Medical Xpress

Worm provides clues about preventing damage caused by low-oxygen during stroke, heart attack

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Neurobiologists at Washington University School of Medicine in St. Louis have identified pathways that allow microscopic worms to survive in a low-oxygen, or hypoxic, environment.

They believe the finding could have implications for conditions such as stroke, heart attack and cancer. Sensitivity to low oxygen helps determine how damaging those medical conditions can be. The researchers report their findings in the Jan. 30 issue of the journal *Science*.

"In stroke and heart attack, cells die because they lack oxygen," explains principal investigator C. Michael Crowder, M.D., Ph.D. "In cancer, the opposite is true. Cancer cells are hypoxia-resistant in many cases, and their potential to spread throughout the body tends to correlate with their degree of hypoxia resistance."

Crowder says it may be possible to develop more effective therapies for stroke and heart attack, on one hand, and cancer, on the other, when scientists better understand how cells protect themselves from oxygen deprivation. In the case of stroke and heart attack, therapies would involve making healthy cells resistant to hypoxia. Cancer therapies might work more effectively if it were possible to make hypoxia-resistant cells more vulnerable to low oxygen levels.

In new experiments, Crowder's team manipulated genes in the worm *Caenorhabditis elegans* to alter the organism's sensitivity to a low-oxygen environment. They did that by identifying a gene that controls the translation of genetic information into specific proteins. Mutant copies of the gene cut translation rates in half, which conferred 100% survival to the animals compared to 100% death in non-mutant worms.

Crowder says that inhibiting translation likely protects cells from hypoxia by reducing energy consumption because making proteins consumes a lot of energy. The researchers were surprised by the degree of resistance to hypoxia when the translation rate was cut. They wanted to find out whether increasing hypoxia resistance was explained only by the fact that the cells were using less energy.

In a second experiment, the researchers introduced another mutation into the worms to evaluate its effect on the original mutation. The second mutation affects a process known as protein folding.

"In some cells, hypoxia has been shown to generate unfolded proteins," says Crowder, the Dr. Seymour and Rose T. Brown Professor in Anesthesiology and professor of developmental biology. "So then you have this load of unfolded proteins that may be toxic and promote cell death from hypoxia. We wondered whether suppressing translation in the cell might make it resistant to hypoxia by reducing the load of unfolded proteins, and that's what we saw."

Folding is important in allowing proteins to function properly. Every protein has shapes and pockets and active sites that bind to other proteins and perform various functions. If a particular protein doesn't "fold" into the proper shape, it can't do its job. It's not clear why that might be toxic, but this study suggests fewer improperly folded proteins make exposure to low oxygen less toxic.

Connecting these discoveries to potential stroke and heart attack therapies will involve several steps. First, Crowder plans to move beyond *C. elegans* to see whether these techniques also will protect neurons in mammals.

"If that happens, then I think there's hope that, eventually, we could target this process for therapy," Crowder says. "At this point in time, I think we're really just scratching the surface of the basic mechanisms of what controls hypoxic injury. It may be that protein translation doesn't ultimately end up being the answer, but maybe it will lead us to an answer. It already has led us to this unfolded protein response that seems to have potential as a therapy."

The challenge in treating stroke is that most cells in the brain continue to get plenty of oxygen. Only the part of the brain directly affected by the stroke becomes hypoxic. So Crowder says potential therapies need to protect brain cells affected by hypoxia without harming other cells that continue to experience normal oxygen levels. Targeting the unfolded protein response is attractive because, in theory, therapies would not bother cells with adequate oxygen but would react with the improper protein folding that occurs in cells not getting enough oxygen. Whether such a strategy will work is unknown.

"Many people have thought they made very promising inroads into stroke therapy over the last 50 years, and none of those treatments have been good enough," Crowder says. "We have no illusions that finding ways to reduce cell death from hypoxia will be easy. But using this approach of randomly mutating genes and seeing what happens helped us to find this unfolded protein response. It works in the worm, so now let's see what happens in mammals."

Paper: Anderson LL, Mao X, Scott BA, Crowder CM. Survival from hypoxia in C. elegans by inactivation of aminoacyl-tRNA synthetases.

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