Unraveling core regulatory programs in lung cancer upon treatment with gemcitabine and docetaxel

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***Short Abstract* — Lung carcinoma is one of the leading causes of cancer with poor survival and life expectancy. A range of chemotherapeutics is used for treatment including Gemcitabine and Docetaxel, however their mode of action does not explain the high variability and resistance. An in-depth study of gene regulation upon treatment has been undertaken to establish targets for combinatorial approach. Quantitative modeling using neural networks has been applied to discover the underlying gene regulatory dynamics.**

Lung carcinoma is one of the leading causes of cancer death with patient survival depending on staging and form of the cancer. Overall 5-year survival of non-small cell cancer patients is around 15% and small-cell around 5% with an average life expectancy with treatment of only 6-12 months [1,2]. A range of effective chemotherapeutics is used for treatment including Gemcitabine [3] and Docetaxel [4], however patient responses remain unpredictable. The well-known mode of action of either drug does not explain the high variability and resistance, therefore an in-depth study of gene regulation upon treatment has been undertaken to establish potential targets for combinatorial approach.

Two metastatic models of human non-small cell lung carcinoma NCI-H460 [5](large-cell carcinoma) and the A549 [6] (adenocarcinoma) were treated with two concentrations of Gemcitabine or Docetaxel (IC50, IC90). RNA samples were gathered in a time-course at a high resolution (0-48h) with corresponding control series and replicates, and hybridized to microarrays for genome-wide expression profiling.

We have recently shown that the long-term cellular behavior is captured and reflected in the cells' gene expression kinetics [7]. Therefore, we have set up a high throughput data analysis and modeling pipeline to describe the dynamics of gene expression. A combination of statistical methods and functional analysis (GO, pathway) has been used to identify significantly differentially expressed genes in each time course. Bayesian clustering of the time-resolved profiles was used to capture the essential temporal organization of gene expression patterns. IC50 concentrations have been selected for modeling of the gene regulatory networks in both cell lines using a Continuous Time Recurrent Neural Network approach [7].

Our global gene expression analysis, ranking and clustering has provided us with a reduced overview of the significant temporally resolved gene profiles. Signaling network reconstruction coupled with modeling has been applied using a centroid approach to capture the regulatory dynamics. CTRNN approach allowed us to define the dynamic interactions between gene patterns, now final gene selection as well as *in silico* simulations and perturbations will be used to predict and evaluate potential targets to reinforce or weaken the intracellular regulation.

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