Quantitative Proteomics and Network Simulations for 3 Patient-Derived Xenograft Models of Pancreatic Cancer

Jin Niu^1, Shichen Shen^1,2, Jun Qu^1,2, Robert M. Straubinger^1,2, Donald E. Mager^1

^1Department of Pharmaceutical Sciences, ^2Center of Excellence in Bioinformatics and Life Sciences, University at Buffalo, SUNY

Objective: To identify the pathways and quantify the proteins involved in the response of pancreatic ductal adenocarcinoma (PDAC) tumors to chemotherapy.

Methods: 3 patient-derived xenograft (PDX) mouse models were treated i.v. with a single dose of gemcitabine (35 mg/kg), Abraxane (15 mg/kg paclitaxel), or their combination. Tumors were harvested and analyzed by quantitative LC/MS proteomics using the IonStar workflow. A total 4500-6500 proteins were quantified in each PDX with no missing values, and 1837 human (cancer cell) and 1035 mouse (stroma) quantified proteins were common all 3. Treatment-mediated differential expression (DE) of proteins compared to vehicle controls were selected based on Student’s t-test (p < 0.05) and fold changes (|FC| >2), and DE proteins were functionally annotated using Ingenuity Pathway Analysis. A Boolean network for protein interactions was constructed for one PDX (#18254) based on literature information, and constrained to DE proteins (Figure 1). Simulations were conducted with the normalized HillCube method using Odefy.

Results: All 3 PDX models demonstrated distinctive protein expression profiles in response to treatment. PDX#14312 exhibited the highest number of DE proteins and PDX#18254 the lowest. Upstream regulator prediction for DE proteins in both cancer and stromal cells of PDX#14312 suggested elevated innate immune responses. However, stromal immune responses appeared suppressed in PDX#18269. Downstream function prediction for cancer cell protein expression common to the 3 PDX models suggested elevated migration/invasion, which implied resistance mechanism(s). Boolean simulations with the network agreed with 70% of the observed DE protein changes and suggested paclitaxel-induced vascular permeability was reversed by combination with gemcitabine.

Conclusion: 3 pancreatic cancer PDXs exhibited different proteomic signatures in response to chemotherapy, which may be associated with inter-individual clinical variability. Quantitative proteomics coupled with network analysis can be used to identify key treatment responses as well as identify crosstalk between cancer cells and their microenvironment in solid tumors.
Fig 1. The protein regulation network for PDX#18254. Yellow box: cancer cells; green box: stromal cells; rectangles with frame: significant DE proteins in response to gemcitabine (G), Abraxane (A), or their combination (COMB); ellipses: biological functions.