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Drug target for triple-negative breast cancer found in new study

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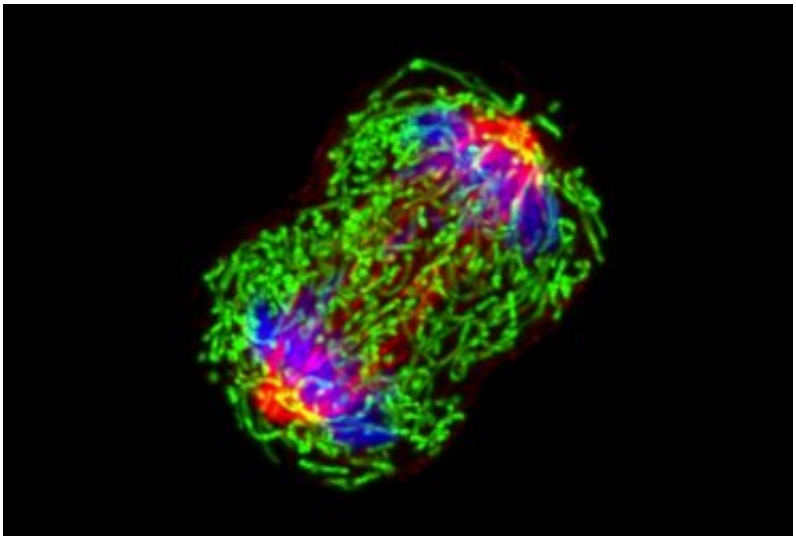

A triple-negative breast cancer cell (MDA-MB-231) in metaphase during cell division. Credit: National Cancer Institute

A team of researchers led by UC San Francisco scientists has identified a new drug target for triple-negative breast cancer, an aggressive disease subtype that has the poorest outcomes and accounts for as many as one in five cases. The findings are particularly noteworthy because drugs that act on the newly discovered target, a protein known as PIM1, are already in clinical trials for leukemia and multiple myeloma.

Triple-negative cancers are so called because they do not express receptors for the hormones estrogen and progesterone, nor for HER2

(human epidermal growth factor 2), and hence patients with these cancers are not candidates for treatment with modern hormonal therapies or the highly effective HER2-targeted drug Herceptin (trastuzumab).

"I'm a breast oncologist, and I've seen too many patients die from triple-negative disease," said senior author Andrei Goga, MD, PhD, professor of cell and tissue biology and of medicine at UCSF, and a member of the Helen Diller Family Comprehensive Cancer Center. "The only treatment we have to offer these patients is chemotherapy, and we desperately need new options."

The new study, published Oct. 24, 2016, in *Nature Medicine*, focused on triple-negative breast cancer also characterized by high levels of a cancer-driving protein called MYC (pronounced "mick"). This strategy grew out of previous work in the Goga's laboratory showing that MYC expression is disproportionately higher in triple-negative tumors than in tumors expressing hormone receptors and/or HER2.

Targeting MYC Expression

Just as triple-negative cancers present a therapeutic challenge, MYC expression in tumors is also a conundrum. MYC's role in cancer was discovered more than 30 years ago in the laboratory of UCSF Nobel laureate and Chancellor Emeritus J. Michael Bishop, MD, and it has since been implicated in many aggressive cancers. But, because of its physical characteristics and its fundamental role in normal cellular function, MYC has long been considered an "undruggable" protein.

To get around this problem, the research team employed an approach to undruggable proteins known as "synthetic lethality," which involves discovering the other proteins upon which these pharmacologically intractable proteins crucially depend to drive cancer growth.

Led by former UCSF postdoctoral fellow Dai Horiuchi, PhD, now assistant professor of pharmacology at Northwestern University's Feinberg School of Medicine, the group searched for synthetic lethal partners of MYC using a clever experimental system developed in collaboration with Paul Yaswen, PhD, of Lawrence Berkeley National Laboratory (Berkeley Lab).

At Berkeley Lab, Yaswen engineered normal breast cells, donated by patients who had undergone breast-reduction surgery, to carry a molecular construct that caused the cells to express MYC only when a particular chemical compound was applied. For experiments aimed at identifying MYC's synthetic lethal partners, such cells may have advantages over the "immortalized" cells commonly used in cancer research, which contain many genetic alterations that make MYC-specific results difficult to discern.

Then, in Goga's UCSF laboratory, thousands of short hairpin RNAs (shRNAs), bits of genetic material that precisely shut down the activity of specific proteins, were sequentially introduced to the engineered cells – in this case, shRNAs targeting proteins called kinases, a common target of cancer drugs, were used.

Synthetic Lethal Relationship

The experiments revealed that MYC depends on a number of kinases to drive cell growth, but especially on one called PIM1. When shRNAs deactivating PIM1 were introduced to cells expressing MYC, those cells died, demonstrating a synthetic lethal relationship between MYC and PIM1.

Zeroing in on this kinase was encouraging, Goga said, because other researchers have shown that genetic-knockout mice that lack the entire family of PIM kinases are slightly smaller than normal mice, but

"basically fine," indicating that a drug targeting just PIM1 may have manageable levels of toxicity in breast cancer patients.

To further assess whether PIM1 expression plays a relevant role in these patients, Horiuchi and Goga partnered with UCSF biostatistician Christina Yau, PhD, assistant adjunct professor of medicine, and UCSF physician-scientist Hope S. Rugo, MD, professor of medicine, to determine whether PIM1 was highly expressed in tissue samples from MYC-positive, triple-negative breast cancer patients.

"We found that PIM1 is indeed highly upregulated in these more aggressive breast cancers that have high MYC expression," Goga said, "and that patients with high PIM1 tend to do more poorly."

The team next tested two preclinical PIM1 inhibitor drugs against MYC-positive cancer. In experiments with cancer cell lines, the PIM1 inhibitors killed cells in a MYC-dependent manner, and in two different mouse models—one in which mice were implanted with patient tumors and the other in which a genetic alteration of MYC predisposes the mice to tumor development – the administration of PIM1 inhibitors resulted in significant tumor regression.

Further bolstering these results, a complementary paper in the same issue of *Nature Medicine* by researchers at the Institute of Cancer Research (ICR) in London, led by Professor Andrew Tutt, also fingered PIM1 as a target in triple-negative breast cancer, and the ICR team arrived at this conclusion using completely different methods than those used by Goga and colleagues.

"The next step is to figure out how to bring this finding into early-phase clinical trials with patients, and we're partnering with pharmaceutical companies to explore this," Goga said. "Since blocking PIM1 makes MYC-driven cancer cells more vulnerable, we're also exploring whether,

for triple-negative cancer, PIM1 inhibitors could be combined with chemotherapy, with other targeted drugs, or even with immunotherapy," he said.

"It's incredibly encouraging to find possible new options for patients with an aggressive cancer like triple negative breast cancer, and that studies conducted by separate teams at leading institutions agree on the implications of the findings," said Alan Ashworth, PhD, FRS, president of UCSF Helen Diller Family Comprehensive Cancer Center, and former CEO of the ICR. "With the UCSF team, thanks to funding by public and private organizations, we're able to harness the team science model for collaborations like this that yield findings with the potential to change things for patients who've had very few options for far too long."

More information: Dai Horiuchi et al. PIM1 kinase inhibition as a targeted therapy against triple-negative breast tumors with elevated MYC expression, *Nature Medicine* (2016). DOI: 10.1038/nm.4213

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