Mohamed Bentires-Alj

Summary of research

Each year 1.4 million new cases of breast cancer occur among women worldwide and 500,000 women die from this disease. In most cases, metastasis is the cause of death. Although progress has been made in broadly understanding breast tumor biology and progression to metastases, most of the relevant molecules and pathways remain undefined.

The goal of M. Bentires-Alj research is to understand the molecular and cellular mechanisms regulating breast cell fate, progression to metastases and resistance to therapy:

Since he joined the FMI in November 2006, his group has successfully addressed key questions in the fields of normal and neoplastic breast cell fate, metastasis, and resistance to targeted therapies at the molecular, cellular, and whole organism levels. Since being at the FMI, his group has produced 24 research papers, 16 reviews/commentaries, 5 papers in review, and 8 patents.

Molecular mechanisms controlling normal and neoplastic breast cell fate

The hierarchically organized mammary gland epithelium consists of differentiated luminal epithelial and basal myoepithelial cells, as well as undifferentiated stem cells and restricted progenitors. Breast cancer is a heterogeneous disease and, besides the nature and number of transforming events and microenvironmental factors, the differentiation state of the cell-of-origin of cancer determines the phenotype, tumorigenicity, and metastatic potential of this malignancy. Hence, it is of paramount importance to understand how the different cell types in the human breast are maintained and regulated.

Example 1: They have elucidated how an early pregnancy protects from mammary cancer: (Meier-Abt F. et al. Breast Cancer Res. 2013, 2014 and Trends in Molecular Medicine 2014).

Example 2: They have demonstrated a fundamental effect of the tyrosine phosphatase SHP2 on tumor maintenance and progression in HER2-positive and triple-negative breast cancers. Their data show that SHP2 is important for self-renewal of breast tumor-initiating cells and for tumor maintenance and progression. These studies provide new insights into signaling cascades that regulate neoplastic breast stem cells and a rationale for targeting SHP2 in breast cancer (Aceto, Nature Medicine 2012; Aceto, Oncotarget 2012; Sausgruber, Oncogene 2014; and 2 patents).

Molecular and cellular mechanisms controlling metastasis

Each year 1.4 million cases of breast cancer will occur among women worldwide and 450,000 women will die from this disease, mostly due to metastasis. Although progress has been made in breast cancer research, we still do not understand the biology of this disease at a level that would explain the process of tumor progression to metastasis and why certain patients respond well to therapy, whereas others develop recurrent disease.

Example 3: They discovered a paradoxical effect of the chemokine CCL2 in metastatic breast cancer. While CCL2 neutralization in mouse models inhibits metastasis, subsequent interruption of CCL2 inhibition leads to an overshoot of metastatic load and accelerates the death of the animals. They have also elucidated the underlying cellular and molecular mechanisms of this rebound (Bonapace, Nature 2014).

Molecular mechanisms controlling breast cancer resistance to PI3K inhibition

The rapid development of highly specific inhibitors targeting key signaling pathways has created much excitement in the cancer research community. The clinical efficacy and low toxicity of some of these rationally designed therapies raised hopes of a new era in the treatment of cancer. Unfortunately, single-agent targeted cancer therapy is usually thwarted by emerging resistance, which leads to tumor recurrence and an inexorable downhill course. Carefully designed combination approaches have been suggested to circumvent these pitfalls.

Example 4: They discovered an IL8/JAK2-evoked positive feedback loop that dampens the efficacy of PI3K/mTOR inhibition. Their results provide a rationale for combined targeting of the PI3K/mTOR and JAK2 pathways in triple-negative breast cancer (Britschgi, Cancer Cell 2012, Drug Resistance Updates 2014 and 2 patents).