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Multi-omics investigation into the link between metal dyshomeostasis and Pt-based chemotherapeutic drug resistance in ovarian cancer

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Early diagnosis often plays an important role in determining cancer treatment outcomes, but the diagnosis of ovarian cancer poses significant challenges [1]. The key to improving treatment outcomes for ovarian cancer patients lies in developing methods to assess cancer drug resistance; the ability to predict patient response towards post-operative treatments would allow for ineffective treatments and harmful side effects to be avoided and alternative treatments to be commenced at earlier stages. However, there are currently no tests to assess chemoresistance approved for clinical use. Chemotherapy using Pt-based compounds (e.g. carboplatin, cisplatin) is a standard cancer treatment, but tumours that are initially responsive may develop chemoresistance, resulting in treatment failure. Several mechanisms underlying tumour cell resistance have been identified so far, including the altered expression of ion channels (Na, Mg, K, and Ca) and Fe-, Cu-, and Zn-binding proteins, but these remain poorly understood and it is unclear whether they can be exploited as markers of resistance [2-4]. With the goal of enhancing our understanding of cisplatin resistance mechanisms in ovarian cancer, elemental quantification (via ICP-MS/MS), high-precision isotopic analysis (via MC-ICP-MS), and proteomics (via LC-MS/MS) were applied to the chemosensitive ovarian cancer cell line, A2780, and its chemoresistant variant, A2780cis (resistance factor = ~10). Novel chromatography methods developed to isolate analytes from endogenous elements and exogenous Pt in cultured cells prior to isotopic analysis will be highlighted. New insights into chemoresistance mechanisms obtained using this multi-omics approach and the association of variations in K, Fe, and Zn concentrations and isotope ratios with differential metalloprotein expression will be discussed.

References

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