# Protein once thought exclusive to neurons helps some cancers grow, spread, defy death

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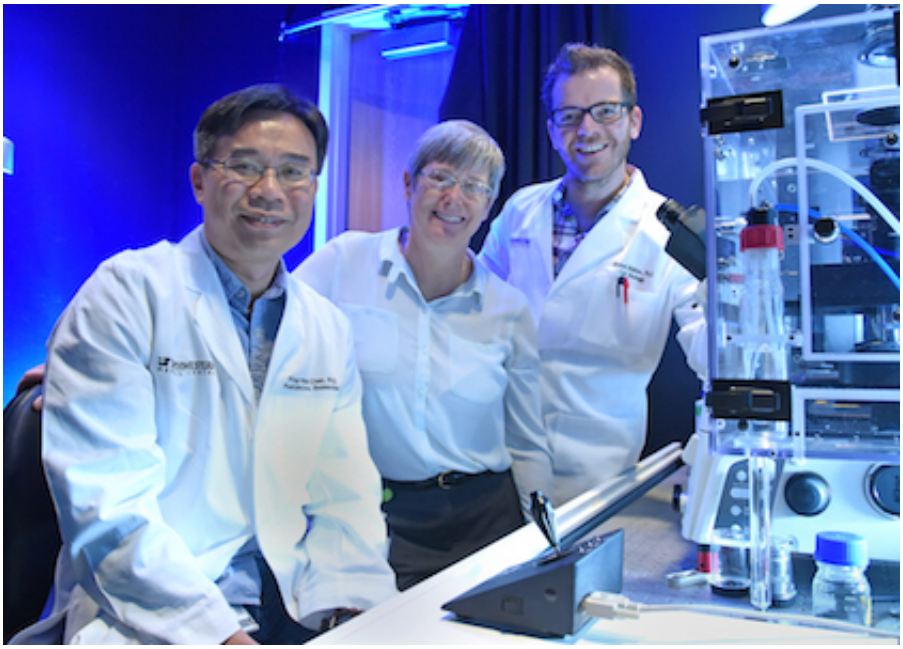

Dr. Ping-Hung Chen, Dr. Sandra Schmid, Dr. Marcel Mettlen and other research team members determined that aggressive cancer cells adapt nerve cell mechanisms to maintain or squelch signals needed to survive and grow. Credit: UT Southwestern

How we think and fall in love are controlled by lightning-fast electrochemical signals across synapses, the dynamic spaces between nerve cells. Until now, nobody knew that cancer cells can repurpose tools of neuronal communication to fuel aggressive tumor growth and spread.

UT Southwestern Medical Center researchers report those findings in two recent studies, one in the *Proceedings of the National Academy of Sciences (PNAS)* and the second in *Developmental Cell*

"Many properties of aggressive cancer growth are driven by altered cell signaling," said Dr. Sandra Schmid, senior author of both papers and Chair of Cell Biology at UT Southwestern. "We found that cancer cells are taking a page from the neuron's signaling playbook to maintain certain beneficial signals and to squelch signals that would harm the cancer cells."

The two studies find that dynamin1 (Dyn1) - a protein once thought to be present only in nerve cells of the brain and spinal cord - is also found in aggressive cancer cells. In nerve cells, or neurons, Dyn1 helps sustain neural transmission by causing rapid endocytosis - the uptake of signaling molecules and receptors into the cell - and their recycling back to the cell surface. These processes ensure that the neurons keep healthy supplies at the ready to refire in rapid succession and also help to amplify or suppress important nerve signals as necessary, Dr. Schmid explained.

"This role is what the cancer cells have figured out. Aggressive cancer cells have usurped the mechanisms that neurons use for the rapid uptake and recycling of neural transmitters. Instead of neural transmitters, the cancer cells use Dyn1 for rapid uptake and recycling of EGF (epidermal growth factor) receptors. Mutations in EGF receptors are drivers of breast and lung cancers," she said of the *Developmental Cell* study.

In order to thrive, cancer cells must multiply faster than nearby noncancerous cells. EGF receptors help them do that, she explained.

Cancer cell survival is another factor in disease progression. In the *PNAS* study, the Schmid lab found that aggressive cancer cells appear to have

adapted neuronal mechanisms to thwart a key cancer-killing pathway triggered by activating "death receptors" (DRs) on cancer cells. Specifically, aggressive cancer cells appear to have adapted ways to selectively activate Dyn1 to suppress DR signaling that usually leads to cancer cell death.

"It is amazing that the aggressive cancers use a signaling pathway to increase the activity of EGF and also turn on Dyn1 pathways to suppress cancer death - so you have this vicious circle," said Dr. Schmid, who holds the Cecil H. Green Distinguished Chair in Cellular and Molecular Biology.

She stressed that less aggressive cancers respond to forms of chemotherapy that repress EGF signaling and/or die in response to the TRAIL-DR pathway. However, aggressive lung and breast cancer cells have adapted ways to commandeer the neuronal mechanisms identified in these studies.

The hope is that this research will someday lead to improved strategies to fight the most aggressive cancers, she said. Currently, her laboratory is conducting research to identify Dyn1 inhibitors as potential anticancer drugs using a 280,000-compound library in a shared facility at UT Southwestern.

"Cancer is a disease of cell biology. To grow, spread, and survive, cancer cells modify normal cellular behavior to their advantage. They can't reinvent the underlying mechanisms, but can adapt them. In these studies, we find that some cancer cells repurpose tools that neurons use in order to get a competitive advantage over nearby normal cells," she said.

Provided by UT Southwestern Medical Center