Friedrich Miescher Institute
for Biomedical Research

Media release, August 12, 2015

Sandra Ziegler Handschin
Communications
Maulbeerstrasse 66
CH-4058 Basel

T +41 61 696 15 39
F +41 61 697 39 76

sandra.ziegler@fmi.ch
www.fmi.ch

Common breast cancer mutation induces multipotency and tumor heterogeneity

Understanding how different cell populations arise within a tumor – so-called tumor heterogeneity – is widely regarded as a major challenge for cancer biology. Mohamed Bentires-Alj and his group at the Friedrich Miescher Institute for Biomedical Research have discovered how the most frequent mutation in human breast cancer leads to tumor heterogeneity. The PI3-kinase mutation forces cells back into a dedifferentiated, stem-like state from which tumors containing cells of various lineages can develop. These results have been published in *Nature*.

Breast cancer is not simply breast cancer – as has been known for some time, tumors grow and develop differently in different patients. This diversity has prompted the development of more individualized therapeutic approaches, which have already shown great promise. Recently, however, scientists discovered that a single tumor is composed of a variety of cell types, with different mutations and developmental potentials. Some of these cell types vary subtly, others substantially, some are frequent, others less so, and they respond differently to therapy. Most importantly, these differences between cells from the same patient have important consequences for how cancer is diagnosed and treated. However, it has remained unclear how tumor heterogeneity arises.

In a study published in *Nature*, Mohamed Bentires-Alj and his group at the Friedrich Miescher Institute for Biomedical Research have now shown how a common breast cancer mutation can lead to tumor heterogeneity.

“Heterogeneity is one of the most important and clinically relevant areas of development, stem cell and cancer research,” says Bentires-Alj. “In *The Origin of Species*, Darwin already discussed an experiment showing that diversity can make communities more productive. This suggests how tumor heterogeneity can affect prognosis, response to therapy and metastasis. Factors that enhance cancer cell fitness are clearly detrimental for patients.”

One of the most frequent genetic alterations occurring in human breast cancer is activation of the PI3-kinase pathway. This signaling pathway is activated in approximately 70% of breast cancers. In 20–40% of cases, activation is due to a mutation in one of the subunits of the PI3-kinase – $PIK3CA^{H1047R}$.

In the study, PhD student Shany Koren, together with colleagues in Bentires-Alj’s group, used *in situ* genetic lineage tracing to unravel the potential of $PIK3CA^{H1047R}$ to induce tumor heterogeneity. Koren explains: “We observed that the mutation forced cells that were already committed to form a particular layer of the mammary gland back into a more stem-like state. These dedifferentiated cells then gave rise to a variety of different cell lineages, thus inducing the formation of multi-lineage tumors.”

Even though these tumors initially all bore the same mutation, after dedifferentiation the cell fates varied substantially, and the tumors formed were heterogeneous – also with respect to prognosis.

Bentires-Alj comments: “This is a first indication of how intra-tumor heterogeneity can arise in PIK3CA mutant cells. While we were able to trace the first steps towards heterogeneous, multi-lineage tumors, we now need even more sophisticated tools to characterize these cells during tumor development. What determines the different outcomes? What are the roles of secondary mutations, and what about the interplay with the environment? Only with this knowledge can we hope to improve our methods of diagnosis and treatment.”

Contact

Dr. Mohamed Bentires-Alj, bentires@fmi.ch, Tel. +41 61 697 40 48
The Bentires-Alj lab investigates fundamental molecular mechanisms controlling normal and neoplastic breast cell fate, metastasis and resistance to targeted therapy.

Original publication

Koren S, Reavie L, Pinto do Couto J, De Silva D, Stadler MB, Roloff T, Britschgi A, Eichlisberger T, Kohler H, Aina O, Cardiff RD, Bentires-Alj M* (2015) PIK3CA^{H1047R} induces multipotency and multi-lineage mammary tumours. *Nature*

About the FMI

The Friedrich Miescher Institute for Biomedical Research (FMI), based in Basel, Switzerland, is a world-class center for basic research in life sciences. It was founded in 1970 as a joint effort of two Basel-based pharmaceutical companies and continues to receive, now as an independent foundation, financial support from Novartis. The FMI is devoted to the pursuit of fundamental biomedical research. Areas of expertise are neurobiology, growth control, which includes signaling pathways, and the epigenetics of stem cell development and cell differentiation. The institute counts 320 collaborators. The FMI also offers training in biomedical research to PhD students and postdoctoral fellows from around the world. In addition, the FMI is affiliated with the University of Basel and with the Novartis Institutes for BioMedical Research. The Director of the FMI since 2004 is Prof. Susan Gasser.