Key to longer life (in flies) lies in just 14 brain cells

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Two years ago, Brown University researchers discovered something startling: Decrease the activity of the cancer-suppressing protein p53 and you can make fruit flies live significantly longer.

Now the same team reports an intriguing follow-up finding. The p53 protein, they found, may work its lifespan-extending magic in only 14 insulin-producing cells in the fly brain.

“It’s quite surprising,” said Johannes Bauer, a postdoctoral research fellow at Brown. “In the fruit fly brain, there are tens of thousands of cells. But we found that it takes a reduction of p53 activity in only 14 of those brain cells to extend lifespan. It was like finding a needle in the haystack – a very small needle at that.”

Bauer is the lead author of the research report, published in the *Proceedings of the National Academy of Sciences*. Brown biology professor Stephen Helfand, senior scientist on the project, will discuss the findings in his keynote address at the Gordon Research Conferences on the Biology of Aging, to be held Sept. 23-28, 2007, in Les Diablerets, Switzerland.

P53 is sometimes called “guardian of the genome” for defending cells against DNA damage. Not enough of the protein can cause cancer; too much, however, can shorten lifespan. But in 2005, Helfand and his lab showed that a targeted decrease of p53 in fruit flies – a decrease specifically in their brain cells – allowed flies to live healthy lives that

were as much as 58 percent longer.

But how, exactly, does p53 do its work in the brain" To find out, Bauer spent a year conducting painstaking experiments. He'd take a batch of young flies, each genetically altered to reduce p53 activity in a small portion of their nervous systems, and watch the flies age. Time and again, the flies lived for about two months – the average lifespan for these insects.

But when Bauer manipulated a cluster of 14 insulin-producing cells in their brains, the flies lived about 15 to 20 percent longer. Bauer ran the experiment again and again – and got the same result.

Bauer and Helfand then wanted to know if this was caloric restriction at work. Studies have shown that low-calorie diets can significantly increase the lifespan of flies, worms, mice and rats. The phenomenon is of intense interest to researchers who study aging. They want to know if caloric restriction works in people and if drugs could be made to mimic its effects.

So researchers restricted the diets of the flies and ran the same experiments. The calorie-restricted flies didn't live any longer when p53 was reduced in the insulin-producing cells. This evidence supports the notion that p53 reduction is one of the direct effects of caloric restriction.

Even more intriguing, Helfand said, is the fact that the 14 insulin-producing cells that seem to be critical for lifespan extension are the equivalent of beta cells in the human pancreas. Beta cells make and release insulin, the hormone that controls the level of glucose in the blood. The research team found that when p53 activity drops, so does insulin-responsive activity in the fat body, the major metabolic organ in the fruit fly.

“Our findings suggest that lifespan regulation is linked to metabolic regulation,” said Helfand, a professor in Brown’s Department of Molecular Biology, Cell Biology and Biochemistry. “The findings also suggest a tight connection between aging and diabetes. And we may have a new laboratory model for studying diabetes and other metabolic diseases.”

Source: Brown University