Researchers identify key metabolic regulators of drug resistance in the fight against pancreatic cancer

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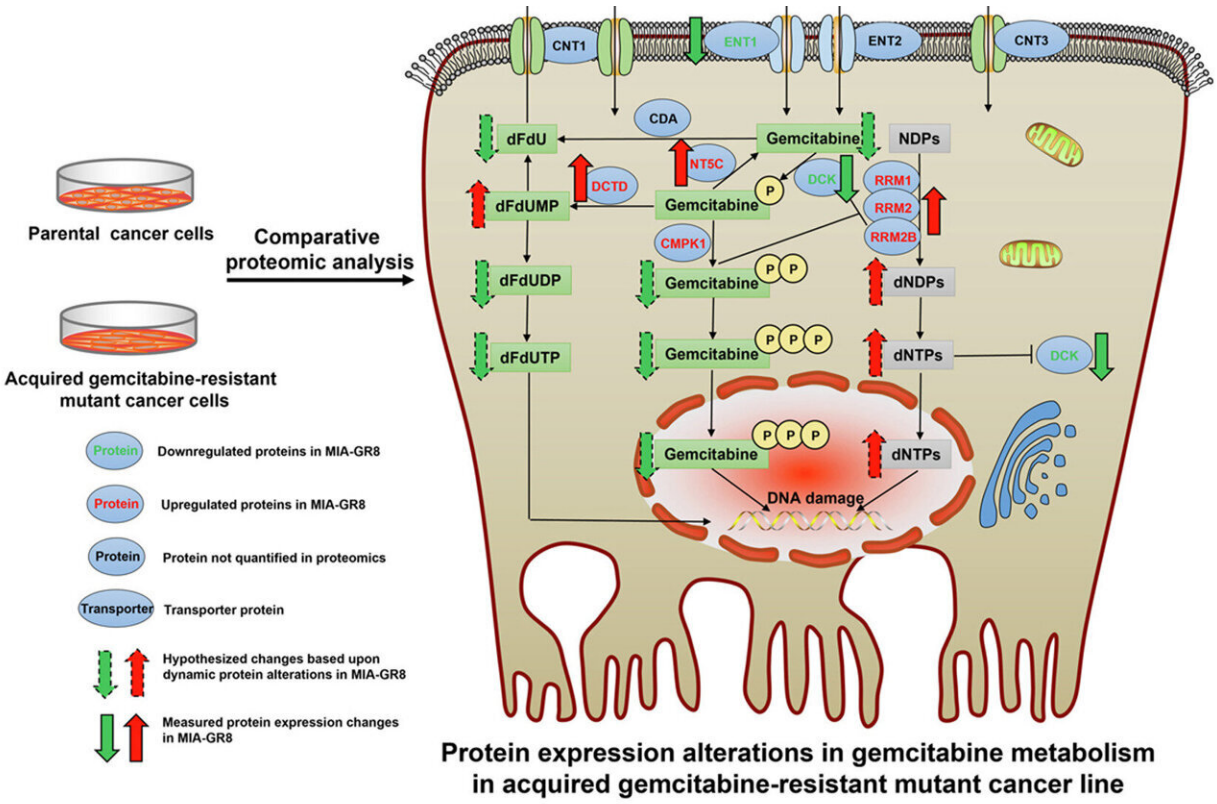

Graphical abstract. Credit: *Molecular & Cellular Proteomics* (2022). DOI: 10.1016/j.mcpro.2022.100409

Researchers from the University at Buffalo School of Pharmacy and

Pharmaceutical Sciences recently published in *Molecular & Cellular Proteomics*, describing their work in identifying key metabolic regulators involved in cancer cell resistance to gemcitabine (Gem), a standard-of-care chemotherapy for pancreatic dual adenocarcinoma (PDAC), the most lethal type of pancreatic cancer.

Robert M. Straubinger, Ph.D., UB Distinguished Professor, and Jun Qu, Ph.D., Professor, both of the Department of Pharmaceutical Sciences, led the research, which included William J. Jusko, Ph.D., SUNY Distinguished Professor, and several of his lab members.

Gemcitabine resistance (GemR) can develop clinically during chemotherapy, resulting in poor patient prognosis. Understanding the molecular mechanisms of Gem resistance has been challenging.

Straubinger and Qu collaborated on the application of a cutting-edge comprehensive, quantitative proteomic analysis approach to identify key metabolic regulators of Gem resistance in PDAC. Their team systematically examined PDAC cancer cells and identified several therapeutic vulnerabilities of drug resistance that could be targeted to improve therapeutic outcomes for PDAC patients experiencing Gem resistance.

Pancreatic adenocarcinoma does not respond well to current treatments or to newer immunotherapies that have worked well in some cancers. Gem is the mainstay drug for PDAC patients but provides only modest survival benefits. Clinically, development of Gem resistance can be rapid and compromises its efficacy.

First author Qingxiang (Nick) Lin, Ph.D.—who performed much of the work as a graduate student of Straubinger's in the Roswell Park Comprehensive Cancer Center Cancer Stress Biology Program and is now a postdoctoral scholar at Massachusetts General Hospital/Harvard

Medical School—developed multiple cancer cell lines that acquired a high degree of Gem resistance.

The team then employed the detailed proteomic analyses to test their hypothesis that the very large loss in Gem sensitivity in the cell lines developed would identify multiple protein functional networks that cooperate in PDAC cells to create a highly drug-resistant state.

Overall, the work has developed a more complete understanding of Gem resistance and established a rational basis for the design of effective therapeutic approaches to overcome Gem resistance in PDAC patients.

The key findings indicated that the overall consequence of multiple protein-level changes observed in highly-GemR cells is that alterations in multiple drug response networks work in concert to reduce the intracellular concentrations of Gem and its active metabolites.

The team noted significant elevations in protein expression within cellular Gem transport and metabolism pathways that would prevent PDAC cells from experiencing lethal Gem-induced stress and damage. The team concludes that approaches to modulate these drug metabolism pathways could overcome Gem resistance therapeutically in PDAC patients, and has been working toward identifying potential "master regulators" that may coordinate the overall drug-resistance response in PDAC cells.

"This research utilizes the cutting-edge global quantitative proteomic analyses to dissect systematically the molecular mechanisms of both acquired and intrinsic drug resistance in pancreatic cancer, and provides systems-level insights that could translate into therapeutic modulations of drug metabolism to overcome the chemo-resistance that frequently develops clinically, and improve the therapy of pancreatic cancer patients," says Lin.

"Understanding that there are adaptations within multiple pathways of cancer cells enables us to focus on new drugs that can combat drug resistance. One obvious focus would be to identify possible 'master regulators' that drive drug resistance, because the changes we observed in highly drug resistant PDAC cells appear to be coordinated toward an overall purpose. Finding drugs that reprogram drug resistant cells would be the key to exploiting these findings, and reverse clinical drug resistance," says Straubinger.

The team continues its work to develop promising drug combination strategies that can reverse drug resistance in PDAC patient tumors. The ultimate hope is that these approaches could move quickly to clinical investigation, benefitting pancreatic cancer patients fighting this highly aggressive and often lethal cancer.

More information: Qingxiang Lin et al, Comparative Proteomic Analysis Identifies Key Metabolic Regulators of Gemcitabine Resistance in Pancreatic Cancer, *Molecular & Cellular Proteomics* (2022). DOI: 10.1016/j.mcpro.2022.100409

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