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Biological insights from quantitative analysis of RTK signaling networks

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Signal transduction mediated by protein phosphorylation regulates many cellular biological processes. Aberrations in protein phosphorylation due to kinase (or phosphatase) mutation or overexpression lead to dysregulation of cellular signaling and has been linked to a variety of pathologies, including cancer, autoimmune, and metabolic disorders. Quantification of specific phosphorylation sites regulating signaling pathways involved in these pathological disorders will enable a better understanding of the genesis and progression of the disease state, providing targets for more effective therapeutic intervention. The combination of mass spectrometry-based analysis of protein phosphorylation with phenotypic measurements and computational modeling has enabled the identification of sections of the signaling network that correlate strongly with biological response to cell perturbation. This approach should yield novel insights into the regulation of biological decisions on the network scale.

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Interactome networks

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For over half a century it has been conjectured that macromolecules form complex networks of functionally interacting components, and that the molecular mechanisms underlying most biological processes correspond to particular steady states adopted by such cellular networks. However, until recently, systems-level theoretical conjectures remained largely unappreciated, mainly because of lack of supporting experimental data.

To generate the information necessary to eventually address how complex cellular networks relate to biology, we initiated, at the scale of the whole proteome, an integrated approach for modeling protein-protein interaction or "interactome" networks. Our main questions are: How are interactome networks organized at the scale of the whole cell? How can we uncover local and global features underlying this organization, and how are interactome networks modified in human disease, such as cancer?

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SYMPOSIUM

Mouse models

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Mouse models of cancer

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1. Infection of newborn mice with replication-competent Moloney Murine Leukemia Virus gives rise to T and B cell lymphomas. The underlying mechanism is proviral activation of proto-oncogenes and inactivation of tumor suppressor genes. We have used retroviral insertional mutagenesis in over 1000 tumor-predisposed KO and control mice to identify new cancer causing genes. The largest specific cohort consisted of p53 and p19Arf KO mice. The resulting dataset with close to 600 common insertion sites marking known and unknown proto-oncogenes, (haploinsuffcient) tumor suppressor genes, and microRNAs, also permitted us to score for genotype-specific common insertion sites and highly significant co-occurrence of mutations and hits in (haploinsufficient) tumor suppressor genes. Clearly, this large dataset provides new information that could not have been extracted from smaller datasets collected previously, illustrating the "added value" of performing these studies on a large scale in a defined genetic background. The approach is complementary to and can confirm the cancer-causing nature of genes identified by other approaches such as SNP analysis and high throughput sequencing of cancer genomes. Illustrating examples will be presented. 2 NSCLC and SCLC can be efficiently induced by Adeno-Cre mediated switching of a floxed mutant Ki-Ras allele or by inactivation of Rb and p53 floxed alleles, respectively. Interestingly, while the same subset of cells are infected by the Adeno-Cre virus, activation of Ki-Ras or inactivation of Rb and p53 results in very different tumors. mSCLC are heterogeneous carrying clonally related cells with neuroendocrine and a progenitor-like marker profile, respectively. We have established a series of cell lines from the mSCLC tumors representing these lineages and performed array CGH analyses using a 1 Mb BAC array. Orthotopic transplantation of both lineages gave rise to tumors although with very different characteristics. We are focusing on these models both as a system to study the consecutive events in tumor development and to test intervention strategies.

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Dissecting tumor suppressor gene networks in vivo

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Apoptosis is a regulated form of cell death that is important for normal development and tissue homeostasis. Senescence produces "genetic death" in that the senescent cell is incapable of further propagation. Both processes are frequently disrupted in cancer cells, and each act as potent barriers to tumorigenesis. Since radiation and many chemotherapeutic agents induce apoptosis or senescence, the integrity of these programs can influence the outcome of cancer therapy. Our laboratory strives to understand how cancer genes control apoptosis and senescence in normal cells, and how mutations that disrupt these processes impact tumor development and therapy. The goal of these efforts is develop therapeutic strategies based on an understanding of drug action and cancer genotype. We currently are using genetically engineered mouse models to understand how apoptosis and senescence are controlled in tumor cells, as well as the response of tumors to conventional and targeted therapeutics. Recent work from our laboratory has incorporated stable and conditional RNA interference to probe tumor suppressor network components in vivo and used integrated oncogenomics approaches and in vivo RNAi interference to identify and characterize new tumor suppressor genes.

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Epidermal stem cells in tissue homeostasis and cancer. Role of Rac1 and Myc

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Adult stem cells are potentially the only long-term tissue residents that can accumulate enough oncogenic mutations resulting in the development of neoplasias. Upon transformation, adult stem cells retain hallmarks of stemness such as self-renewal, high proliferation potential, and tissue-remodelling activities, among others, but loose the ability to follow the organizational cues that restrain uncontrolled growth and invasion in healthy tissues. We have previously shown that Rac1 GTPase is required to maintain epidermal stem cells quiescent and located within their niche. Upon deletion of Rac1, epidermal stem cells exit the niche through a by-functional mechanism, cell cycle entry and egression from the stem cell niche that ultimately results in loss of self-renewal of the entire epidermal unit. Mechanistically, Rac1 exerts some of its epidermal effects via PAK2-mediated phosphorylation of the transcription factor c-Myc. Here we propose a novel function of Rac1 and c-Myc in epidermal stem cells and squamous tumours. Phosphorylation of Myc, downstream of PAK2, regulates quiescence and self-renewal of skin progenitors, affects the onset of differentiation, and modulates homing to the stem cell niche. In addition, phospho-Myc changes the invading and tissue remodelling potential of epidermal progenitors, and squamous cell carcinomas in 3D and 2D assays. Thus, we propose that the Rac/PAK2/Myc axis is required to sustain epidermal stem cell homeostasis and that deregulation of this pathway might play a role in epidermal neoplasias.

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Integrative comparative oncogenomics of mouse and human tumors

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An increasing compendium of mutant genes and their tumor biological impact has informed the rational development of effective targeted therapies and the use of such agents in appropriate patient populations. This genetic paradigm now motivates intensive efforts in cancer gene discovery and validation. High-resolution genome scanning technologies, such as array-based comparative genome hybridization (array-CGH), have uncovered highly re-arranged human cancer genomes harboring strikingly large numbers of recurrent copy number alterations (CNAs). The challenge of deciphering this complexity is furthered by the presence of 'causal' genomic events targeting cancer-relevant genes as well as bystander "genomic noise". Cross-species triangulation with tumor-associated alterations in refined genetically engineered mouse (GEM) models is a powerful filter to