**Development of nano-antioxidants targeting injured muscles and their application in muscle diseases**

**Gai Kanazawa1**, Hitoshi Maeda 1.2, Hiroshi Watanabe 3, Toru Maruyama 1.

1 Department of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, JAPAN;

2Department of Biopharmaceutics, Kyoto Pharmaceutical University, Kyoto, JAPAN;

3 Department of Clinical Pharmacy and Therapeutics, Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, JAPAN.

**Background and aims.**

In sarcopenia, which is characterized by skeletal muscle atrophy and reduced muscle strength, excessive production of reactive oxygen species (ROS) in muscle tissue disrupts intracellular redox balance and contributes to disease progression. Therefore, the development of antioxidant therapies targeting muscle tissue is highly desired. Human serum albumin (HSA) is known to exhibit high binding affinity to secreted protein acidic and rich in cysteine (SPARC), a myokine that is markedly upregulated in muscle tissue during muscle degradation. In this study, we developed edaravone-loaded HSA-NPs, an HSA-based nanoparticle formulation incorporating the antioxidant edaravone. We then evaluated its intrinsic muscle-targeting properties and therapeutic efficacy in a disuse-induced muscle atrophy model, a representative pathophysiological condition of sarcopenia.

**Methods.**

HSA-NPs was prepared by reducing the intramolecular disulfide bonds of HSA using reduced glutathione, followed by mixing with edaravone. A hindlimb unloading (HU) model was established by suspending the hindlimbs of mice to induce disuse muscle atrophy.

**Results.**

Using hydrogen peroxide-treated cells and SPARC-silenced cell lines, we demonstrated that SPARC plays a critical role in the intracellular uptake of HSA-NPs by muscle cells. Western blot analysis of hindlimb muscle tissue from HU mice revealed an upregulation of SPARC expression. Furthermore, administration of Evans Blue dye—a marker known to bind albumin—to HU mice led to its accumulation in the atrophied hindlimb muscles, indicating that HSA exhibits tropism toward damaged muscle tissue. Consistently, in HU mice treated with HSA-NPs, reactive oxygen species (ROS) levels in the hindlimb muscles were significantly reduced, and both muscle atrophy and muscle strength were markedly improved.

**Conclusion/Discussion.**

Edaravone-loaded HSA-NPs, which exhibit tropism toward damaged muscle tissue, are expected to serve as a novel antioxidant therapeutic strategy for sarcopenia.