Structure and Function Relationship of Adiponectin as an Anti-aging Hormone

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Yu Wang obtained her PhD degree at the University of Auckland in 2003. She has been working on Proteomics-related research area for more than eight years and helped the establishment of the Proteomic Facility Centre in the University of Auckland. In year 2004, she moved to HKU and is now working in the Genome Research Centre.

Her main research interests have been in the elucidation of the signal transduction pathways and biological actions of metabolic hormones. Especially, she has used proteomics-based approaches to discover novel signalling molecules and hormones that are involved in the pathogenesis of aging-related metabolic diseases. Her recent work on structural and functional characterization of adiponectin has contributed significantly to our understanding of adiponectin biology. Her group is the first one that demonstrated the therapeutical potentials of adiponectin in the treatment of aging-related liver diseases.

In addition to its roles in energy storage, it is now well known that adipose tissue (fat) can secret many hormones and cytokines, which are collectively called adipokines. Abnormal productions of adipokines directly contribute to aging-related metabolic diseases, such as Type 2 Diabetes, coronary heart disease, hypertension and certain forms of cancers. Adiponectin is a fat cell-derived metabolic hormone with direct anti-diabetic, anti-atherogenic and anti-inflammatory activities. The plasma levels of this hormone are significantly decreased in human subjects with Type 2 Diabetes, insulin resistance, ischemic heart disease, essential hypertension, impaired vasoreactivity and endothelial dysfunction. Moreover, the hypoadiponectinemia is also a contributing factor to increased risks of endometrial cancer and breast cancer.

We have used two-dimensional gel electrophoresis-based proteomic strategies to study the secretome of 3T3-L1 adipocytes and discovered that endogenous adiponectin is posttranslationally modified by hydroxylation and glycosylation. Using a variety of proteomic technologies and NMR analysis, we were able to characterize the detailed modification sites and their attached glycoside profiles. Adiponectin with proper posttranslational modifications can form three high order structures with the apparent molecular weights of 690, 460 and 230 kDa respectively. Our evidence suggests that the posttranslational modifications of adiponectin are critically involved in the formation of the 690 kDa form of adiponectin, which is the major form that has insulin-sensitizing and anti-diabetic activities. Depletion of the posttranslational modifications by site-directed mutagenesis significantly attenuated the insulin-sensitizing, lipid-clearing and anti-inflammatory activities of adiponectin in liver. More recently, we have also found that the three forms of adiponectin can selectively bind to different mitogenic growth factors and inhibit their effects on the proliferation of smooth muscle cells, which might partly contribute to the anti-atherogenic functions of this important metabolic hormone.

In summary, our studies suggest that the biological functions of adiponectin could be regulated at the posttranslational level by modulating the hydroxylation and glycosylation as well as its high order structural protein assembly.