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Integrating MS proteomics in the Medicinal Chemistry pipeline as powerful tool to overcome drug resistance issues in colorectal cancer

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Recent technological developments in high resolution mass spectrometry now allow the deep characterization of complex in vitro and in vivo biological systems. By processing thousands of proteins and quantifying their fluctuations in expression, the combination of MS proteomics with bioinformatics allows the investigation of the subcellular mechanisms triggered by a drug administration or a combination of medicines1. Also, the brand-new invention of peptide labelling kits, like the TMT-tagging system (Thermo Fisher), makes it possible to analyse multiple samples in a single MS run, detecting even smaller differences in protein concentrations. By exploiting this powerful tool, the Drug Discovery Network has recently examined the mechanism of action of their novel thymidylate synthase inhibitors (namely dimer destabilizers, or Ddis), that induce cancer cell death by targeting the enzyme at the interface of the two monomers. Unlike 5-FU and antifolates, this innovative medicinal chemistry strategy delays/halts drug resistance onset2. Herein, by MS proteomics, we demonstrate that the co-administration of a low-dose of Ddis with 5-FU, with respect to 5-FU only, significantly reduces the drug sentitization in HCT-116 cells. Overall, we have identified a total of 5900 proteins, 19 of which differentially expressed proteins (DEPs), i.e. whose expression is significantly different from control cells. These proteins were investigated with dedicated bioinformatic tools, which suggested a strong overexpression of the RNA catabolic process (Nonsense Mediated Decay pathway), mitochondrial ATP-related metabolism, and pro-apoptotic p53 path for the drug combination (PI3K and mTORR), whereas 5-FU-only effect is less significant (no DEP was identified). Interestingly, despite both treatments have evidenced TS downregulation, only in drug combination the SHMT enzyme significantly decreases, which may suggest a folate imbalance. Overall, this study contributes to the demonstration MS proteomics is a powerful tool to speed up the drug discovery pipeline, providing insightful information about molecular mechanisms of drugs.

References:

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