Harbingers of aging

January 29 2016

Midlife crisis in the insect world: In a new study, Ludwig-Maximilians-Universitaet (LMU) in Munich researchers have detected age-dependent alterations in metabolism and gene regulation in middle-aged fruitflies, and show that these effects are linked to a reduction in lifespan.

The aging process is accompanied by characteristic changes in physiology whose overall effect is to decrease the capacity for tissue repair and increase susceptibility to metabolic disease. In particular, the overall level of metabolic activity falls, and errors in the regulation of gene activity become more frequent. Now, a collaborative study by two

research groups at LMU's Biomedical Center, led by Axel Imhof (Professor of Molecular Biology) and Andreas Ladurner (Professor of Physiological Chemistry), has shown in the fruitfly Drosophila melanogaster that such age-dependent changes are already detectable in middle age. Genetic investigation of the signal pathways involved in mediating this effect identified a common process—the modification of proteins by the attachment of so-called acetyl groups (CH3COO-) to proteins—that links the age-related changes at the metabolic and genetic levels. Their findings appear in the journal *EMBO reports*.

As we age, the efficiency of the mitochondria progressively declines. Mitochondria are subcellular organelles in the cells of higher organisms that convert nutrients into biochemically usable energy. Mitochondria also possess their own genome, and mutations in this mitochondrial DNA have been linked to a reduction in lifespan. Paradoxically, however, several studies have shown that reducing levels of mitochondrial activity—by restricting food intake, for instance—can actually extend lifespan. "These findings imply that the primary cause of aging cannot simply lie in a reduction in overall metabolic activity, so the whole issue must be more complicated than that," Imhof points out. Most studies of the aging process employ comparisons between young and old individuals belonging to the same species. "However, in aged animals, many of the potentially relevant physiological operations no longer function optimally, which makes it difficult to probe their interactions. That is why we chose to look in Drosophila to see whether we could find any characteristic metabolic changes or other striking modifications in flies on the threshold of old age and, if so, ask how these processes interact with each other," he explains.

Rates of protein modification rise

The two teams first made the surprising discovery that middle-aged male flies (7 weeks old) actually consume more oxygen than their younger

conspecifics. This points to a metabolic readjustment which is accompanied by an increase in mitochondrial activity.—And indeed, the researchers noted a rise in the intracellular concentration of acetyl-CoA in these flies. Acetyl-CoA is a metabolite that is produced in the mitochondria, which participates in large number of processes in energy metabolism. Furthermore, it is an important source of acetyl groups for the chemical modification of proteins. "Acetyl groups are attached to specific positions in certain proteins by dedicated enzymes, and can be removed by a separate set of enzymes. These modifications modulate the functions of the proteins to which they are added," Ladurner explains. "And our experiments have shown that many proteins are much more likely to be found in acetylated form in middle-aged flies than in younger individuals."

Strikingly, this is true not only for proteins that are involved in basic metabolism, but also for proteins that are directly responsible for regulating gene expression. In the cell nucleus, the genomic DNA molecules are wrapped around "spools" made of proteins called histones. These spools or "nucleosomes" are tightly packed together, and keep the nuclear DNA in a compact, condensed form. Various chemical modifications of the nucleosomal histones—including acetylation—regulate the accessibility of the DNA to the enzymes required for gene expression, and thus determine which genes are active at any given time. "We were able to show that the histones in middle-aged flies are overacetylated," Imhof says. "This reduces the packing density of the DNA, and with it the stringency of gene regulation. The overall result is a rise in the level of errors in the expression of the genetic information, because genetic material that should be maintained in a repressed state can now be reactivated." And Ladurner adds: "In the prime of their lives, fruitflies begin to produce a surfeit of acetylated proteins, which turns out to be too much of a good thing."

Inhibiting acetylation increases lifespan

Taken together, these findings indicate that changes in acetylation may be a key factor in the process of natural aging, reflecting alterations in basic metabolism as well as modifying gene regulation. "A rise in the level of protein acetylation seems to be linked to a decrease in life expectancy," says Ladurner. "For inhibition of an acetylase enzyme which specifically attaches acetyl groups to histones, or attenuation of the rate of synthesis of acetyl-CoA—which reduces the supply of acetyl groups - reverses many of the age-dependent modifications seen in these animals, and both interventions are associated with a longer and more active lifespan."

The researchers are now planning to look for comparable effects in mammals. "If that turns out to be the case, then the enzymes that specifically acetylate histones might well be interesting targets for the development of novel therapeutic agents that correct age-dependent dysregulation," says Imhof. "Partial inhibitors that reduce enzyme activity without completely blocking it would probably be most effective in this context."

More information: S. Peleg et al. Life span extension by targeting a link between metabolism and histone acetylation in Drosophila, *EMBO reports* (2016). DOI: 10.15252/embr.201541132

Provided by Ludwig Maximilian University of Munich