

Calorie restriction limits and obesity fuels development of epithelial cancers

A restricted-calorie diet inhibited the development of precancerous growths in a two-step model of skin cancer, reducing the activation of two signaling pathways known to contribute to cancer growth and development, researchers at The University of Texas M. D. Anderson Cancer Center report today at the American Association for Cancer Research annual meeting.

An obesity-inducing diet, by contrast, activated those pathways, said first author Tricia Moore, a graduate student in M. D. Anderson's Department of Carcinogenesis.

"These results, while tested in a mouse model of skin cancer, are broadly applicable to epithelial cancers in other tissues," said senior author John DiGiovanni, Ph.D., director of the Department of Carcinogenesis and of M.D. Anderson's Science Park - Research Division in Smithville, Texas.

Epithelial cancers arise in the epithelium - the tissue that lines the surfaces and cavities of the body's organs. They comprise 80 percent of all cancers.

"Calorie restriction and obesity directly affect activation of the cell surface receptors epidermal growth factor (EGFR) and insulin-like growth factor (IGF-1R)," Moore said. "These receptors then affect signaling in downstream molecular pathways such as Akt and mTOR."

"Calorie restriction, which we refer to as negative energy balance, inhibits this signaling, and obesity, or positive energy balance, enhances signaling through these pathways, leading to cell growth, proliferation and survival," Moore said.

Dietary energy balance refers to the relationship between caloric intake and energy expenditure. Previous research, both experimental and epidemiological, suggests that chronic positive energy balance, which can lead to obesity, increases the risk of developing a variety of cancers, DiGiovanni said, while negative balance often decreases risk.

This study employed four diets, two representing calorie reductions of 30 percent and 15 percent, a control diet including 10 percent kilocalories from fat, and an obesity-inducing diet consisting of 60 percent kilocalories from fat. Agents were then given to the mice to induce premalignant lesions called papillomas, which are precursors to cancer.

Those on the calorie restricted diets had statistically significant inhibition of papilloma formation compared with the other two diets.

In a separate experiment the development of carcinomas and the effect of dietary energy balance on conversion of papillomas to carcinomas was evaluated. This study demonstrated that dietary energy balance determines the number of carcinomas found through its effects on the number of premalignant lesions but does not affect the rate of malignant conversion.

Akt and mTOR pathways are known to be important for skin tumor development in this model system. In addition, increased Akt and mTOR signaling are linked to the growth, proliferation and survival of many human cancers.

"These findings provide the basis for future translational studies targeting Akt/mTOR pathways through combinations of lifestyle and pharmacologic approaches to prevent and control obesity-related epithelial

cancers in humans," DiGiovanni said.

Source: University of Texas M. D. Anderson Cancer Center

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