Talazoparib interacts with oncolytic reovirus to enhance death-inducing signalling complex (DISC)-mediated apoptosis and immune response


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Background

○ Oncolytic viruses have shown potential in human clinical trials (Reoviridae RT3D), a naturally occurring human double-stranded RNA virus, has shown preclinical efficacy in the treatment of a wide range of tumour types and has now reached randomized phase I testing in clinical trials.

○ Early clinical studies have shown that RT3D has modest monotherapy efficacy and has been used in combination regimens with platinum chemotherapy. However, not all patients benefit from these treatments, highlighting a need to identify therapeutic opportunities for combining oncolytic viruses with other novel anti-cancer drugs.

○ We performed a high-throughput drug screen to explore a non-biased approach in determining any oncogenic, viral-interactions between RT3D and a range of different cancer drugs in the A375 melanoma cancer cell line.

Identification of potential combination therapies with RT3D

A375 cells were treated with 100 nM of 300 different drugs and 250 different combinations for 48 hours. We monitored cell survival using the CellTiter-Glo luminescence assay (Promega). 

Potential oncologically active drug combinations were identified from the screen and validated using caspase 3 and PARP expression following RT3D infection to detect any enhanced apoptosis.

Talazoparib potentiates RT3D anti-tumour activity in an A375 xenograft model

CD1 nude mice carrying A375 tumour xenografts were treated with oral administration of vehicle or 0.1 mg/kg talazoparib from Day 1. RT3D was injected intratumorally on Day 3 at 1x10⁶ pfu given in the combination with or without talazoparib. 

Cell viability was measured 72 h post infection using CellTiter-Glo luminescence cell viability assay. The 2.3 fold change in cell viability was taken as the standardised value from (i) the median of triplicate samples normalized to virus only versus untreated (ii) the mean of viable only versus untreated and (iii) the median absolute deviation between the drug and DMSO control. These were plotted on a waterfall plot as shown.

Fig 3: Loss of PARP-1 is synthetically lethal with RT3D

RT3D sensitivity was assessed in HaCaT PARP-1-potent cells, PARP-1+ and PARP-1 null (closely G3 and G2B) and cytotoxicity carried out by MTT 72 hours infection at R. Cell viability was carried out to assess RT3D and talazoparib in HaCaT, PARP-1 potent model (PARP-1** & PARP-1+) as shown by crystal violet assays (A) and SRDD cell viability assays (C). Western analysis was carried out to assess apoptosis as shown by cleavage of caspase 3 and PARP as members of apoptosis and PAR expression following infection. Equal loading was measured by pestling for tubulin (D).

Summary

○ Talazoparib, a potent PARP inhibitor, was identified as one of the top hits from the screen and was investigated in combination with RT3D in a panel of melanoma cell lines.

○ RT3D in combination with talazoparib had a significantly enhanced effect both in vitro and in vivo.

○ Death-inducing signalling complex (DISC) mediates apoptotic cell death following RT3D and talazoparib treatment where interaction between DISC and poly-ADP ribosylation (PAR) chains following RT3D infection is interrupted in the presence of talazoparib.

○ Talazoparib enhances IFN-γ signaling pathways through RIG-I - through PARP-1 trapping on RIG-I which leads to enhanced signalling via this pathway.

○ We saw anti-tumour efficacy in a 4434 immunocompetent mouse model following RT3D and talazoparib treatment and this correlated with an increase in an immune response.

Conclusion

Our data provide a strong rationale for the combination of oncolytic viruses with PARP1 inhibitors to exploit immunogenic response in cancer treatment.