Researchers at the University of Arizona College of Medicine – Tucson are exploring whether dietary interventions that extend lifespan increase or decrease immune defense against infection.

"Research has shown that consuming fewer calories, while maintaining sufficient nutrients, extends lifespan, and there are ongoing clinical studies in humans. However, aging also is associated with increased susceptibility to diseases," said Dr. Nikolich-Žugich, co-director of the UA Center on Aging and principal investigator of the "Longevity Extension and Immune Function in Aging" study.

UA researchers are beginning to study lifespan extension and immune function, thanks to a two-year $403,751 grant from the National Institute on Aging, part of the National Institutes of Health.

"Remarkable extension of lifespan has been achieved in organisms by lowering calorie intake or tricking cells into thinking that there is not enough food. These manipulations are being considered for potentially increasing lifespan in humans," Nikolich-Žugich said. "It is critical to understand the effects of these interventions upon physiological function of older organisms, as any increase in longevity must be accompanied by improved quality of life."

Rapamycin, or Rapa, a drug used to keep the body from rejecting organ and bone marrow transplants, blocks an enzyme that controls cellular division. Rapa has been shown to extend lifespan in mice; however, the effects of chronic low-dose Rapa-mediated treatment on resistance to infection remain unknown.

"Our study will test whether life-extending dietary interventions may improve or impair survival from, and immunity to, infection, allowing us to evaluate whether manipulations of nutrient pathways may be safe and desirable to achieve optimal healthy longevity," said Nikolich-Žugich, who also is chairman of the UA Department of Immunobiology and the Elizabeth Bowman Professor in Medical Research at the UA College of Medicine – Tucson and a member of the UA BIOS Institute.

"While calorie restriction appears to improve immune function and homeostasis in old animals, the few infectious challenge experiments suggest increased susceptibility to infection. Our exploratory proposal aims to test the hypothesis that calorie restriction and drugs that trick the cells into thinking that there is not enough food, such as Rapa, could be deleterious for protective immunity, because they may curtail full development of immune responses," Nikolich-Žugich said.

UA researchers will look for protective T cell and antibody responses to West Nile Virus – a virus transmitted by arthropods, such as mosquitoes or ticks – or listeria – a food-borne bacterium that causes high mortality in older adults. Researchers will measure the efficacy and the type of the immune response.

"We aim to dissect possible defects and discover whether we may use Rapa as is or whether we may need to seek for similar compounds with beneficial effects in healthy aging across different tissues," Nikolich-Žugich said.

Nearly one quarter of the U.S. population will be over age 65 by 2040, according to the U.S. Census Bureau, and those who reach age 65 will live, on average, 19.2 years longer. Ensuring the healthy and productive lives of that very large group is becoming an urgent priority, Nikolich-Žugich says.

A paper related to the UA study was published in the July 15 issue of *The Journal of Immunology*, a publication of the American Association of Immunologists Inc. The lead author of the paper, which is titled "Immune Memory Boosting Dose of Rapamycin Impairs Macrophage Vesicle Acidification and Curtails Glycolysis in Effector CD8 Cells, Impairing Defense against Acute Infections," is Emily L. Goldberg, a postdoctoral research associate in the Department of Immunobiology and member of the UA Center on Aging. Other UA researchers who contributed to the paper include the following UA Center on Aging members: Nikolich-Žugich; Megan J. Smithey, research assistant professor in the Department of Immunobiology; Lydia K. Lutes, undergraduate laboratory assistant in the Department of Immunobiology and an undergraduate student in the UA College of Science’s Department of Molecular and Cellular Biology; Jennifer L. Uhrlaub, research associate in the Department of Immunobiology.

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