'Anti-Atkins' low protein diet extends lifespan in flies

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Flies fed an "anti-Atkins" low protein diet live longer because their mitochondria function better. The research, done at the Buck Institute for Age Research, shows that the molecular mechanisms responsible for the lifespan extension in the flies have important implications for human aging and diseases such as obesity, diabetes and cancer.

The findings, which appear in the October 2 edition of *Cell*, also provide a new level of understanding of the regulation of mitochondrial genes and open new avenues of inquiry into the interplay between mitochondrial function, diet and energy metabolism.

Mitochondria act as the "powerhouse" of the cells. It is well known that mitochondrial function worsens with age in many species and in humans with Type II diabetes and obesity. "Our study shows that dietary restriction can enhance mitochondrial function hence offsetting the age-related decline in its performance," said Buck faculty member Pankaj Kapahi, PhD, lead author of the study.

The research provides the first genome-wide study of how proteins are translated under dietary restriction in any organism. The researchers report the unexpected finding that while there is a reduction in protein synthesis globally with the low protein diet, the activity of specific genes involved in generating energy in the mitochondria are increased, Kapahi said. That activity, which takes place at the level of conversion of RNA to protein, is important for the protective effects of dietary restriction, Kapahi said. "There have been correlative studies that show

mitochondria change with dietary restriction, this research provides a causal relationship between diet and mitochondrial function," he said.

The study describes a novel mechanism for how mitochondrial genes are converted from RNA to protein by a particular protein (d4EBP). Flies fed a low protein diet showed an uptick in activity of d4EBP, which is involved in a signaling pathway that mediates cell growth in response to nutrient availability called TOR (target of rapamycin). The research showed that d4EBP is necessary for lifespan extension upon dietary restriction. When the activity of the protein was genetically "knocked out" the flies did not live longer, even when fed the low protein diet. When the activity of d4EBP was enhanced, lifespan was extended, even when the flies ate a rich diet.

The research calls into question the health benefits of high-protein diets which are often used by humans to lose weight Kapahi said. The long-term impacts of such diets have not been examined in humans; they are likely to be harmful, he said. "In flies, we see that the long-lived diet is a low protein diet and what we have found here is a mechanism for how that may be working," Kapahi said.

The study provides a significant advance in understanding the role of 4EBP, a downstream molecular target of TOR, which mediates a switch in metabolism to extend lifespan, Kapahi said. A recent study appearing in the Nature showed that feeding rapamycin (an antibiotic used to prevent the rejection of organ and bone marrow transplants) to mice inhibited TOR and extended their lifespan. The Buck Institute study implies an important role for 4EBP and mitochondrial function as excellent targets to explore their role in lifespan extension in mammals, Kapahi said.

Source: Buck Institute for Age Research