Tumor Biology

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Molecular dissection of malignant tumor progression, metastasis and therapy resistance

The vast majority of cancer patient deaths are due to the systemic dissemination of cancer cells throughout the body and the seeding and outgrowth of secondary tumors (metastases) in distant organs. One major objective of our research is the identification and characterization of those cancer cells that are able to initiate and complete the metastatic process and to overcome current cancer therapies. In particular, we focus on the molecular mechanisms underlying the transition from benign tumors to malignant cancers and the metastatic dissemination of tumor cells. Moreover, we have set out to delineate the genes and pathways that allow cancer cells to evade from therapy. In addition to cultured tumor cell lines *in vitro*, we employ transplantation and transgenic mouse models of specific cancer types to determine causal connections between the expression of particular genes and tumor progression, metastasis and drug resistance *in vivo*.

The development of malignant tumors is in part characterized by a tumor cell's capability to overcome cell-cell adhesion and to invade surrounding tissue by a process referred to as epithelial-mesenchymal-transition (EMT). An EMT underlies the conversion of epithelial, differentiated cells to mesenchymal, migratory and invasive cells. In the past years, we have learned that an EMT occurs in multiple stages and is regulated by sophisticated molecular networks regulating the expression of a large number of protein, lncRNA and miRNA-encoding genes. More recently, we have noted that an EMT also selects for cancer cells exhibiting hallmarks of cancer stem cells and increased drug resistance. Notably, we have identified a large number of transcription factors that act as master regulators not only in the initiation and execution of the morphogenic process of an EMT but also in providing survival signals to cancer cells and thus allowing cancer cells to seed and grow metastases in distant organs. We investigate the direct target genes of these transcription factors and their role in tumor metastasis. We also assess the role of miRNAs and lnRNAs and their target genes in the regulation of an EMT and of metastatic dissemination. With these experimental approaches we aim at identifying the master regulators of an EMT and cancer metastasis and we plan to scrutinize their potential as therapeutic targets for preventing metastatic disease.

In a second line of research, we investigate the molecular pathways underlying the development of evasive resistance to targeted cancer therapy. We employ a number of cultured cancer cell lines and mouse models to study the pathological, physiological and molecular consequences of therapies targeting tumor angiogenesis and malignant tumor progression. In particular, we use cell biological, biochemical and bioinformatical analysis to delineate the molecular pathways allowing cancer cells to escape from targeted therapy. Recently, we have found that tumors shift their metabolism to glycolysis and acquire a status of metabolic symbiosis between individual cells of a tumor to overcome anti-angiogenic therapy. Finally, in collaboration with pharmaceutical companies we are investigating the efficacy and biological consequences of various anti-angiogenic and anti-metastatic cancer treatments.

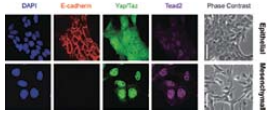

Fig. 1: Tead2 upregulation and Yap/Taz subcellular localization during EMT. Morphological differences between epithelial and mesenchymal counterparts of murine breast cancer cells (phase contrast, scale bar, 50 µm). Immunofluorescent staining of Tead2 and its co-factors Yap and Taz shows their increased expression and nuclear translocation in mesenchymal cells where they activate the expression of genes involved in EMT and metastasis. E-cadherin staining shows epithelial cell junctions. DAPI was used to visualize nuclei (scale bars, 25 µm; Diepenbruck, Waldmeier *et al.*, 2014).

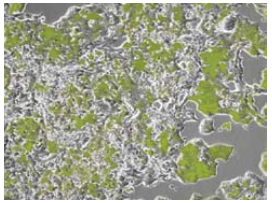

Fig. 2: IGF-II production as a public goods games network. The microscopic picture shows a co-culture of cancer cells which do not produce IGF-II (colorless cells) and cancer cells which express IGF-II (green cells). Both cell types require IGF-II for their survival and they compete against each other to reach a specific homeostasis of producer cells and consumer cells. Guess who will win (answer: Archetti *et al.*, 2015).

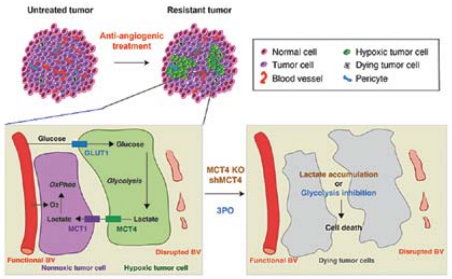

Fig. 3: Targeting metabolic symbiosis overcomes resistance to anti-angiogenic therapy. Metabolic symbiosis as a mechanism underlying evasive resistance to anti-angiogenic therapy by the multi-kinase inhibitors nintedanib and sunitinib. Inhibition of glycolysis by 3PO or genetic ablation of the lactate exporter MCT4 in tumor cells disrupts metabolic symbiosis, overrides therapy resistance, and suppresses tumor growth (Pisarsky, Bill *et al.*, 2016).

Selected Publications

Pisarsky L, Bill R, Fagiani E, Dimeloe S, Goosen RW, Hagmann J, Hess C, Christofori G. (2016) Targeting metabolic symbiosis to overcome resistance to antiangiogenic therapy. Cell Reports 15, 1161–1174

Bill R, Fagiani E, Zumsteg A, Antoniadis H, Johansson D, Albrecht I, Hilberg F, Christofori G. (2015) Nintedanib is a highly effective therapeutic for neuroendocrine carcinoma of the pancreas (PNET) in the Rip1Tag2 transgenic mouse model. Clinical Cancer Res. 21, 4856–4867

Archetti M, Ferraro D, Christofori G. (2015) Heterogeneity for IGF-II production maintained by public goods dynamics in neuroendocrine pancreatic cancer. Proc. Natl. Acad. Sci. USA 112, 1833–1838

Diepenbruck M, Waldmeier L, Ivanek R, Berninger P, Arnold P, van Nimwegen E, Christofori G. (2014) Tead2 expression levels control Yap/Taz nuclear localization and epithelial-mesenchymal transition. J. Cell Sci. 127, 1523–1536

Fantozzi A, Gruber DC, Pisarsky L, Heck C, Kunita A, Yilmaz M, Meyer-Schaller N, Cornille K, Hopfer U, Bentires-Alj M, Christofori, G. (2014) VEGF-mediated angiogenesis links EMT-induced cancer stemness to tumor initiation. Cancer Res. 74, 1566–1575

Connection to Clinical Practice

Markus Heim, Walter Weber
Department of Biomedicine, University Hospital Basel

Evasive resistance to targeted therapy and tumor heterogeneity

The development of resistance to targeted cancer therapy (evasive resistance) has appeared a major obstacle in treating the disease. In two network projects connecting patient care (Markus Heim), biomedical research (Mike Hall, Biozentrum) and computational biology (Niko Beerenwinkel and Jörg Stelling, D-BSSE, ETHZ, Basel), we aim at the molecular dissection of the pathways underlying the development of drug resistance to current cancer therapy. We have generated drug-sensitive cell lines and their drug-resistant counterparts and novel transgenic and patient-derived xenografted (PDX) mouse models of hepatocellular carcinoma (HCC) which recapitulate the development of HCC in patients. These cellular and animal models are now being used for molecular, biochemical and genomic analysis of the processes underlying evasive resistance and to test first alternative therapies to overcome evasive resistance. These projects are supported by a European Research Council (ERC) Synergy Grant and by a SystemsX.ch MTD Grant.

In a second network project, in collaboration with the Department of Surgery of the University Hospital Basel (Walter Weber) and basic and computational researchers of the Friedrich-Miescher-Institute in Basel (Mohammed Bentires-Alj and Michael Stadler), the University of Zürich (Bernd Bodenmiller) and IBM Rüschlikon (Maria Rodriguez), we address basic questions regarding breast cancer cell heterogeneity in patients and in experimental models and aim at identifying the cancer-propagating, metastatic breast cancer cell population and learn about the genetic programs driving these cells. This project is funded by a SystemsX.ch MTD Grant.