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# THE RETINOIC ACID RECEPTOR $\gamma$ —RESPONSIVE GENE TRANSGLUTAMINASE 2 INDUCES MYOTUBE HYPERTROPHY AS A SECRETORY PROTEIN

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Skeletal muscle plays critical roles not only in physical activity such as posture and locomotion, but also in metabolism of glucose and lipids. The loss of skeletal muscle mass results in physical inactivity and higher prevalence of metabolic diseases such as obese and type 2 diabetes. The provitamin A  $\beta$ -carotene is the major dietary source of vitamin A.  $\beta$ -carotene is converted into all-*trans* retinal and is metabolized to all-*trans* retinoic acid (ATRA). Our previous study showed that dietary  $\beta$ -carotene increases mass and induces functional hypertrophy in the soleus muscle in mice. However, its molecular mechanism remains unclear. In the present study, we investigated whether or how retinoic acid receptor is involved in  $\beta$ -carotene-increased muscle mass. Small interference RNA (siRNA) mediated knockdown of RAR $\gamma$  inhibited  $\beta$ -carotene-increased soleus muscle mass in mice. Conditioned medium from ATRA-stimulated myotubes promoted protein synthesis and induced hypertrophy in murine C2C12 myotubes. We used RNA-sequencing and bioinformatics analyses to study gene expression of ATRA-dependent secreted proteins. Transglutaminase 2 (TGM2) was predicted to be one of ATRA-increased secretory proteins in myotubes. In the soleus muscle of  $\beta$ -carotene-administered mice and in ATRA-stimulated myotubes, the expression of TGM2 was increased. Knockdown of RAR $\gamma$  has down-regulated ATRA- or  $\beta$ -carotene-dependent TGM2 expression. TGM2 expression was increased in conditioned medium from ATRA-stimulated myotubes. Extracellular recombinant TGM2 promoted protein synthesis and hypertrophy and induced the phosphorylation of Akt, mTOR and p70S6K in myotubes. These results indicated that ATRA up-regulated TGM2 expression through RAR $\gamma$  and that extracellular TGM2 induced myotube hypertrophy, perhaps by activating Akt-mTOR signaling-mediated protein synthesis.

## Biography

Yamaji R has completed his PhD in Osaka Prefecture University, Japan. He is the Professor of Osaka Prefecture University. He is interested in what kinds of food components including nutrients have beneficial effects on skeletal muscle health and how they exert their function. He is serving as an Editorial Board Member of *J Nutr Sci Vitaminol*.

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