P024 The role of checkpoint kinase Chk1 in 5-fluorouracil mediated DNA damage

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Metastatic colorectal cancer is incurable and there is a need to define molecular targets to improve therapeutic efficacy. 5-fluorouracil (5-FU), a nucleotide analogue and thymidylate synthase inhibitor, is the most commonly used cytotoxic drug in the treatment of colon cancer. We investigated the role of the Checkpoint kinase, Chk1, in the cellular response to 5-FU treatment using DT40 cells carrying a knockout mutation of this kinase. We demonstrate that in wild type cells 5-FU causes phosphorylation of Chk1 and activation of the intra S-phase checkpoint. This was reversed on addition of thymidine but not uridine, consistent with 5-FU causing a DNA damage mediated S-phase arrest. The addition of 5-FU to Chk1 null cells inhibited cell growth through a G1 arrest but it was impossible to reverse this arrest by thymidine addition. Clonogenic cell survival assays demonstrated that Chk1 null cells were at least 25 fold more sensitive to 5-FU than their wildtype counterparts, indicating that the S-phase, but not the G1 arrest, was protective. This data indicates that Chk1 inhibitors may provide a therapeutic strategy in combination with 5-FU in the treatment of colon cancer.