained with antibodies against Cdc7 and p53 and the cell cycle phenotype markers Mcm2, geminin and histone-H3. Staining was quantified using a labelling index derived from counting >1000 cells.

**Results:** Cdc7 expression levels were significantly raised in p53 mutant tumours compared to tumours with intact p53 (12.9% vs 6.3%;  $p < 0.001$ ). Furthermore, the p53 mutant/Cdc7 high tumours displayed increased proliferative activity as assessed by cell cycle phenotype, with actively cycling phenotype III tumours significantly over-represented in p53 mutant vs wild type tumours (79.6% vs 49.6%;  $p < 0.001$ ).

**Conclusion:** This study supports the hypothesis that Cdc7 kinase is subject to p53-mediated downregulation and that abrogation of this pathway may play an important role in the tumourigenesis of p53-mutant breast cancers.