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Cell death mystery yields new suspect for cancer drug development

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A mysterious form of cell death, coded in proteins and enzymes, led to a discovery by UNC researchers uncovering a prime suspect for new cancer drug development.

CIB1 is a protein discovered in the lab of Leslie Parise, PhD , professor and chair of the department of biochemistry at the University of North Carolina at Chapel Hill. The small calcium binding protein is found in all kinds of cells.

Cassandra Moran, DO, was a pediatric oncology fellow at UNC prior to accepting a faculty position at Duke University. She is interested in neuroblastoma, a deadly form of childhood brain cancer. While working in the Parise lab at UNC as a resident, she found that decreasing CIB1 in neuroblastoma cells caused cell death.

Cancer is a disease of uncontrolled cell growth, so the ability to cause cancer cell death in the lab is exciting to researchers – but the UNC team couldn't figure out how it was happening.

Tina Leisner, PhD, a UNC research associate in biochemistry, picked up where Dr. Moran left off when she returned to her clinical training.

"It was a mystery how loss of CIB1 was causing cell death. We knew that it wasn't the most common mechanism for programmed cell death, called apoptosis, which occurs when enzymes called caspases become activated, leading to the destruction of cellular DNA. These cells were

not activating caspases, yet they were dying. It was fascinating, but frustrating at the same time," said Leisner.

What Dr. Leisner and her colleagues found, in the end, is that CIB1 is a master regulator of two pathways that cancer cells use to avoid normal mechanisms for programmed cell death. These two pathways, researchers believe, create "alternate routes" for cell survival and proliferation that may help cancer cells outsmart drug therapy. When one pathway is blocked, the other still sends signals downstream to cause cancer cell survival.

"What we eventually discovered is that CIB1 sits on top of two cell survival pathways, called PI3K/AKT and MEK/ERK. When we knock out CIB1, both pathways grind to a halt. Cells lose AKT signaling, causing another enzyme called GAPDH to accumulate in the cell's nucleus.Cells also lose ERK signaling, which together with GAPDH accumulation in the nucleus cause neuroblastoma cell death. In the language of people who aren't biochemists, knocking out CIB1 cuts off the escape routes for the cell signals that cause uncontrolled growth, making CIB1 a very promising drug target," said Dr. Parise.

This multi-pathway action is key to developing more effective drugs. Despite the approval of several targeted therapies in recent years, many cancers eventually become resistant to therapy.

"What is even more exciting," Leisner adds, "is that it works in completely different types of cancer cells. We successfully replicated the neuroblastoma findings in triple-negative breast cancer cells, meaning that new drugs targeted to CIB1 might work very broadly."

More information: The team's findings were published in the journal *Oncogene*.

Provided by University of North Carolina Health Care