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Scientists discover disease control mechanism

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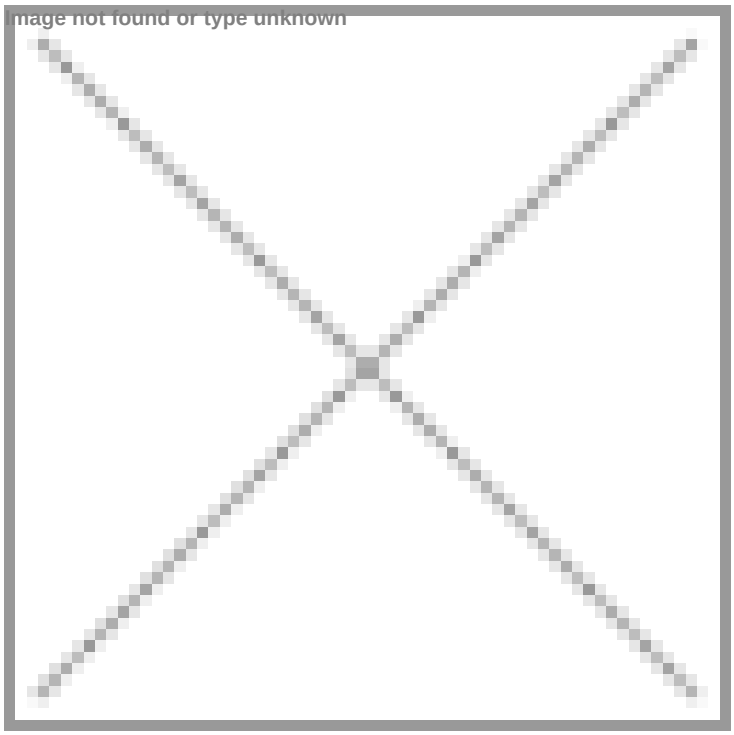
Scientists discover obesity, cancer control mechanism



Singapore: A*STAR scientists from the Institute of Molecular and Cell Biology (IMCB) and the Singapore Bioimaging Consortium (SBIC) have discovered a new signalling pathway that controls both obesity and atherosclerosis. The team demonstrated, for the first time, that mice deficient in the Wip1 gene were resistant to weight gain and atherosclerosis via regulation of the Ataxia telangiectasia mutated gene (ATM) and its downstream signalling molecule mTor.

These groundbreaking findings were published in the journal *Cell Metabolism* and may provide significant new avenues for therapeutic interventions for obesity and atherosclerosis.

Obesity and atherosclerosis-related diseases account for over one-third of deaths in the Western world. Controlling these conditions remains a major challenge due to an incomplete understanding of the molecular pathways involved. Atherosclerosis, a progressive disease of the large arteries, is an underlying cause of many cardiovascular diseases. In Singapore, 10.8 percent of our population is obese and cardiovascular disease accounted for 31.9 percent of all deaths in 2010.

Obesity and atherosclerosis are accompanied by the accumulation of lipid droplets in adipocytes (fat cells) and in foam cells respectively. Foam cells can subsequently rupture, damaging blood vessels, and contributing to further progression of atherosclerosis. The scientists discovered that Wip1 deficient mice, even when fed a high-fat diet, were resistant to obesity and atherosclerosis by preventing the accumulation of lipid droplets. This appeared to be through increased autophagy, the

normal process by which the body degrades its own cellular components. They showed that the Wip1 deficient mice exhibited increased activity of ATM which decreased mTor signalling, resulting in increased autophagy. This degraded the lipid droplets and suppressed obesity and atherosclerosis.

"This is the first time that Wip1-dependent regulation of ATM-mTor pathway has been linked to authophagy and cholesterol efflux thus providing an entirely new avenue for treatment of obesity and atherosclerosis," said Dr Dmitry Bulavin, Senior Principal Investigator at IMCB and lead author of this paper.

The scientists are hopeful that this ATM-mTor pathway could similarly map onto cancer to suppress tumour progression. Similar to suppression of obesity and atherosclerosis, activation of autophagy in cancer cells could result in degradation of cellular content that is essential for cancer cells to sustain rapid proliferation. This, in turn, will result in suppression of cancer growth.

Dr Dmitry Bulavin said, "We are building on this research to investigate if the same mechanism could also control tumour progression and hence potentially unlock new therapeutic treatments targeting Wip1, ATM and mTor in cancer as well and the preliminary results are promising."