Neurons, brain cancer cells require the same little-known protein for long-term survival

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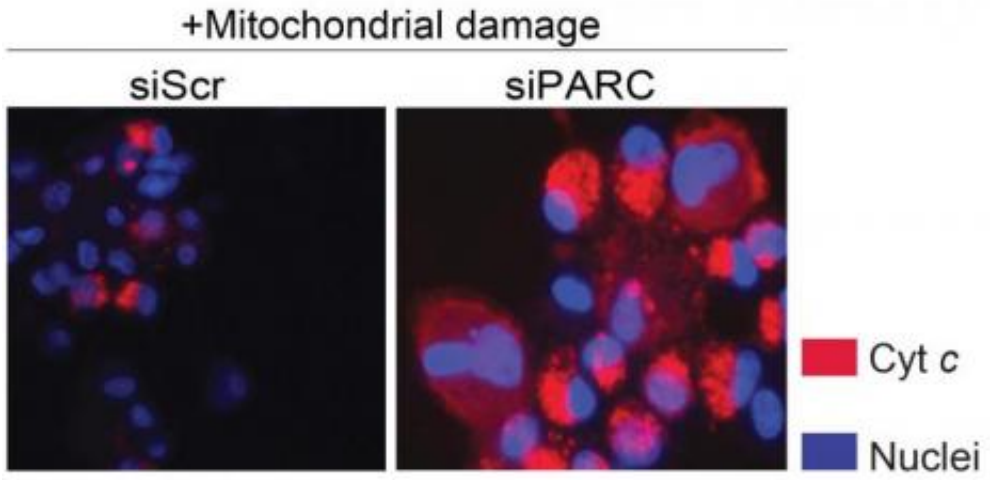

In brain cancer cells, the protein PARC plays a key role in long-term cell survival. In both images, the red represents the protein cytochrome c, which is released when mitochondria are damaged and trigger apoptosis -- cell suicide. At left, injured brain cancer cells exhibit little cytochrome c; they use the protein PARC to degrade the released cytochrome c, allowing the cancer cells to survive. At right, when researchers reduced PARC, cytochrome c accumulated, allowing apoptosis to carry on. Credit: Vivian Gama, PhD, UNC School of Medicine

Researchers at the UNC School of Medicine have discovered that the protein PARC/CUL9 helps neurons and brain cancer cells override the biochemical mechanisms that lead to cell death in most other cells. In neurons, long-term survival allows for proper brain function as we age. In brain cancer cells, though, long-term survival contributes to tumor

growth and the spread of the disease.

These results, published in the journal *Science Signaling*, not only identify a previously unknown mechanism used by neurons for their much-needed survival, but show that brain cancer cells hijack the same mechanism for their own survival.

The discovery will lead to new investigations of brain cancer treatments and provides insight into Parkinson's disease, including a potential new research tool for scientists.

"PARC is very similar to Parkin, a protein that's mutated in Parkinson's disease," said Mohanish Deshmukh, a professor of cell biology and physiology and senior author of the *Science Signaling* paper. "We think they might work in tandem to protect neurons."

If so, researchers can investigate the interplay between these proteins to create better drugs to treat the second-most prevalent neurodegenerative disease after Alzheimer's disease.

Vivian Gama, PhD, a postdoctoral fellow in Deshmukh's lab, led the experiments in cell cultures and animal models. First, she used external stimuli to promote the damage of mitochondria – the energy sources for cells. In most cell types, when mitochondria are damaged, they release a protein called cytochrome c, which triggers a cascade of biochemical steps that end in cell death – a process known as apoptosis.

Working with neurons, though, Gama found that the protein PARC/CUL9 blocked this process; it degraded cytochrome c, halted apoptosis, and allowed for long-term cell survival. "In this setting, we want PARC to do that because we want neurons to survive as long as possible," said Gama, first author of the *Science Signaling* paper.

Deshmukh, a member of the UNC Neuroscience Center and the UNC Lineberger Comprehensive Cancer Center, said, "In Parkinson's disease, we know that Parkin targets damaged mitochondria for degradation. However, exactly what happens to the proteins, such as cytochrome c, that are released from the damaged mitochondria has been unknown. Now, we think PARC plays a role in this process."

Deshmukh and Gama's work could lead to an alternative way to study Parkinson's disease. Other researchers have created mouse models that lack the Parkin gene, but Gama said these models don't have many of the hallmark symptoms that human patients have, making the model less than desirable for researchers. "Our hypothesis is that in the absence of Parkin, PARC still does the job," Gama said, "as it may allow cells to survive."

Gama and Deshmukh are now creating a model that lacks both the Parkin and PARC genes.

They will also investigate PARC as a target for cancer treatment.

"We tested several cancer cell lines and found that PARC degrades cytochrome c in medulloblastoma, a cancer of the central nervous system and in neuroblastoma, a cancer of the peripheral nervous system," Gama said. "Not all cytochrome c is degraded; there are likely other factors involved. But PARC is an important player."

When Gama and colleagues triggered the apoptotic process in brain cancer cells, they found that PARC allowed the cells to survive. When PARC was inhibited, the cells were more vulnerable to stress and damage, which means they could be more vulnerable to compounds aimed at destroying them.

Deshmukh said, "We show that brain cancer cells co-opt PARC to

bypass apoptosis in the same way that neurons do and for the exact same purpose."

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