Abstract 1

Perturbation biology infers cell signaling networks and guides discovery of effective combination therapies in cancer

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Quantitative understanding how proteomic changes collectively drive signaling pathway alterations in cancer cells is arguably the most important target in the field of cancer systems biology. To achieve this goal, perturbation biology was developed and advanced for inferring cell signaling networks and guiding discovery of effective combination therapies in cancer. Here, we improved and applied perturbation biology method to study signaling networks of SKMEL-133 melanoma cell lines. Using belief propagation based inference algorithm, we reconstructed the signaling network of SKMEL-133 from experimental measurements of 99 (phospho)proteomic/phenotypic entities under 89 perturbation conditions by reverse phase protein assays. Importantly, analyses revealed that proteins are able to remotely influence activities of faraway connected proteins in the signaling network. Through *in silico* perturbations of combinatorial protein targets, we found that protein entities are nonlinearly coupled in the network to have effects on the other protein/phenotypic activities. Furthermore, our results uncovered potentially actionable combinations of protein targets, inhibitions of which may have synergistic effect and potentially overcome resistance to cancer therapies.

Abstract 2

Phosphoproteomics-guided discovery of effective combination therapies in cancer

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Quantitative description and classification of aberrant pathway activities in tumors can inform design of effective cancer therapies as most targeted agents inhibit tumor cell proliferation by blocking oncogenic signaling. However, development of such therapies has been a challenge since multiple oncogenic pathways can be co-activated in a given tumor and the pathway activation patterns vary substantially even within similar tumor types. Therefore, tumor-specific combination therapies are required to block multiple aberrant pathways. Our strategy involves an algorithmic approach to classify actionable oncogenic pathway signatures in large tumor/cell line cohorts and experimental testing of combination therapies specific to each oncogenic signature. For this purpose, we developed an integrated bioinformatics pipeline and a high-throughput experimental validation platform. We analyzed the expression and phosphorylation level changes of > 200 proteins in > 7000 tumor samples available from the TCGA project and > 600 cell lines. The phosphoproteomic data was collected at MDACC using the reverse phase protein array technology. We employed an iterative machine-learning algorithm that couples feature selection with clustering to identify a combination of discriminant and actionable protein biomarkers shared within each tumor subcohort. We identified the actionable targets within each subcohort specific oncogenic signaling signature in collaboration with domain experts and through database searches. Our results uncovered potentially actionable combinations of protein targets shared among subcohorts of tumors and cell lines over a large number of lineages. We are testing our predictions with drug combinations in cell lines that share the target oncogenic signaling signature. The most promising combination therapy candidates will be tested in patient derived xenograft models. We expect our strategy will expedite the global efforts for precision therapy development as the experimentally validated drug combinations will be nominated for basket clinical trials at MDACC and elsewhere.