【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Agricultural sciences)

Title of Project : Development of methods to regulate abnormality of insulin-like activity by modulation of function of insulin receptor substrates-associated complex

Shin-Ichiro Takahashi
(The University of Tokyo, Graduate School of Agriculture and Life Sciences, Associate Professor)

Research Area : Animal life science, Animal production science
Keyword : Metabolism/Endocrine control, insulin-like activities

【Purpose and Background of the Research】

Insulin and insulin-like growth factors (IGFs) are major anabolic hormones, which play essential roles in neonatal/postnatal growth and development, maturation, maintenance of metabolism and aging *etc.* Bioactivities of these hormones are mediated by tyrosine phosphorylation of insulin receptor substrates (IRSs) by cognate receptor-tyrosine kinases followed by activation of the downstream pathways. When these insulin-like activities are extremely depressed or potentiated in response to other extracellular factors or under some conditions, the consequences can include cancer and overgrowth, or diabetes, growth retardation and early aging.

However, the precise mechanisms of action of each factor or condition are not yet clear. Elucidation of each mechanism is very important for the development of specific treatments for each disease. Our ongoing investigations to identify proteins that interact with IRSs and elucidate their functions in signal transduction of insulin/IGF are driven by accumulated data showing that IRS-associated proteins (IRSAPs) modulate IRS tyrosine phosphorylation induced by insulin/IGF. IRSs and associated proteins form a >700 kDa protein complex (we call it IRSome). Based on these results, our study is undertaken to identify IRSAPs whose interaction with IRSs increases and thereby influences the development of the above diseases.

We screen chemical compounds for ability to inhibit interaction between IRS and each IRSAP, and show that these chemicals are effective in prevention of these diseases.

【Research Methods】

We have already identified over 40 proteins that can interact with IRSs in insulin/IGF target cells. Firstly, we determine the specific IRSAP whose interaction increases in cells or organs where insulin-like activities are extremely depressed or potentiated. We will utilize cancer cells, cells treated with other extracellular factors and organs prepared from model animals, such as diabetes, and growth disorders. We then elucidate whether the IRSAPs determined do cause depression or enhancement of tyrosine phosphorylation of IRSs in response to insulin/IGF and if those responses are followed by modulation of insulin-like activities. We screen chemical compounds that inhibit interaction between IRS and the specific IRSAP and check the effect of these chemicals on insulin/IGF signaling as well as insulin-like activities in cells or organs prepared from model animals.

【Expected Research Achievements and Scientific Significance】

Our study elucidates novel molecular mechanisms that modulate insulin-like activities promoting diabetes, cancer, growth disorders and aging. In addition, small chemicals that inhibit interaction between IRS and the specific IRSAP are possibly utilized as the lead compounds for anti-diabetes, cancer, growth-disorders and aging drugs.

【Publications Relevant to the Project】

・Fukushima T *et. al.*, Insulin receptor substrates form high-molecular-mass complexes that modulate their availability to insulin/insulin-like growth factor-I receptor tyrosine kinases. *Biochem Biophys Res Commun* 404: 767-773 (2011)
・Yoneyama Y, *et. al.*, AP-1 complex regulates endosomal localization of insulin receptor substrate -1 required for insulin-like growth factor-I-dependent DNA synthesis. *Mol. Cell Biol.* 33:1991-2003. (2013)

【Term of Project】 FY2013-2017

【Budget Allocation】 166, 000 Thousand Yen

【Homepage Address and Other Contact Information】

http://endo.ar.a.u-tokyo.ac.jp/lab/shingroup/index.html