Characterization of differences in IGF1 and insulin induced proteomic signaling cascades

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Short Abstract — **Understanding the roles of insulin-like growth factor 1 (IGF1) and insulin signaling in breast cancer is still a major challenge. To tackle this problem, an iterative experimentation-computation workflow is employed using a screen of time-series protein expression profiles. The computation step included utilization of different linear models, where directed networks of time translation are constructed and analyzed to find novel temporal differences between IGF1 and insulin stimulation conditions. Promising results have been obtained pointing out links between intercellular trafficking with Akt signaling, and lipid biogenesis with MAPK cascade. The results confirmed that these inferred interactions are acquired differentially downstream of IGF1 and insulin, in vitro.**

Keywords — **Insulin-like growth factor I (IGF1), insulin, signaling, time-translation, mathematical modeling, IGF1R, InsR**

I. Introduction

THE downstream effects of both insulin-like growth factor I (IGF1) and insulin are different in normal and disease states. Under normal conditions, IGF1 is a proliferation and development factor whereas insulin has a major role of glucose homeostasis [1]. Multiple investigations have shown evidence of the similar functions of the two hormones in cancer progression, escape from apoptosis, and proliferation. There are also studies showing the association of raised blood levels of IGF1 to increased cancer risk [2]. The IGF1 receptors (IGF1R) and insulin receptors (InsR) have high sequence and structural similarities. The two receptors are heterotetrameric receptor tyrosine kinases with disulfide linked two alpha-beta dimers. Each ligand can bind to the other receptor with a lower affinity than the original agonist. There are studies on how ligand binding affects subsequent auto-phosphorylation of the intracellular kinase domains the receptors [3, 4].

Hence, understanding system dynamics downstream of IGF1 and insulin, and finding possible pathway dysregulatory mechanisms are needed. Our approach selects a set of rationally ranked pathway protein candidates from which perturbation experiments are carried out to check the validity of predictions.

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II. Methods & Results

The data used in this study included 108 protein expression profiles, either in total or phosphorylated form, at different time points of stimulation with IGF1 or insulin in 21 breast cancer cell lines.

A. Time translation models

The dataset is filtered and proteins with lowest variance values are excluded. Remaining 43 protein profiles are feature centered and normalized.

Linear time-translation (Eqn. 1) matrices (matrix $\boldsymbol{T}$) are constructed using three different methods; (1) covariance matrices, (2) inverse covariance matrices of maximum entropy, and (3) sparse regression matrices determined using lasso [5]. Each model is constructed using serum-free medium conditioned data as time zero (matrix $\boldsymbol{X}$) and a time point of stimulation as the next time point (matrix $\boldsymbol{Y}$).

$$\boldsymbol{Y} = \boldsymbol{T} \cdot \boldsymbol{X} \qquad \textbf{(Eqn. 1)}$$

The time-translation matrices obtained are different for each pair of time-translation and for each hormone stimulation condition.

B. Analyses of time-translation models

The different time-translation models for the same time point but with different hormone stimulation are compared using the highest magnitude interaction values and a list of ranked experimental candidates is generated. Top-ranked candidate experiments are currently under evaluation. Preliminary results confirmed differential effect of caveolin-1 knock-down on Akt phosphorylation in IGF1 and insulin conditions in MDA-MB-231 cells.

III. Conclusion

The computationally scalable reverse-engineering models of cellular networks in a temporal setting introduced here provided us a framework to elucidate experimental targets of pharmacological importance in a cost effective way

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