

## Adipocyte-selective disruption of SIRT1 accelerates high fat diet- and ageing-induced insulin resistance by inducing cellular senescence in mice

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**Objective:** SIRT1 is an NAD<sup>+</sup>-dependent histone deacetylase that antagonises ageing-associated diseases in multiple tissues. However, the physiological function of SIRT1 in adipocytes remains unknown. This study sought to address whether and how adipocyte SIRT1 modulates the systemic energy homeostasis and insulin resistance.

**Methods:** Adipocyte-selective knockout mice of SIRT1 (AKO) were obtained by crossing the *Sirt1*<sup>fllox/fllox</sup> mice with the adipocyte-specific Cre transgenic mice (aP2-Cre). *Sirt1*<sup>fllox/fllox</sup> mice were used as the wild type (WT) control. Basic metabolic parameters including body weight, food consumption and the levels of blood glucose and lipids were monitored bi-weekly. Glucose tolerance and insulin sensitivity were evaluated by glucose tolerance test and insulin tolerance test. Serum concentration of insulin and adiponectin was quantified by in-house immunoassays. The extent of pro-inflammatory cytokine expression and immune cell infiltration were determined by quantitative PCR (qPCR). The adipose tissue senescence was assessed by  $\beta$ -galactosidase staining and qPCR analysis for senescence-related genes p16<sup>INK4A</sup> and p21<sup>WAF1</sup>. The relative telomere length in primary adipocytes was examined by flowcytometry based fluorescence in-situ hybridisation (flow-FISH).

**Results:** WT mice and AKO mice had similar levels of body weight and food intake. However, adipocyte-specific deletion of SIRT1 accelerated high fat diet- and ageing- induced glucose intolerance and insulin resistance in mice. The exacerbation of high fat diet evoked insulin resistance in AKO mice was further corroborated by the impaired insulin signalling in peripheral tissues including liver and muscle. Moreover, a higher level of ectopic fat accumulation was observed in AKO mice compared to the WT control. A more active inflammation status was observed in SIRT1 deficient adipose tissues, exemplified by a higher extent of immune cell infiltration and elevated expression of proinflammatory cytokines. Mechanistically, ablation of SIRT1 in adipocytes caused a more pronounced senescence-like phenotype of adipose tissues in mice upon high fat diet or ageing. Flow-FISH analysis demonstrated that SIRT1 deficient adipocytes had a shorter telomere compared to that in the intact adipocytes.

**Conclusion:** SIRT1 maintains the stability of telomere in adipocytes, which in turn protects the adipose tissue from high fat diet- and ageing-induced senescence and malfunctioning. Senescent adipose tissue, characterised by elevated inflammation and decreased adiponectin secretion, eventually leads to the derangement of systemic energy homeostasis.

## Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: a prospective cohort study

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**Background:** Despite World Health Organization recommendations, the rate of 23-valent pneumococcal (PPV) and influenza (TIV) vaccination among elderly persons in Hong Kong, China, is exceptionally low because of doubts about effectiveness of vaccination. The efficacy of dual vaccination remains unknown.

**Methods:** From 3 December 2007 to 30 June 2008, we conducted a prospective cohort study by recruiting outpatients aged  $\geq 65$  years with chronic illness to participate in a PPV and TIV vaccination programme. All were observed until 31 March 2009. The outcome of subjects, including the rates of death, hospitalisation, pneumonia, ischaemic stroke, acute myocardial infarction, and coronary and intensive care admissions, were determined.

**Results:** Of the 36 636 subjects recruited, 7292 received both PPV and TIV, 2076 received TIV vaccine alone, 1875 received PPV alone, and 25 393 were unvaccinated, with a duration of follow-up of 45 834 person-years. Baseline characteristics were well-matched between the groups, except that there were fewer male patients in the PPV and TIV group and fewer cases of comorbid chronic obstructive pulmonary disease among unvaccinated persons. At week 64 from commencement of the study, dual-vaccinees experienced fewer deaths (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.55-0.77;  $P < 0.001$ ) and fewer cases of pneumonia (HR, 0.57; 95% CI, 0.51-0.64;  $P < 0.001$ ), ischaemic stroke (HR, 0.67; 95% CI, 0.54-0.83;  $P < 0.001$ ), and acute myocardial infarction (HR, 0.52; 95% CI, 0.38-0.71;  $P < 0.001$ ), compared with unvaccinated subjects. Dual vaccination resulted in fewer coronary (HR, 0.59; 95% CI, 0.44-0.79;  $P < 0.001$ ) and intensive care admissions (HR, 0.45; 95% CI, 0.22-0.94;  $P = 0.03$ ), compared with among unvaccinated subjects.

**Conclusions:** Dual vaccination with PPV and TIV is effective in protecting elderly persons with chronic illness from developing complications from respiratory, cardiovascular, and cerebrovascular diseases, thereby reducing hospitalisation, coronary or intensive care admissions, and death.

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