ACTIVATION OF CELL AGEING PATHWAYS WITH NOVEL SMALL MOLECULES FOR CANCER TREATMENT

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Introduction: Many frontline cancer therapies function by directly or indirectly causing DNA damage and thus cell death. In their most simple form these drugs target a physiological differentiating feature of cancer cells: they tend to be more actively proliferating than normal cells. This causes well-known side-effects that result from the death of highly proliferative normal cells, notably in the gut and immune system. Recent trend in cancer research has been the development of treatment that kills cancer cells without also damaging the normal cells in the patient - a concept known as the therapeutic window. New approach therefore is p53 tumour suppressor gene and its frequent loss in cancer. Although many cancer cells have deactivated G1 checkpoint they may still retain a residual G2 checkpoint involving ATR/p38MAPK/MK2. Work using transgenic mice has recently demonstrated that genetic disruption of the p38/MK2 pathway specifically sensitizes p53-null mouse cells to DNA damaging agents. That could be due to p53-null cells in the presence of ablation of p38/MK2 pathways lose both G1 and G2 DNA damage checkpoint function, and enter mitosis despite the presence of DNA damage, where they die by "mitotic catastrophe".

Materials and methods: Cancer cell lines were purchased from ATCC and treated with DNA damaging agents in the presence and absence of both p38 and MK2 inhibitors (SB203580 -10uM and MK2/3 - 1uM). DNA damaging agents were used at the following concentrations: Doxorubicin (10uM), Cisplatin (200uM) and Etoposide (5uM).

Results and Conclusion: DNA damaging agents produced a profound effect on the cell cycle profile of these cell lines in a manner that is consistent with the degree of cell viability that is seen using the viable cell assay. Given the relatively modest effects of the p38/MK2 inhibitor drugs on cell viability at the concentrations used, no major shift in cell cycle was seen following treatment with these drugs. This further confirms the expected result that these inhibitors do not affect the cell cycle directly in themselves, but may do so subtly in conjunction with DNA damage.