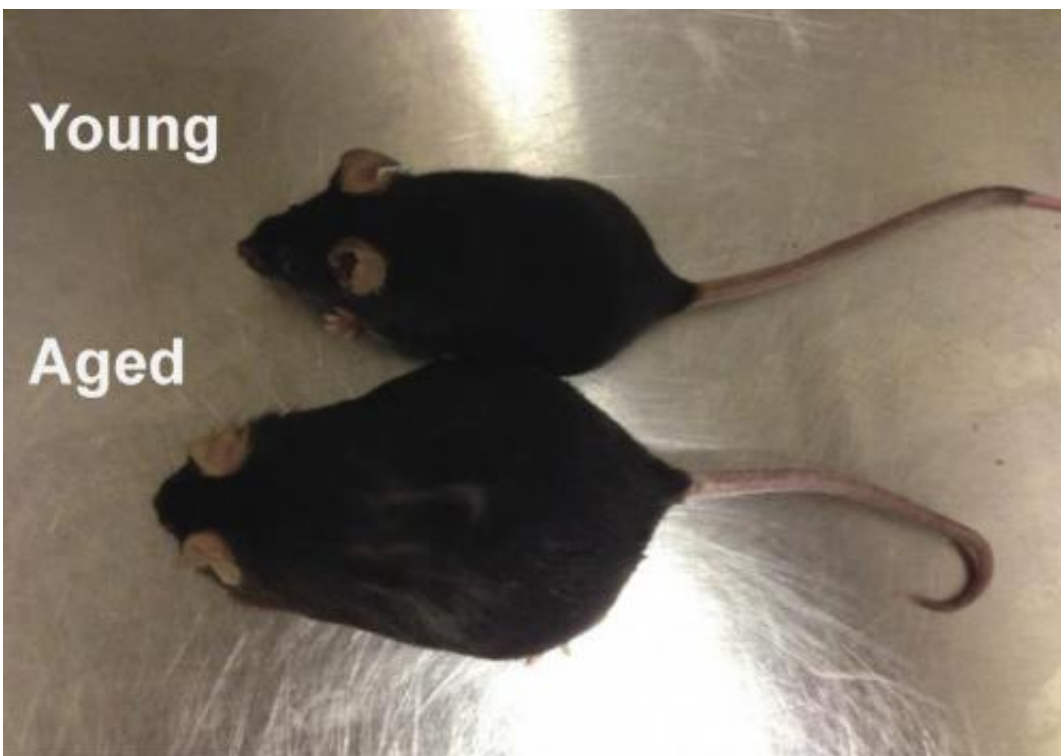


Immunotherapy for cancer toxic with obesity: Researchers link increased body fat and lethal drug reactions in mice

November 3 2014



New research suggests that the accumulation of fat in older mice, as displayed here, is responsible for their increased susceptibility to deadly inflammation in response to anti-cancer immunotherapy. Credit: Mirsoian et al, 2014

Immunotherapy that can be effective against tumors in young, thin mice can be lethal to obese ones, a new study by UC Davis researchers has

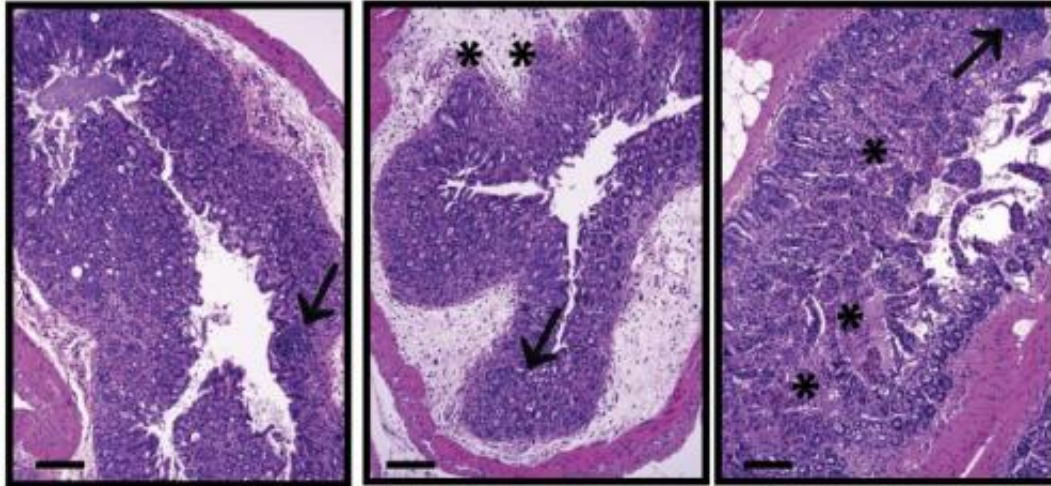
found. The findings, published online today in *The Journal of Experimental Medicine*, suggest a possible link between body fat and the risk of toxicity from some types of immunotherapy.

The study comes at a time of great excitement about immunotherapy drugs, which are being developed and used increasingly against cancer, particularly in melanoma and kidney and prostate cancers.

Immunotherapies use immune components, such as antibodies or cytokines, to stimulate or suppress the immune system to help the body recognize, fight and kill tumors.

Immunotherapies fall into many classes, including systemic stimulatory regimens, inhibitors of checkpoint blockade and cell-mediated vaccines. Despite the progress made in their development in the last decade, many of these agents induce severe, often limiting toxicities in patients, hindering their use. UC Davis researchers have been working with mouse models to determine if there is a subset of patients for whom certain types of immunotherapies are especially toxic.

"Cancer is primarily considered a disease of the aged, and yet preclinical studies generally use young, lean animal models that may not be reflective of the 'typical' cancer patient," said study lead author Annie Mirsoian. "Aging is a dynamic process that is characterized by increases in inflammatory factors, as well as a shift in body composition, where there is a gradual loss of lean muscle mass and an increase in fat accumulation, which effect how the immune system functions."



Compared with young healthy mice (left), young obese (middle) and older (right) mice had increased organ damage (marked by arrows and asterisks) after anti-cancer immunotherapy. Credit: Mirsoian et al, 2014

Mirsoian, part of the immunology graduate group in the UC Davis Department of Dermatology, said the study sought to determine if by adjusting the mouse model to more closely reflect the cancer patient phenotype (advanced age and overweight), researchers could better understand the discrepancies between animal study outcomes and those in patients in the clinic. Their studies examined aged mice on standard diets and compared those to aged mice that were calorie-restricted throughout life.

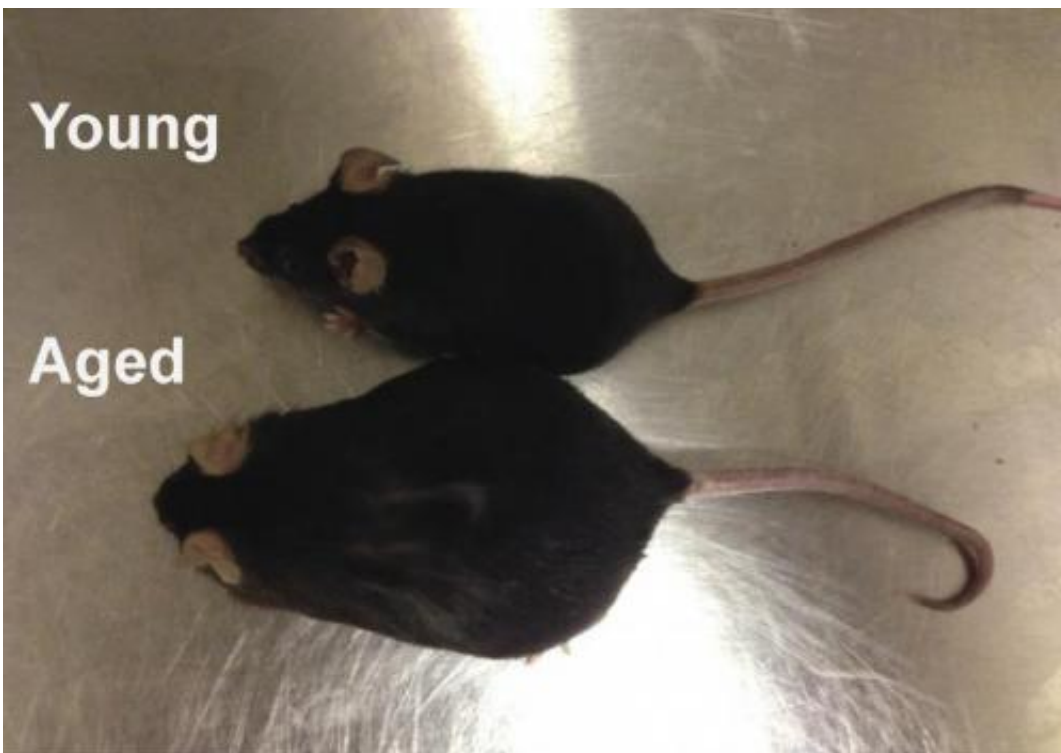
The researchers found that calorie restriction plays a protective role against toxicity. When laboratory aged mice ate their standard diet freely throughout life, they became obese and ultimately experienced lethal adverse reactions after receiving a systemic immunotherapy regimen.

"We know that people who are obese in general are at higher risk for complications from surgery, radiation and chemotherapy," said study co-author Arta Monjazeb, assistant professor in the UC Davis Department

of Radiation Oncology. "We know that obese people have higher levels of inflammatory markers in their blood, but there is a lack of data examining the effects of obesity on cancer treatment outcomes."

In follow-up experiments, the researchers found that young mice that are obese also endure similar toxic consequences, demonstrating that fat is a critical factor in toxic responses to stimulatory anti-cancer immunotherapy regimens.

"It is important to note, however, that the aged mice on standard diets succumbed to lethality at a quicker rate than young obese mice," said Mirsoian. "Although our data demonstrate that obesity plays a central role in the development of adverse effects, future studies will focus on examining the aged immune system and cellular characteristics that may have enhanced the sensitivity of these mice to inflammation."

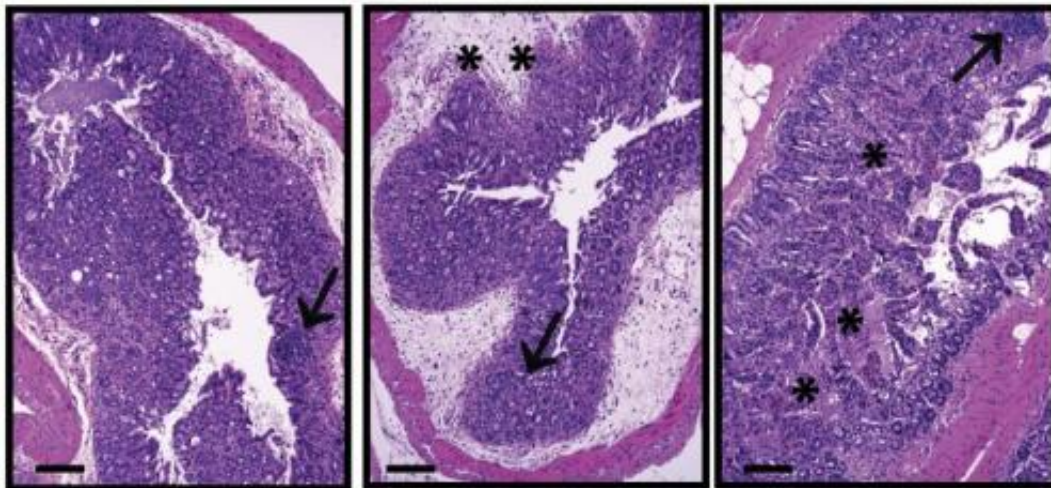


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here, is responsible for their increased susceptibility to deadly inflammation in response to anti-cancer immunotherapy. Credit: Mirsoian et al, 2014

The study, to appear in the Nov. 17 print edition of the *Journal of Experimental Medicine*, follows the researchers' earlier paper, which demonstrated that while young, lean mice tolerate immunotherapy regimens without toxicity, the same regimen for an aged cohort resulted in lethal consequences. The new paper takes a deeper look into how fat deposition throughout aging can be critical in determining treatment tolerance and efficacy.

"Obesity has become an epidemic in our society, and is now also affecting younger populations," said Mirsoian. "Therefore, it's likely that what the 'typical' cancer patient looks like will change. Our findings demonstrate the importance of having preclinical animal models that reflect the clinical scenario.



Compared with young healthy mice (left), young obese (middle) and older (right) mice had increased organ damage (marked by arrows and asterisks) after anti-cancer immunotherapy. Credit: Mirsoian et al, 2014

Changing the characteristics of our mouse models allowed for a more accurate determination of possible adverse reactions to therapy, and more closely modeled what has been reported in the clinic with stimulatory immunotherapies."

The authors said that factors like age, fat content and the types of infections experienced throughout life together shape how the immune system reacts, and they will continue to work on improving their modeling system to reflect these changes. They project that improvements in mouse modeling may help produce data that can better modulate treatment choices for patients, as well as identify early which patients would benefit from the inclusion of drugs to prevent adverse reactions while maintaining anti-cancer efficacy.

More information: Mirsoian, A., et al. 2014. *J. Exp. Med.* [DOI: 10.1084/jem.20140116](https://doi.org/10.1084/jem.20140116)

Provided by UC Davis

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