Abstract: 72O

A combination screen finds inhibition of GCN2 sensitises growth of MDA-MB-231 and HPAFII cancer cell lines to CDK inhibitors

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The GCN2/ATF4 pathway is responsible for the activation, recruitment and synthesis of numerous effectors to restore amino acid homeostasis in cells experiencing amino acid insufficiency. This pathway is therefore highly relevant to the biology of cancer cells, given their elevated demands for amino acids and the poorly vascularised milieus they frequently occupy. To date, several GCN2 inhibitors have been developed to explore the therapeutic potential of disabling the GCN2/ATF4 signalling axis in cancer cells. TAP20 is one such inhibitor developed by Merck KGaA and was utilised in this study in a combination screen identifying synergistic drug interactions. Briefly, twenty-six experimental and approved drugs were titrated in six cancer cell lines to assess respective growth IC_{50} concentrations. These drugs were then combined with TAP20 at concentrations below their IC_{50} to evaluate additive, antagonistic or synergistic interactions in growth assays. Pairings with favourable coefficients of drug interactions were further tested using isobologram analysis. The growth suppressing effects of the pan-CDK inhibitors flavopiridol and seliciclib were identified among other drugs as being potentiated by TAP20 in two of the six studied cell lines: MDA-MB-231 breast cancer and HPAFII pancreatic cancer cells. A literature review suggested CDK7, a common target of both pan-CDK inhibitors, is likely involved in GCN2/ATF4 signal transduction and the overall cellular stress response to amino acid deprivation. Accordingly, a CDK7-selective inhibitor (THZ-1) was tested and found to potently synergise with TAP20. These combinations were also investigated in matrix invasion assays using 143B osteosarcoma cells. While the synergistic effects of the drug combinations were largely confined to the growth assays, the application of TAP20 alone was found to restrict invasion at concentrations well below its growth IC_{50}. Lastly, while this study did not elucidate the precise mechanistic relationships by which these synergistic drug interactions yield synthetic lethality in cancer cells, it did highlight the promising utility and potential of GCN2 inhibitors as an additional tool in the chemotherapeutic arsenal.