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4077/7: "Quantitative Proteomics Reveals Novel Immunomodulatory Pathways of Resistance to PARP Therapy"

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Background

Pharmacological inhibition of PARP results in the specific killing of BRCA1/2 deficient tumor cells due to a synthetic lethal interaction between the concomitant impairment in homologous recombination and the DNA damage response. Despite the success of this approach, resistance to PARP inhibition has been observed in majority of patients with advanced cancer. Novel ways of interrogating PARP resistance are necessary to further elucidate the mechanisms of drug resistance and help identify ways to overcome it. To probe potential mechanisms of resistance we applied data-independent acquisition (DIA) mass spectrometry for unbiased global protein quantification in patient derived xenografts with demonstrated resistance to PARP inhibitors.

Methods

Patient-derived tumor xenografts (PDTXs) were generated from breast cancer patient tumor material implanted in severely immuno-compromised NOD-scid IL2rgnull (NSG) mice. PDTXs, developed as part of the CRUK Cambridge Institute biobank of PDTXs, have previously undergone extensive molecular profiling. PDTXs and short-term cultured PDTX cells (or PDTCs) capture most of originating patient's sample features, including heterogeneity, and consequently, the PDTX/PDTC platform is a robust intermediate in oncogenic drug development. Resistance to the PARP inhibitors AZD-2281 (olaparib) and BMN-673 (talazoparib) was tested ex vivo in PDTCs from 6 sensitive and 11 resistant PDTXs. Deep quantitative proteome profiling of PDTXs samples was conducted by applying an LC-MS/MS setup operated in DIA mode. Data was extracted using Spectronaut™ (Biognosys) with a sample specific spectral library. Pathway analysis was conducted to highlight dysregulated biological functions and pathways and the proteomics data was correlated with transcriptomics readouts.

Results

LC-MS/MS profiling allowed the identification of more than 11'000 proteins with more than 8'700 proteins quantified across the samples. 448 human and 430 murine proteins were significantly changed between PARP inhibitor resistant and sensitive PDTX models. Resistant models were characterized by increased expression of DNA damage response proteins including ATR and FANCD2, downregulation of TP53, TP53BP1, POLB and H2AFX, and upregulated EGFR, BRAF, ERBB2, STAT3, MLLT4 and CDKN2A. Most interestingly, we observed upregulation of human CD47/SIRPa immunomodulatory signals and upregulation of mouse Ly6G, CSF1R and SHP-1 suggesting the infiltration of immunosuppressive neutrophils and monocytes in the tumor microenvironment in the models resistant to PARP inhibition.

Conclusions

To our knowledge, this is the first report aiming at interrogating PARP inhibitor resistance with unbiased quantitative proteomics. The proteomics data confirmed prior observations of resistance mechanisms to PARP and elucidated potential novel mechanisms involving modulation of the immune response in resistant tumors.

Session: Mechanisms of Sensitivity and Resistance to Targeting DNA Damage Repair (Virtual Poster Session)

Category: EXPERIMENTAL AND MOLECULAR THERAPEUTICS: Drug Resistance