Friedrich Miescher Institute
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Combination therapy for incurable metastatic breast cancer to circumvent therapy resistance

In an excellent collaboration, scientists from the Friedrich Miescher Institute for Biomedical Research and industry discover how resistance mechanisms arise during the treatment of incurable metastatic breast cancer and suggest strategies to circumvent these by a combination therapy. Their results are published in the latest issue of *Cancer Cell*.

Triple-negative breast cancers are the bad guys among the different types of breast cancer. They affect younger women, metastasize more easily, are tougher to treat and once treated become therapy resistant faster. They are triple-negative because they lack the three alterations that usually cause breast cancer: up-regulation of the receptors for estrogen and progesterone, and activation of the oncogene HER2/Neu. The absence of these alterations is a hallmark of triple-negative breast cancers. However, what truly happens at the molecular level in these tumor cells is still unclear. Therefore a better mechanistic understanding of the tumor biology is direly needed to improve the treatment options for these patients.

Scientists from the Friedrich Miescher Institute for Biomedical Research (FMI) and the Novartis Institutes for BioMedical Research (NIBR) in Basel have now gained exciting new insights into the molecular mechanisms in triple-negative breast cancers. In today's issue of the renowned scientific journal *Cancer Cell* they show in detail how resistance to therapy develops and how this can be circumvented by mechanism-based combination therapies.

One of the most frequently hyper-activated signaling cascades in cancer is the PI3K/mTOR pathway. Not surprisingly, numerous inhibitors of the different nodes in this pathway have been developed and are in clinical trials. However, the efficacy of the inhibitors has been hampered because of resistance mechanisms that develop during treatment. Mohamed Bentires-Alj and authors now show that inhibition of the PI3K pathway leads to the activation of a parallel pathway, called the JAK2/STAT5 pathway. This pathway in turn stimulates proliferation and migration, two hallmarks of cancer that should be inhibited. It does so mostly through a secreted factor called IL-8. What is more, the team could show that this resistance mechanism kicks in particularly frequently in triple-negative breast cancers. "Our study nicely demonstrates that to win the arms race against cancer, it is of paramount importance to go beyond single targeted therapy and identify the right combination treatment strategies for the right subset of patients" said Adrian Britschgi, Postdoctoral Fellow in Bentires-Alj's group and first author of the study. Indeed, as soon as the scientists suppressed the resistance mechanisms by inhibiting both pathways simultaneously breast cancer cells started to die, tumor growth was curtailed and metastasis reduced in cellular and mouse tumor models, respectively.

For a future therapy of triple-negative breast cancer these findings could have an impact on two levels. First, IL-8 should be an excellent marker to determine if the PI3K/mTOR inhibitor therapy has triggered resistance mechanisms. Second, in these cases, the study provides a rationale for co-targeting both pathways using a combination therapy consisting of PI3K/mTOR and JAK2/STAT5 inhibitors.

"To cure cancer, it is crucial to understand the "wiring diagram" of cancer cells and the attributes of metastasis. In our study we leverage basic mechanistic understanding of

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metastatic breast cancer into a potential therapy for a currently incurable disease," said Bentires-Alj. Both investigators emphasize that "this work is an excellent example of how an academic institution pursuing basic research and industry can work together to address an unmet medical need for the benefit of patients."

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Britschgi A, Andraos R, Brinkhaus H, Klebba I, Romanet V, Müller U, Murakami M, Radimerski T, Bentires-Alj M. (2012) JAK2/STAT5 inhibition circumvents resistance to PI3K/mTOR blockade: A rationale for cotargeting these pathways in metastatic breast cancer. Cancer Cell

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 is now supported by the Novartis Research Foundation. The FMI is devoted to the pursuit of fundamental biomedical research. Areas of expertise are neurobiology, mechanisms of cancer, which includes signaling pathways, and the epigenetics of stem cell development and cell differentiation. The institute counts 320 collaborators. The FMI 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. The Director of the FMI since 2004 is Prof. Susan Gasser.