【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Development of a Novel Anti-Aging Strategy by Elucidating the Mechanisms Regulating Aging through a Muscle Centric Organ Network

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Research Project Number : 15H05789 Researcher Number : 00396714
Research Area : Diabetes and Metabolism
Keyword : Aging, Signal Transduction, Diabetes

【Purpose and Background of the Research】

Japan, which has been rapidly becoming an aged society, urgently seeks for an efficient strategy to provide the people with a healthy and socially active long lifespan. Compared to the Caucasians, the East Asians are prone to develop a life-style related disease, such as diabetes and cardiovascular disease, by aging even in the non-obese or mildly obese state. Indeed, aging deteriorates muscle volume and quality, namely sarcopenia, leading to the development of insulin resistance and decline in activity of daily life. Sarcopenia impairs socially active and independent living of the aged people by causing a variety of life-style related diseases and frailty.

We hypothesize that healthy muscle maintained by insulin signaling communicates with other organs thereby preventing whole body aging. The aim of this study is to elucidate the mechanisms of sarcopenia by impairment of insulin action and dysregulation of the muscle centric organ network, allowing us to develop a novel and efficient anti-aging therapy.

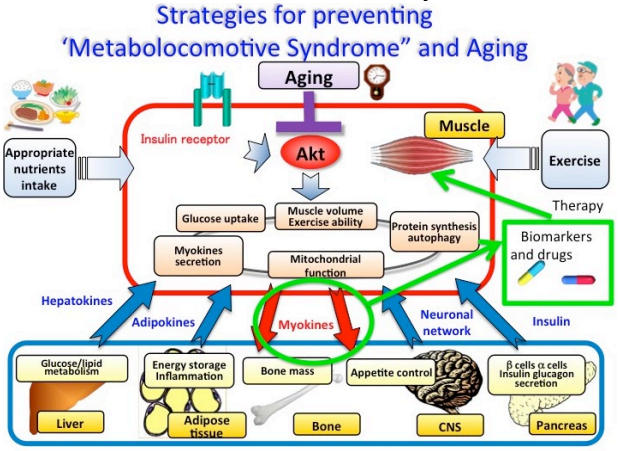
【Research Methods】

Based on the analyses of diabetic animal models, we hypothesized that aging impairs insulin signaling, especially Akt activity, in muscle, leading to the development of sarcopenia, which in turn exacerbates insulin resistance, resulting in further progress in sarcopenia. To assess this hypothesis, we have generated muscle specific Akt1/Akt2 double knockout (mAktDKO) mouse, and found that mAktDKO mice exhibit premature sarcopenia and whole body aging phenotypes, such as osteopenia. In this study, we try to identify pathways or factors downstream of Akt regulating sarcopeina and whole body aging by performing transcriptome, metabolome and signaling studies using mAktDKO mice and analyzing those mice with deletion of TSC2 or FoxO proteins. Furthermore, we try to explore the mechanism maintaining youth and homeostasis by investigating aging biomarkers in various tissues and cognitive functions of wild type and mAktDKO mice. Moreover, we will test the effect of specific nutrients or exercise on the prevention of sarcopenia in wild type and mAktDKO mice.

【Expected Research Achievements and Scientific Significance】

Through this project, useful biomarkers and compounds for preventing sarcopenia and aging will be developed. A novel disease concept, “Metabolocomotive syndrome”, caused by dysregulation of the muscle centric organ network, will be established

【Publications Relevant to the Project】



Iwabu M et al. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. ***Nature*** 464:1313-1319, 2010

Lu M et al. Insulin regulates liver metabolism in vivo in the absence of hepatic Akt and Foxo1. ***Nat Med*** 18:388-395, 2012

【Term of Project】

FY2015-2019

【Budget Allocation】

153,800 Thousand Yen

【Homepage Address and Other Contact Information】

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