Department of Cell Physiology
Division of Aerospace Medicine

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General Summary

Our main research interests are gravitational physiology and aerospace medicine.

Research Activities

Regulation of cytosolic Ca^{2+} concentration in Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD), the most common and severe form of muscular dystrophy in childhood, is an X-linked disease caused by deficiency of dystrophin protein in muscle. The absence of dystrophin causes increased Ca^{2+} influx and an abnormal cytosolic Ca^{2+} homeostasis of myofibers, leading to increased necrosis. Several underlying mechanisms have been suggested to cause this abnormal cytosolic Ca^{2+} regulation in dystrophic muscle. Therefore, the aim of this study was to identify new therapeutic targets based on cytosolic Ca^{2+} regulation for DMD. Among several mechanisms, a decrease in the activity of sarco(endo)plasmic reticulum calcium ATPase (SERCA) has been considered as a primary cause of cytosolic Ca^{2+} overload in DMD, because SERCA accounts for > 70% of Ca^{2+} removal from cytosol. We found that the level of sarcolipin, an intrinsic inhibitory sarcoplasmic reticulum protein of SERCA, is abnormally high in dystrophic muscle. In this study, we determined the physiological relevance of sarcolipin in DMD following loss-of function by deletion of the gene sarcolipin (*SLN*). Knockdown of *SLN* ameliorated the cytosolic Ca^{2+} homeostasis and the dystrophic phenotype in a mouse model of DMD. These findings suggest that *SLN* is a novel target for DMD therapy.

In addition, we found a significant decrease in the muscle weight and cross sectional area of muscle fibers, although the number of fibers did not differ with the increased cytosolic Ca^{2+} concentration. For the mechanisms of reduction in the cross-sectional area and weight, we considered 3 possibilities, namely fiber atrophy, fiber type changes, and autophagy. An increasing number of type 2A fibers and the atrophy of type 2B fibers were observed. Peroxisome proliferator-activated receptorγ coactivator-1α (PGC1α), which can alter fiber types from fast to slow, was up-regulated in the tibialis anterior muscle. Also up-regulated were atrogin-1, muscle RING finger protein 1, and phosphorylation of Forkhead Box class O, which can induce muscular atrophy. In contrast, autophagy signals, such as microtubule-associated protein 1 light chain 3 (LC3) A and B, were not altered. These results suggest that an increase in cytosolic Ca^{2+} concentration changes the muscle fiber type and induces muscle atrophy.

Phenotypic analysis of juvenile onset dilated cardiomyopathy mouse model

Dilated cardiomyopathy (DCM) is characterized by cardiac dilation and pump failure. A fundamental therapy for DCM has not been established. In particular, DCM that develops

at a young age has a poor prognosis. The troponin T amino acid mutation (ΔK210) knock-in mouse (ΔK210-KI), generated by Dr. Sachio Morimoto and others, is considered to have the similar phenotype as a human child with juvenile DCM (Circ Res. 2007; 101: 185-94). However, neither the neonatal period nor the weaning period has been examined in detail. The purpose of this study was to investigate cardiac pathology and changes in gene expression in ΔK210-KI during the neonatal and weaning periods and to identify early progression factors of DCM. We found that cardiac hypertrophy has already developed at birth in homozygous ΔK210-KI mice. Furthermore, we are doing research to develop gene therapy by replacing mutant troponin T with normal troponin T overexpression.

Molecular mechanisms of intracellular Ca^{2+} mediated muscle atrophy

Muscle atrophy induced by tail-suspension and denervation increases the expression of sarcolipin, which negatively regulates intracellular Ca^{2+} dynamics in muscle cells. To clarify the relationship of intracellular Ca^{2+} dynamics to muscle atrophy, we analyzed the changes in gene expression in denervated sarcolipin knock-out mice and denervated wild-type mice. We found that muscle atrophy in denervated sarcolipin KO mice was less than that in denervated wild-type mice. We are now examining the molecular mechanisms of this change.

Publications

Tanihata J, Nagata T[1], Ito N[1], Saito T[1], Nakamura A[2], Minamisawa S, Aoki Y[1], Ruegg UT[3], Takeda S[1] ([1]NCNP, [2]Shinsyu Univ, [3]Univ Geneva). Truncated dystrophin ameliorates the dystrophic phenotype of mdx mice by reducing sarcolipin-mediated SERCA inhibition. *Biochem Biophys Res Commun.* 2018; **505:** 51-9.