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UCLA Find Yields Further Insight Into Causes of Parkinson's Disease

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In humans, a dearth of the neurotransmitter dopamine has long been known to play a role in Parkinson's disease. It is also known that mutations in a protein called parkin cause a form of Parkinson's that is inherited.

Now, UCLA scientists, reporting in the Jan. 31 issue of *The Journal of Neuroscience*, have put the two together. Using a new model of Parkinson's disease they developed in the simple Drosophila (fruit fly), the researchers show for the first time that a mutated form of the human parkin gene inserted into Drosophila specifically results in the death of dopaminergic cells, ultimately resulting in Parkinson's-like motor dysfunction in the fly. Thus, the interaction of mutant parkin with dopamine may be key to understanding the cause of familial Parkinson's disease — Parkinson's that runs in families.

Conventional wisdom has held that parkin is recessive, meaning that two copies of the mutated gene were required in order to see the clinical signs of Parkinson's disease. But the researchers, led by George Jackson, M.D., Ph.D., UCLA associate professor of neurology and senior scientist at the Semel Institute for Neuroscience and Human Behavior at UCLA, wanted to see if they could get the protein to act in a dominant fashion, so they put only one copy of the mutation into their fly model. The result was the death of the neurons that use dopamine, the neurotransmitter long implicated in Parkinson's disease.

"We put the mutant parkin in all different kinds of tissues and in

different kinds of neurons, and it was toxic only to the ones that used dopamine," Jackson said. "No one's shown this degree of specificity for dopaminergic neurons."

Having a genetic model of Parkinson's disease (PD) in the fruit fly will allow researchers to run mass testing, or "screens," of genes in order to find the novel pathways — networks of interacting proteins that carry out biological functions — that control survival of those dopaminergic neurons.

"Since a lot of those pathways regulating cell survival and death are conserved by evolution all the way from flies to humans," said Jackson, "if we find those genes in the fly, they may represent new therapeutic targets for PD in humans."

The researchers examined the results not only from a genetic standpoint but from a behavioral standpoint as well. To measure the progression of Parkinson's disease in the fly, they designed a small series of rotating glass cylinders that they christened a "fly rotarod." A healthy fly placed inside the hollow cylinder would simply cling to the wall during the slow 360-degree loop. But flies with Parkinson's disease would fall, depending on the progression of their disease. The researchers used infrared beams to measure when they fell.

The researchers also plan to use their fly model to test a library of some 5,000 drug compounds approved by the Food and Drug Administration to see which ones might stop disease progression. If they find one that works, such a compound, which could serve as a kind of skeleton for other therapeutic drugs, could then be tested in mouse models and eventually in humans.

While non-scientists may have trouble understanding how a simple fruit fly can have implications for humans, Jackson said that, thanks to the

biological similarities between species, "the point of what we do is that if we find things, then ultimately, we can examine them in humans."

Source: UCLA