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THE ROLES AND MECHANISMS OF ADIPOCYTOKINES IN INSULIN RESISTANCE

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Obesity, characterized by adipocyte hypertrophy, is a major cause of insulin resistance, type 2 diabetes, hyperlipidaemia and hypertension, clustering of risk factors for atherosclerosis. Interestingly, lipodystrophy, characterized by defective adipocyte differentiation, is also associated with insulin resistance, diabetes and hyperlipidaemia. We therefore hypothesized that differentiated adipocytes secrete factors protecting against insulin resistance, diabetes and hyperlipidaemia, and both deficiency of these factors by lipodystrophy and impaired secretion of these factors by obesity (adipocyte hypertrophy) can cause insulin resistance. By systematic expression profiling analysis of white adipose tissue of heterozygous PPAR γ knockout mice, which showed small adipocytes and protection from high-fat diet-induced adipocyte hypertrophy and insulin resistance, we have identified expressions of adiponectin and leptin to be markedly upregulated. In contrast, those of tumour necrosis factor (TNF) α and resistin were markedly downregulated. Adiponectin administration partially ameliorated and combination of leptin and adiponectin completely ameliorated insulin resistance of lipodystrophic mice. Moreover, high-fat diet caused adipocyte hypertrophy, reduction of adiponectin secretion and insulin resistance in KKAY mice, which was partially ameliorated by replenishment of adiponectin. Moreover, *de novo* generation of small differentiated adipocytes together with apoptotic death of hypertrophic adipocytes by thiazolidinediones (PPAR γ agonist) was associated with upregulation of adiponectin, downregulation of TNF α and amelioration of insulin resistance. Phenotypes of adiponectin transgenic mice and adiponectin knockout mice were consistent with the conclusion that adiponectin plays an important role in the physiological regulation of insulin sensitivity. Adiponectin by interacting its cell surface receptors stimulates AMP kinase and PPAR α pathway, leading to amelioration of insulin resistance. We have

recently cloned adiponectin receptors (AdipoR1 and AdipoR2), whose structures and functions will be presented.

Thus, we propose that small adipocytes with increased expressions of insulin sensitizing hormones such as adiponectin as well as decreased expressions of adipokines causing insulin resistance such as TNF α are associated with insulin sensitivity, whereas hypertrophic adipocytes with decreased expressions of insulin sensitizing hormones as well as increased expressions of adipokines causing insulin resistance are associated with insulin resistance which may be a central mechanism to cause life style-related disease.

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