

PERSONALISED MEDICINE APPLIED TO IMMUNOTHERAPEUTICS

=0.39, $p < 0.01$), RAD51 ($r = 0.33$, $p < 0.01$). This upregulation requires ATM/ATR/Chk1 kinases (Chk2_pt68; $r = 0.36$, $p < 0.01$ and Chk1_ps296; $r = 0.33$, $p < 0.01$). Interestingly Jab-1 expression was correlated with both Chk-1 ($r = 0.27$, $p < 0.01$) and PD-L1 ($r = 0.22$, $p < 0.01$). We further investigate for the possible signaling mechanism for the correlation and found activation of oncogenic signaling in a cancer type specific manner. PI3K/AKT/mTOR/S6K, INFgamma/ JAK/STAT/IRF1 and Ras/BRAF/MEK/ERK were involved in mechanism of increased PD-L1 expression.

Conclusions: DSB-mediated immune activation is balanced by concomitant inhibitory signaling, via the checkpoint kinases ATM, ATR, and Chk1 driven PD-L1 expression in tumors. These observations have important clinical implications for therapy selection, particularly following progression on DNA damaging agents suggesting that PD-1/PD-L1 inhibitors may be a useful therapeutic strategy (with or without concurrent DNA damaging agents) for tumors.

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51P DNA damage ATR/Chk1 checkpoint signalling increases PD-L1 immune checkpoint activation and its implication for personalised combination therapy

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Background: DNA double-strand break (DSB) is the most critical type of genotoxic stress. Clinical studies have revealed a link between genomic instability and response to anti-PD-1/PD-L1 therapy in cancer management. We investigated role of DBS repair and ATR/Chk1 DNA damage checkpoint in regulating PD-L1 expression and their use in therapy selection and study design.

Methods: Protein expression data proteins and phosphoproteins with major clinical outcome endpoints were obtained from The Cancer Genome Atlas project. A statistical correlation analysis was performed between the expression and distribution DBS repair and ATR/Chk1 DNA damage checkpoint pathway and PD-L1. Signaling network was also analysed for of therapeutic target identification.

Results: The expression and distribution patterns of PD-L1 was measured in 7694 samples from 32 cancer type. Increased expression of PD-L1 was associated with higher tumor stage and grade. Analyses of the DNA damage ATR/Chk1 checkpoint signalling revealed strong correlation of PDL1 expression. PD-L1 expression in was upregulated in response to DSBs with strong correlation with MRE11 (correlation coefficient (r)