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NEWS AND VIEWS

Insulin, longevity, and genetic analysis of metabolism

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In a 1989 Hollywood hit "Sex, Lies, and Videotapes", director Steven Soderbergh told a story of an incestuous affair between a hot-shot lawyer and the sister of his married wife. An over-stayed visit by a drifter whose unusual fetish of videotaping conversations about sex lives of women deconvoluted this adulterous entangle. In the biological life, persistent bias can also throw off a balance such as the homeostasis delicately constructed among metabolism, longevity, and the insulin signaling pathway. In a recent paper published in *Cell Metabolism*, Yong Liu's group at the Shanghai Institute of Nutritional Sciences and Liangyou Rui's group at the University of Michigan Medical School reported that alteration of metabolism through genetic deletion of SH2B, a gene encoding an adaptor protein required for insulin signaling, causes significant changes in the life span of affected fruitflies and mice. While the man-made and the god-made stories show only a slight superficial analogy in form, they both unfold through serendipitous analyses of seemingly unrelated events, a theme that reoccurringly underscores the importance of basic research.

For as long as human in existence, the quest for longevity has been an unattainable craving of the rich and powerful. Countless alchemical recipes were tried and wrong, but longevity seems to favor puritanic living with disciplined and restricted access to food. Now, modern science has offered an explanation for this irony in the revelation of a causal connection between restricted calorie-intake and longevity. It all began about a dozen years ago with studies in Gary Ruvkun's laboratory at Harvard Medical School and Cynthia Kenyon's laboratory at UCSF on the microscopic earth worm, *Caenorhabditis elegans*, a nematode used by biologists as a favored model animal for genetic analyses. Under high temperature and reduced bacterial food intake, normal nematodes adjust their body metabolism and energy expenditure from sustaining growth and reproduction to a diapause arrest or the dauer state, which is a self-preservation mode that helps the animal to weather through harsh environmental conditions. A large number of mutations have been isolated that render the mutant nematodes to enter the dauer state without environmental preconditions. Many of these dauer-formation (daf) mutants turned out to be elements of the *C. elegans* insulin-like signaling pathways. For instance, *daf-2* encodes the membrane receptor for insulin-like ligands whereas *daf-16* encodes a worm homolog of mammalian FKHR transcription factors. What is really interesting is that these daf mutants affecting the nematode insulin-like signaling live 2–3 times longer than their wild type counterparts! These findings indicated that the life span of a multicellular organism, as complex as it is, is still subject to control by genetic programs as specific single gene mutations can prolong the life span. It is clear now that a number of cell signaling pathways influence the life span of living organisms as diverse as the baker's yeast, *C. elegans*, Drosophila, and mammals. Mutations in the signaling pathways including Insulin/IGF-1, the target of rapamycin (Tor), AMP kinase, and Sirtuins, seem to send instructions to slow down metabolism, such that the rate of wear and tear on cell functions taxed by the reactive oxygen species-induced damages on proteins, lipids, and nucleic acids will be reduced. In this sense, reduced Insulin/IGF-1 signaling has the similar effect as calorie restriction. On a philosophical note, it is intriguing how the functions of these signaling pathways are conserved during evolution to control life span across different animal phyla. After all, evolution cannot apply direct selection pressure against traits beyond reproduction. It is possible that these longevity genes are co-evolved with their pre-reproduction functions of helping cells to cope with environmental stress. This notion has born out in numerous experiments.

Genetic regulation of life span in mammals, especially the humans, is much more complex. Reduced Insulin/IGF-1 secretion or insulin resistance as the result of impairment of its signaling pathway leads to obesity and diabetes. Nevertheless, mouse models do exist that showed significant

increase of life expectancy. These include Snell and Ames mice that affect growth hormone production because of mutations in the pituitary factor 1 gene. Inhibition of growth hormone signaling reduces body sizes and increases insulin sensitivity and glucose tolerance. As the result, the life span of Snell and Ames mice can increase 20%–50%, depending on genetic background and diet. The fat-specific insulin receptor knockout (FIRKO) mice have 20% longer median and maximal life span than their wild type control littermates, probably because blocking insulin in fat lowers circulating triglycerides and reduces body fat mass.

The insulin/IGF-1 receptors are tyrosine kinases and like all other membrane-bound tyrosin kinase receptors, they themselves are phosphorylated at several tyrosine residues located in the cytoplasmic domain. These phosphotyrosine residues are recognized by adaptor proteins, which serve as assembly platforms for recruiting downstream signaling molecules. One of such phosphotyrosine-binding adaptor proteins is SH2B, which was identified as a binding partner of the insulin receptor. In 2004, Liangyou Rui's lab showed age-dependent insulin resistence and glucose intolerance in SH2B knockout mice, confirming the role of SH2B in insulin signaling. Now in a collaborative effort, Yong Liu's group and Rui's group cloned the Drosophila homolog of SH2B gene and decided to compare the roles of SH2B in the regulation of longevity in Drosophila and mice. First of all, they found that SH2B regulates body growth in both species since disruption of Drosophila SH2B, dSH2B, by transposon p-element insertion caused 11% decrease in body length and 21% reduction in body weight; knocking SH2B in mice also resulted in the similar reduction in body length as well as weight. As expected, SH2B is also required for lipid and carbohydrate metabolism. Genetic deletion of dSH2B significantly extended the life span of the affected fruitflies, with more noticeable effect on females than males; however, genetic deletion of SH2B in mice showed opposite effect: the median life expectancy of female SH2B null mice is about 50% less than the wild type control mice and the male mice also showed similar reduction when SH2B was inactivated. The reduction in the life span cannot be all accountable by the diabetic conditions associated with inactivation of insulin signaling, because at least in female mice the blood glucose level was maintained in the normal range. So, while it is certain that SH2B is involved in the longevity regulation through its role in insulin/IGF-1 signal transduction, much remains to be learned about the full complement of this gene's function.

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