Protein interactions involving LARP1 in chemotherapy resistant ovarian cancer cells

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Ovarian cancer (OC) is the most lethal gynecological malignancy accounting for 152,000 deaths annually worldwide. Due to the lack of a validated diagnostic tool, patients usually present with disseminated disease and the majority will develop resistance to platinum chemotherapy. Resensitizng OC to cisplatin-based chemotherapy is an unmet clinical need. The RNA-binding protein LARP1 is highly expressed in OC and is a post-transcriptional regulator of cell survival and tumorigenesis. LARP1 depletion using RNA interference (RNAi) restores platinum sensitivity in cisplatin-resistant OC cell lines and shows a synergistic anti-tumour effect with cisplatin. We explored the effect of this resensitization on the efficiency of protein translation using the Surface Sensing of Translation (SUnSET) method. Whilst cisplatin-induced genotoxic stress attenuated *de novo* protein synthesis in platinum sensitive (OVCAR3) cells, this was not observed in platinum-resistant OVCAR8 cells where residual protein synthesis was maintained. However this residual translation was completely abolished after RNAi to LARP1 suggesting that, in the OVCAR8 cells, LARP1 maintains protein synthesis during genotoxic stress. Although LARP1 is known to bind Poly A binding protein (PABP) we questioned whether other interacting partners might also regulate this response. Using immunoprecipitation followed by ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) in OVCAR3 and OVCAR8 cells before and after cisplatin treatment, we identified PABPC1, PABPC4 and YB-1 as strong interactors with LARP1. By western blotting, Duolink Proximity Ligation Assay and Immunofluorescence we then confirmed these candidates as being complexed with LARP1. We are currently elucidating the functional role of these interactions on the LARP1-mediated genotoxic stress response with the overall aim of identifying therapeutic strategies to overcome platinum-resistance in ovarian cancer.