New functional understanding outlines therapy for untreatable breast cancer

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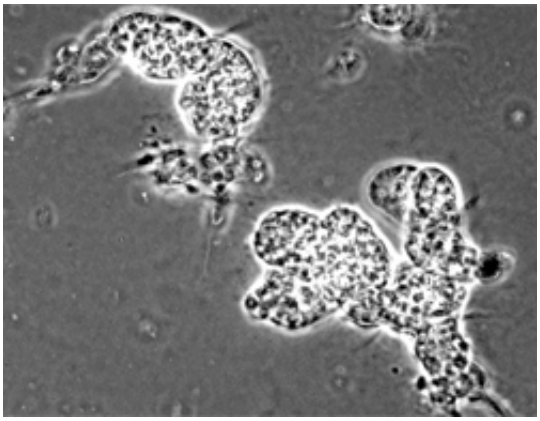


Human mammary epithelial cells growing in 3D cultures. Top: Mammary cells with compromised phosphatase. Bottom: Normal cells. In these cultures the cells grow in a matrix rich environment containing laminin and collagen IV.

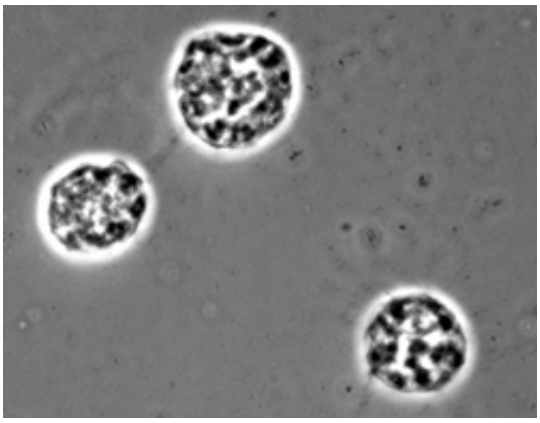
Cancer biologists from the Friedrich Miescher Institute for Biomedical Research have been part of a collaborative effort that identified a novel rationale for the treatment of currently not curable triple-negative breast cancers (TNBC). Using an array of state of the art technologies, they found that in these cancers the protein tyrosine phosphatase PTPN12 is compromised. Importantly, these researchers discovered that PTPN12 acts in normal cells to suppress the activity of multiple protein tyrosine kinases in concert. In TNBC cells, tumor causing protein tyrosine kinases such as HER2, EGFR, and PDGFR- are activated due to the loss of function of PTPN12. A novel therapeutic approach for TNBC would

therefore combine different protein kinase inhibitors based on the cancer-specific profile of activated protein kinases.

For a majority of breast cancer patients, the advent of therapies targeting specific receptors in the tumor has brought increased survival rates. However, 20% of all breast cancers are currently not treatable. These triple-negative breast cancers (TNBC) lack the hallmarks for cancer that characterize the treatable tumors: they do not over-produce steroid hormone receptors such as estrogen receptor and progesterone receptor, or the receptor tyrosine kinase HER2. What's more, the key signaling events that drive TNBCs were not known.

Collaborating scientists from the Baylor College of Medicine in Houston, Harvard Medical School in Boston, Yale University in New Haven and the Friedrich Miescher Institute for Biomedical Research (FMI) in Basel have now identified through unbiased screens a tumor suppressor phosphatase that is frequently compromised in TNBC. Once the function of PTPN12 tyrosine phosphatase is impaired then signaling events are activated that lead to cancer. In TNBC the absence of PTPN12 leads to an over-activation of oncogenic tyrosine kinases such as HER2 and EGFR. Their results are published in this month's scientific journal Cell.

"It is gratifying to see that the ten years we spent developing the RNAi methods and the transformation system to identify this novel tumor suppressor has finally paid off and led us to a potential therapy for breast and lung cancers." said Stephen Elledge, a professor with Howard Hughes Medical Institute and Harvard Medical School in Boston.



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Under the project leadership of Thomas Westbrook from Baylor College of Medicine in Houston, the scientists have used a multitude of state of the art technologies to further chronicle the function of PTPN12 and the events leading to cancer progression. Momo Bentires-Alj, group leader at the FMI, and his PhD student Nicola Aceto brought an important technology to the project that allowed the study of the effects of PTPN12 inactivation ex vivo. In their 3D cultures they could mimic changes seen in the progression of breast cancer and manipulate it such that the role of PTPN12 could be further dissected. Together with their colleagues, the FMI scientists could show that PTPN12 depletion disrupts normal acini formation leading to aberrant 3D structures and increases anchorage independent proliferation. Using newly developed RNAi and proteomic technologies, the Westbrook and Elledge labs showed that bringing back a functional PTPN12 into tumor cells inhibited specific tyrosine kinases and substantially reduced the tumorigenic and metastatic potential of these cells. The same was true when the PTPN12 impaired cells were treated with a cocktail of tyrosine kinase inhibitors that inactivated the PTPN12 regulated, hyperactive

kinases. These results show that some TNBCs depend on the action of PTPN12 regulated kinases. With these new insights, one can now outline a rational therapeutic approach for TNBCs. By combining available inhibitors of those tyrosine kinases constrained by PTPN12, for instance lapatimib (a dual inhibitor of HER2 and EGFR) together with sunitimib (a more broad kinase inhibitor), one hopes to be able to halt the progression of TNBCs with a loss of function of PTPN12.

"Our discovery that PTPN12 impairs tumorigenesis and metastasis by restraining multiple tyrosine kinases in concert leads us to 2 critical advances. First, we can now rationally combine tyrosine kinase-inhibitors in cancers (like TNBC) that were previously thought intractable to such therapies. Second, these discoveries open up a new field of mapping what other phosphatases constrain tyrosine kinases and how we can exploit this knowledge for cancer therapy," comments Thomas Westbrook.

"This is an excellent example of how mechanistic and functional understanding of cancer, aided by state of the art technologies, can lead to novel approaches for treating currently incurable diseases" adds Bentires-Alj.

The FMI contribution to this publication joins ranks with other outstanding results on protein kinases and phosphatases and their roles in cancer development and progression from the FMI in the last two decades. This success is based on a longstanding interest of several FMI group leaders in these molecules.

More information: Publication in *Cell*

Provided by Friedrich Miescher Institute for Biomedical Research