

New insights into protein reveal potential therapy for breast cancer

November 29 2017, by Anna Williams



Killer T cells surround a cancer cell. Credit: NIH

Northwestern Medicine scientists have discovered a new function for a protein called SET1B in the cytoplasm of cells, and demonstrated that targeting its role in regulating cellular metabolism may be able to treat



triple-negative breast cancer.

The findings were published in the journal Genes and Development.

"This is a major discovery," said principal investigator Ali Shilatifard, PhD, the Robert Francis Furchgott Professor and chair of Biochemistry and Molecular Genetics.

Lu Wang, PhD, a postdoctoral fellow in Shilatifard's laboratory, was the first author of the study.

SET1B is one of the six members of COMPASS, a family of enzymes which was first characterized by Shilatifard close to 20 years ago. The complex is known to be critical to gene expression: COMPASS catalyzes a key molecular event called histone methylation, which influences whether genes are turned on or off.

Dysregulation and mutations in some COMPASS genes have since been implicated in many types of human diseases, including cancer. But the function of SET1B, and its relationship with cancer, had remained unclear.

In the current study, the scientists first discovered that the majority of SET1B resides in the cytoplasm of cells—a surprising finding, given that all other members of COMPASS are found mainly in the nucleus.

"SET1B is also essential to the viability of different cancer cells, especially human <u>breast cancer</u>," Wang explained. "When the gene is deleted in <u>triple-negative breast cancer</u> using the gene-editing tool CRISPR, the cells do not survive. Interestingly, normal epithelia cells are fine with the depletion of SET1B."

To further understand SET1B's link to cancer growth, the scientists



demonstrated that loss of SET1B leads to increased expression of several genes that modulate fatty acid metabolism—indicating a novel function for SET1B in regulating metabolic processes.

The Shilatifard laboratory also explored how these findings might offer novel strategies for treating <u>breast</u> cancer.

"At first, we thought about how to target SET1B—but a crystal structure of this 300kd protein doesn't exist, so we can't design a small molecule targeting it," Wang explained. "So we looked at the major downstream genes to target instead."

ADIPOR1 is one of the genes the scientists discovered was regulated by SET1B. ADIPOR1 is the receptor for adiponectin, a hormone that is known to have anti-diabetic effects. A Japanese research group had already developed a small molecule agonist drug to activate that receptor, called AdipoRon. As <u>reported</u> in *Nature* in 2013, AdipoRon improved insulin resistance and extend the lifespan of obese diabetic mice.

Given their discovery about the close relationship between SET1B and ADIPOR1, the Northwestern scientists decided to investigate using AdipoRon to treat triple-negative breast cancer. Triple-negative breast cancer is a type of breast cancer that lacks the three receptors targeted in common therapies, and as such, can be difficult to treat.

The team discovered that AdipoRon was capable of killing triplenegative <u>breast cancer cells</u> in vitro, and further demonstrated in a mouse model of the cancer that treatment with the drug significantly reduced tumor size and increased animal survival.

Wang noted that the current study is the first to demonstrate how this small molecule drug, which has been used for the treatment of diabetes,



could be used to treat human cancer.

In future studies, Shilatifard and his team intend to further analyze clinical data that suggest a correlation between SET1B gene expression and breast cancer patient survival, as well as investigate the development of other compounds that might target SET1B for <u>cancer</u> treatments.

More information: Lu Wang et al. A cytoplasmic COMPASS is necessary for cell survival and triple-negative breast cancer pathogenesis by regulating metabolism, *Genes & Development* (2017). DOI: <u>10.1101/gad.306092.117</u>

Provided by Northwestern University

Citation: New insights into protein reveal potential therapy for breast cancer (2017, November 29) retrieved 21 May 2024 from https://medicalxpress.com/news/2017-11-insights-protein-reveal-potential-therapy.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.