

P044 Sensitization of hypoxic tumour cells through inhibition of PRP is oxygen dependent and correlates with decreased homologous recombination

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Inhibition of PARP has proved to effectively sensitize cells which lack essential components of the homologous repair pathway, for example BRCA1 and 2. Homologous recombination has been shown to be reduced in cells exposed to severe hypoxia primarily as a result of the repression of specific proteins including BRCA1 and 2 but also Rad51. We proposed that PARP inhibition might therefore also sensitize hypoxic cells. We have shown that pharmacological inhibition of PARP does indeed reduce colony formation after hypoxia/reoxygenation but this is dependent of the level of hypoxia. Cells treated at levels of hypoxia which induce HIF1 expression but do not repress homologous recombination were unaffected by PARP inhibition. Sensitivity to PARP inhibitors correlates with levels of hypoxia that reduce proteins involved in homologous recombination. Severe hypoxia initiates a DNA damage response mediated by both ATM and ATR which is unaffected by PARP inhibition. In contrast, in response to reoxygenation we have observed repair defects when PARP activity is reduced. Our data suggests a role for PARP inhibitors in the treatment of all solid malignancies as opposed to just those harbouring BRCA1/2 mutations.