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Fruit fly discovery generates buzz about brain-damaging disorder in children

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Johns Hopkins researchers have used fruit flies to gain new insights into a brain-damaging disorder afflicting children. Their work suggests a possible therapy for the disease, for which there is currently no treatment.

The researchers genetically modified flies to exhibit symptoms of mucolipidosis type IV (ML4), a disease in which nerve cells in the brain and elsewhere die. They discovered that the nerve cell death and progression of the disease is linked to a build-up of toxic waste in cells. Surprisingly, cell death is delayed by introducing normal blood cells into the flies. The work, reported in the Nov. 26 issue of *Cell*, suggests that bone marrow transplantation may help children affected by this disease and possibly related disorders.

"ML4 is one of 40 so-called lysosomal storage disorders which together account for the most common cause of neurodegeneration in children," says Craig Montell, Ph.D., professor of biological chemistry at the Johns Hopkins University School of Medicine.

The starting point was previous knowledge that the ML4 disease is caused by loss of the human TRPML1 protein, which works in the membranes of the garbage-collector organelles inside of cells. These organelles, lysosomes, break down damaged cellular material. The Johns Hopkins team created flies lacking the TRPML gene and then tested the effect of that "knockout" on motor skills. Healthy, normal flies naturally climb upward quickly after they are tapped down to the bottom of a

tube, regardless of their age. But the researchers found that the mutant animals were unable to move up the tubes rapidly. This problem in motor activity worsened in older flies, demonstrating the same progressive loss of motor function that characterizes ML4.

Without TRPML, cells build up toxic contents and eventually die. The Johns Hopkins researchers found that the noxious contents then bust out of the dying cells and speed up the demise of neighboring cells, causing an explosion of cell death that fans the fires of neurodegeneration, intensifying the impaired motor function and retinal degeneration that are hallmarks of ML4.
When the scientists put the TRPML gene back into neurons of the mutant flies, neurodegeneration was prevented and normal climbing ability restored.

The surprise came when, in a standard control experiment, the researchers hoped to show that it was the presence of normal TRPML in nerve cells, rather than any other cell type, that restored motor function. So they put the normal TRPML gene back into non-nerve cells, in this case blood cells.

"In the control experiment, no one expected any effects, much less the dramatic improvement that we saw," Montell says. "Essentially, putting TRPML back into blood cells "rescued" the mutant flies from symptoms of the disease." According to Montell, the TRPML-containing blood cells cleared away dying nerve cells before they could release their toxic contents and kill neighboring cells, thereby preventing rapid neurodegeneration and motor problems.

"After a bit of brainstorming, we came up with the idea that if putting TRPML back into blood cells could do this in flies, maybe it could do so in other animals, including people, using bone marrow transplants to reconstitute blood cells with normal TRPML," adds Montell, whose team

now is using mice engineered with ML4 to test their response to bone marrow transplantation.

"Bone marrow transplantation is an excellent idea," says Pierluigi Nicotera, M.D., Ph.D., an expert in neurodegeneration and member of the British Medical Research Council, who described the research paper as "one of the best I've seen in the past few years in this field."

"The rationale that's proposed is crystal clear. If you can even stave off the progression of this disease by clearing off dying neurons, it would be a big advance. "

Randy Yudenfriend Glaser, president of the ML4 foundation (www.ML4.org), and the mother of two children, ages 24 and 18, with the lysosomal disorder, calls the work " very exciting," but, as does Montell, cautions ML4 families "to take a deep breath" and realize that more work needs to be done before clinical application.

Says Montell, "It is exciting that the first idea for a treatment for this childhood disease came from fruit fly research. The key insight was the result of using a combination of techniques uniquely available in fly research."

Source: Johns Hopkins Medical Institutions