Consequences of feedbacks in mammalian signal transduction for cancer therapy

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***Short Abstract* — Signal transduction pathways are often equipped with negative feedbacks. These feedbacks are often strong and of physiological importance as they provide robustness and signal homeostasis to the cell. However, these feedbacks constitute a major obstacle for targeted therapies in cancer treatment, as they counteract drug action and cause cross-activation of other pathways. Here we present a combined experimental and theoretical analysis of signal transduction conducted on a panel of cancer cell lines to systematically quantify feedbacks in EGF-Receptor signaling, and their consequences for cancer therapy.**

***Keywords* — Signal transduction, Cell fate decision, Cancer, Mathematical modeling**

I. Introduction

SIGNAL transduction pathways relay information about the cellular surrounding to the nucleus, where they influence the activity of genes and ultimately control cell fate. As protein levels within signal transduction pathways vary strongly from cell to cell, the question arises how the signal transduction network can transmit information despite noise in protein levels. We and others have studied feedbacks in the mammalian signaling pathways downstream of the EGF-receptor (EGFR), and found that there are a multitude of feedbacks that act on both the post-translational and the transcriptional level [1-2]. We have also shown that a very strong feedback from the MAP-Kinase ERK to RAF provides robustness against uncertainty of protein levels [3]. This feedback counteracts drug action, and makes cells insensitive to targeted therapeutics in the pathway. Here, we investigated systematically how the feedback structure of this signaling network differs between different cancer cell lines in order to: First, understand how signaling differs quantitatively and qualitatively between cells; second, by combining with genomics data, to identify which mutations alter the feedback structure; third, use this information to identify possible combinatorial interventions for cancer therapy.

II. Results and Conclusions

Here, we developed and applied a combined experimental and computational approach to systematically quantify signal transduction downstream of the EGFR in a panel of colon cancer cell lines. Experimentally, we performed defined perturbations (using ligands to receptors and experimental drugs alone and in combination), and measured signaling status by a high-sample-throughput proteomics platform. We used this data to estimate parameters for mathematical models to quantitatively describe the signaling pathways by an approach similar to modular response analysis. We developed an analytical identifiability analysis, which automatically reduces the model such that we can reliably estimate the parameters and compare these between different cell lines.

Interestingly, the parameters within the main signaling pathways were comparable between the different cell lines. This shows that signaling pathways do have a core that behaves quantitatively similar in different cells. In contrast, many parameters that relate to the receptors, and the nuclear network downstream of the core signaling pathways are very variable between cells. We concluded from this analysis that signaling pathways also follow a bow-tie structure, with very rigid core and flexible inputs and outputs that cancer-cells can rewire to meet their needs.

When analyzing the effect of drugs in the model, we found that EGFR-directed therapy, one of the few options in the clinics today, was not effective if there are mutations in MAPK signaling. However, our model predicted and experiments confirmed that EGFR-directed therapy is efficient when provided with an additional inhibitor further downstream. We could trace the success of combinatorial treatment back to a long feedback, by which the kinase ERK negatively regulates the EGF-Receptor. When ERK activity is reduced, EGFR activity rises and activates a survival pathway, thus the EGFR has to be inhibited to prevent cell survival.

Our studies show that it is essential to quantitatively dissect the feedback structure in order to efficiently target signal transduction in cancer cell lines. Short, strong feedbacks, such as from ERK to RAF are serious obstacles for targeted therapies. Long feedbacks, such as the feedback to the EGFR, do cross-activate other pathways that branch out below the receptor level. To prevent this, combinatorial treatments need to be designed.

References

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