O2PLS as an integrative tool in systems oncology

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Altered metabolism is a universal characteristic of cancer that is implicated in such clinically relevant phenotypes as metastasis and chemotherapy resistance. Regulation of metabolic reprogramming in the context of heterogeneous genomic context of cancer is poorly understood. Systematic integration of omics data can unravel interconnectivity of multiple components of this regulation. We approached such integration through joint analysis of metabolic, gene expression and microRNA data. For this we employed a statistical integration method, O2PLS, for combining data from the well-characterized NCI-60 cancer cell line panel.

O2PLS is a generalization of OPLS approach that combines orthogonal signal correction (OSC) and Partial Least Square (PLS) analyses (1). OPLS allows separating variation in the data matrix X into the following parts: correlated to the response Y, systemically non-related (orthogonal) to Y and the residual variance. Such a segregation allows examining the sources of variation. With the use of the bidirectional O2PLS method we were able to focus on the correlations of interest between sets of multidimentional data and achieve improved interpretability of the results. With this work we demonstrate that O2PLS is a versatile tool for data integration through joint analysis of metabolomics, transcriptomic and microRNA data. We combined knowledge- and literature-based selection of molecules of interest (based on GWAS, metabolic reconstruction and target prediction) with rigorous cross-validation to identify correlations of interest between metabolites and microRNAs, as well as between metabolites and mRNAs. We identified microRNA modules associated with catabolic and anabolic processes, as well as defined NT5E as a novel regulator of cancer metabolism. We confirmed the observed correlations using other datasets and furthermore demonstrated the implication of NT5E in intrinsic and acquired resistance to chemotherapy in ovarian cancer and various cancer subtypes.

With this we present an integrative biology approach to the study of cancer cell molecular profiles (‘systems oncology’) that facilitates discovery of novel players in cancer metabolism, progression and therapy resistance.

1. Trygg J, Wold S: O2-PLS, a two-block (X-Y) latent variable regression (LVR) method with an integral OSC filter. J Chemometrics 2003, 17:53–64