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MicroRNA cooperation mutes breast cancer oncogenes

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A University of Colorado Cancer Center study recently published in the journal *Cell Death & Disease* shows that turning up a few microRNAs a little may offer as much anti-breast-cancer activity as turning up one microRNA a lot – and without the unwanted side effects.

It's a bit like the classic thought experiment known as the "tumor problem" formulated by Karl Dunker in 1945 and used frequently in the problem-solving literature: Imagine a person suffers from a malignant tumor in the center of her body. Radiation strong enough to kill the tumor kills any healthy tissue through which it passes. Without operating or killing healthy tissue, how can a doctor use radiation to kill the tumor?

The answer is to target the tumor from many angles – many weak rays of radiation pass harmlessly through healthy tissue, but their combined power at the point of the tumor is enough to kill it.

In the present study, CU Cancer Center investigators used "weak" induction of multiple microRNAs that combined from many angles to regulate the known breast cancer oncogenes erbB2/erbB3 (the "tumor") without regulating non-target genes (the "healthy tissue").

"Imagine you have a microRNA that regulates genes A and B. Then you have another microRNA that regulates genes B and C. You amplify each microRNA to a degree that doesn't effect gene A or C, but their combined effect regulates gene B," says Bolin Liu, MD, assistant professor in the Department of Pathology at the University of Colorado

School of Medicine.

microRNA is an attractive target in cancer therapy – more microRNA can lead to less gene expression, turning down or off the oncogenes that cause cancer. However, to get the desired effect on gene expression frequently requires enhancing microRNA expression 100- or 1,000-fold (or more). And the induced microRNA likely has other genetic targets – it will turn down other genes as well as the oncogene, sometimes with unfortunate consequences.

"The current study showed that two microRNAs enhanced only 3-to-6 times their natural expression could cooperate to regulate an oncogene that had previously only been affected by a microRNA enhanced by many, many times this amount," Liu says.

Specifically, the group's work shows that no one alone, but any two of the three microRNAs that regulate erbB2/erbB3 expression can affect the levels of proteins produced by the genes. These are miR-125a, miR-15b, and miR-205, which act in concert to regulate the expression of erbB2/erbB3, which are cancer-causing products of the oncogenes.

But in general, the group's novel technique could have implications far past erbB2/erbB3, allowing researchers and eventually doctors to mute the genes they want to mute without also dampening the expression of genes regulated by only one or only the other microRNA partner.

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