Modeling Cancer Metastasis using Global, Quantitative and Integrative Network Biology

In order to respond to alterations in its environment, a cell has to integrate multiple input-cues and modulate its signaling networks accordingly, in order to elicit a specific response such as proliferation or apoptosis. This process becomes significantly altered during cancer development, with genomic modifications giving rise to differential protein dynamics, ultimately resulting in disease. The exact molecular signaling networks underlying specific disease phenotypes remain elusive, as the definition thereof requires extensive analysis of not only the genomic and proteomic landscapes within a particular tumor, but also the phenotypic response to perturbations. Thus, there is a critical need for an integrative global approach, which assesses a biological system such as cancer from several molecular aspects in an un-biased fashion.

This thesis summarizes the efforts that were undertaken as part of my PhD in an attempt to positively contribute to this fundamental challenge. The thesis is divided into four parts. In Chapter I, we introduce the complexity of cancer, and describe some underlying causes and ways to study the disease from different molecular perspectives. There is a nearly infinite number of biological aspects that would need to be understood to enable comprehensive treatment regimens specific to each patient (i.e. personalized medicine). However, in the approaches outlined in this thesis, we chose metastasis as a key process for interrogating the clinical potential of targeting cancer networks using Network Biology.

Technologies key to this, such as Mass Spectrometry (MS), Next-Generation Sequencing (NGS) and High-Content Screening (HCS) are briefly described. In Chapter II, we cover how signaling networks and mutational data can be modeled in order to gain a better understanding of molecular processes which are fundamental to tumorigenesis. In Article 1, we propose a novel framework for how cancer mutations can be studied by taking into account their effect at the protein network level. In Article 2, we demonstrate how global, quantitative data on phosphorylation dynamics can be generated using MS, and how this can be modeled using a computational framework for deciphering kinase-substrate dynamics. This framework is described in depth in Article 3, and covers the design of KinomeXplorer, which allows the prediction of kinases responsible for modulating observed phosphorylation dynamics in a given biological sample. In Chapter III, we move into Integrative Network Biology, where, by combining two fundamental technologies (MS & NGS), we can obtain more in-depth insights into the links between cellular phenotype and genotype. Article 4 describes the proof-of-principle concept of how one can look at DNA mutations and protein dynamics in an integrative fashion. This has, for example, allowed us to investigate how mutations at the DNA level are propagated at the proteome level. Article 5 demonstrates how by taking a global, multi-platform approach, combined with extensive computational analysis, it is possible to gain a better understanding of colorectal cancer metastasis, and obtain potential clinical benefits. Chapter IV briefly summarizes the findings of the thesis and closes by proposing some future directions based on the work that was presented. Overall, the thesis aims to demonstrate the value of deploying several experimental platforms, each studying a different biological aspect, combined with in-depth computational analysis, in order to shed light on the fundamental molecular processes which underlie a complex disease like cancer and provide possible avenues for therapeutic intervention.

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