Tumor heterogeneity, metastasis and resistance

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Mechanisms of breast tumor heterogeneity, metastasis and resistance

Breast cancer is diagnosed in ~1.5 million women worldwide and ~500,000 lives are lost to the disease annually, the vast majority due to metastasis. Curing metastatic breast cancer represents an unmet medical need. Patients may do well after surgery and adjuvant treatment but drug-resistant, fatal metastases often develop. Critical to the phenomenon of resistance is tumor heterogeneity and this is the thread connecting the research in our lab.

At the molecular, cellular, and whole organism levels, we assess mechanisms that influence normal and neoplastic breast stem cells, metastasis, and resistance to therapy. We explore both cell autonomous (genetics, epigenetic, and proteomic) and non-cell autonomous mechanisms (immune cells, adipcoytes, etc).

We use systems medicine quantitative methods, unbiased pooled shRNA, CRISPR, transposon-based screens, and hypothesis-driven approaches. Computational biology is a very important part of our research. Moreover, we use multiphoton intravital imaging to assess the interactions between cancer cells and immune cells. These interdisciplinary projects seek to elucidate the integrated effects of signaling pathways and epigenetics on breast cell fate and tumor heterogeneity, and to leverage this mechanistic understanding into therapy. With clinicians from the University Hospital of Basel, we are building a breast cancer personalized medicine program wish should ultimately improve treatment for patients (Fig. 1).

M. Bentires-Alj is the founder and president of the European Network for Breast Development and Cancer (www.enbdc.org) that fosters global interactions between labs in these areas, and co-founder with Profs. Walter Paul Weber, Gerhard Christofori and Christoph Rochlitz of the Basel Breast Consortium (www.BaselBC.org), which is committed to promoting local basic, clinical, and translational interdisciplinary research projects within Switzerland.

Molecular mechanisms controlling normal and neoplastic breast stem cells:

PIK3CA^{H1047R} induces multipotency and multi-lineage mammary tumors. Two major cell lineages organized in a bi-layered structure constitute the mammary gland epithelium: the luminal layer lining the ducts and the alveoli and the myoepithelial layer with a basal location. A key issue in breast cancer biology is the effect of genomic lesions in specific mammary cell lineages on tumor heterogeneity and progression. The impact of transforming events on fate conversion in cancer cells-of-origin and thus their contribution to tumor heterogeneity remains largely elusive. Using in situ genetic lineage tracing and limiting dilution transplantation, we have unraveled the potential of PIK3CA^{H1047R}, one of the most frequent mutations occurring in human breast cancer, to induce multipotency during tumorigenesis in the mammary gland. Our results define a key effect of PIK3CA^{H1047R} on mammary cell fate in the pre-neoplastic mammary gland and show that the cell-of-origin of PIK3CA^{H1047R} tumors dictates their malignancy, thus revealing a mechanism underlying tumor heterogeneity and aggressiveness (Fig. 2) (Koren *et al.*, Nature 2015).

Fig. 1: Research topics in the Bentires-Alj lab (https://bentireslab.org/)

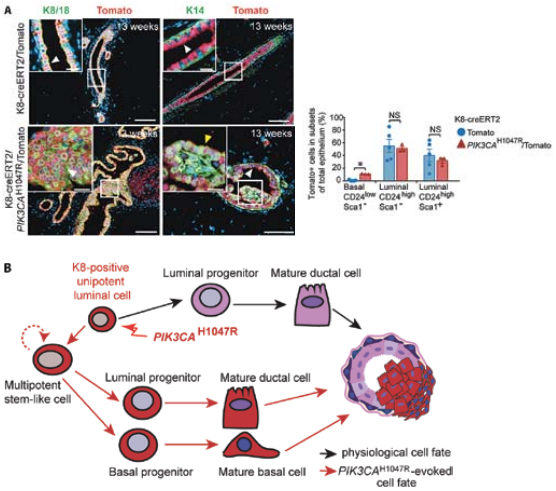

Fig. 2: Mutant PIK3CA induces mammary cell plasticity.
A. Representative images of 13-week tracing and FACS quantification of Tomato-positive mammary epithelial basal (CD24^{Low}Sca1^{+}) and luminal (CD24^{low}Sca1$^{-/+}$) subsets from K8-CreERT2/Tomato (n=5) and K8-CreERT2/*PIK3CA*^{H1047R}/Tomato mice (n=3) indicating that the expression of *PIK3CA*^{H1047R} induces cell plasticity. White arrowheads indicate luminal and yellow arrowheads indicate basal Tomato-labelled cells. Scale bars, 100 µm, 20 µm (magnifications). *P<0.05; NS: not significant
B. Model of the effect of *PIK3CA*^{H1047R} on cell fate in preneoplastic mammary glands. Under physiological conditions K8-positive luminal cells contribute to the homeostasis of luminal cells in the adult mammary gland (black arrows). Expression of *PIK3CA*^{H1047R} in cells results in dedifferentiation into a multipotent stem-like state from which cells further differentiate to basal and luminal mammary epithelial cells, contributing to mostly mixed-lineage malignant tumors (red arrows).

Molecular mechanisms controlling metastasis:

Discontinuation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis. We have discovered a paradoxical effect of the CC chemokine ligand 2 (CCL2) in metastatic breast cancer. Secretion of CCL2 by mammary tumors recruits CCR2-expressing inflammatory monocytes to primary tumors and metastatic sites, and CCL2 neutralization in mice inhibits metastasis by retaining monocytes in the bone marrow. Surprisingly, interruption of CCL2 inhibition leads to an overshoot of metastases and accelerates death. This is the result of monocyte release from the bone marrow, enhancement of cancer cell mobilization from the primary tumor, as well as blood vessel formation and increased proliferation of metastatic cells in the lungs in an IL-6/VEGF-A-dependent manner. Our results call for caution when considering anti-CCL2 agents as monotherapy in metastatic disease and highlight the tumor microenvironment as a critical determinant of successful anti-metastatic therapy (Bonapace *et al.*, Nature 2014).

Connection to Clinical Practice

Prof. Drs. Walter Paul Weber, Christoph Rochlitz, Viola Heinzelmann-Schwarz, Soysal Savas Deniz, Simone Münst Soysal

Selected Publications

Koren S, Reavie L, Couto JP, De Silva D, Stadler MB, Roloff T, Britschgi A, Eichlisberger T, Kohler H, Aina O, *et al.* (2015) PIK3CA(H1047R) induces multipotency and multi-lineage mammary tumours. Nature 525, 114–118

Sausgruber N, Coissieux MM, Britschgi A, Wyckoff J, Aceto N, Leroy C, Stadler MB, Voshol H, Bonenfant D, Bentires-Alj M. (2015) Tyrosine phosphatase SHP2 increases cell motility in triple-negative breast cancer through the activation of SRC-family kinases. Oncogene 34, 2272–2278

Koren S, Bentires-Alj M. (2015). Breast Tumor Heterogeneity: Source of Fitness, Hurdle for Therapy. Molecular cell 60, 537–546

Ramos P, Bentires-Alj M. (2015) Mechanism-based cancer therapy: resistance to therapy, therapy for resistance. Oncogene 34, 3617–3626

Bonapace L, Coissieux MM, Wyckoff J, Mertz KD, Varga Z, Junt T, Bentires-Alj M. (2014) Cessation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis. Nature 515, 130–133