Role of Ghrelin receptor in sarcopenia: Involvement of Redox Signaling and RANKL

MARIAM A. OTHMAN, JOO-HYUN KIM, KHALED Y. KAMAL & JOHN LAWLER

Redox & Cell signaling laboratory, Department of Health & Kinesiology, Texas A&M University, College Station, TX

Category: Doctoral

Advisor / Mentor: Lawler, John (jml2621@tamu.edu)

ABSTRACT

Sarcopenia is aging-induced debilitating loss of skeletal muscle strength and function. Evidence from aging research suggests an integration of disrupted mechanotransduction and oxidative stress elevation that leads to muscle atrophy. Ghrelin is a 28 amino acid peptide hormone circulating in both acylated (AG) and unacylated (UAG) forms that acts as a nutrient sensor and metabolic regulator. Acylated ghrelin then binds to the growth hormone secretagogue receptor (GHS-R) or the "ghrelin receptor." Emerging evidence indicates that GHS-R knockout may hold greater promise in protecting against sarcopenia and fasting-induced atrophy (Wu 2020, Sun 2020). Furthermore, ghrelin can promote the elevation of nNOS, which is important as nNOS is critical to the preservation of the morphology and strength of the skeletal muscle (Lawler, 2021). Ghrelin can also stimulate protective proteins (e.g., HSP70, SIRT1), which attenuate Nox2 and ROS production. In our laboratory, recent preliminary data demonstrated positive feedback between Nox2 and RANKL that amplifies pathology and attenuates ca2+ overload, damage, and inflammation in dystrophic skeletal muscle. However, this feedback between RANKL and Nox2, and the redox regulation in sarcopenia is unknown. **PURPOSE**: Thus, we propose that GHS-R-dependent ghrelin pathways attenuate the markers of damage, inflammation, and redox regulation that mitigate the RANKL/Nox2 feedback and fibrosis in the aged muscles-induced sarcopenia. **METHODS**: Two different age C57Bl/6 mice were divided into four different groups (n = 6/group): ***(a)*** 11 months middle age wildtype, ***(b)*** Middle age WT + GHS-R -/-, (c) 23 months old age wildtype, ***(d)*** old age WT + GHS-R -/-. At the end of the experiments, gastrocnemius muscles were dissected and snap-frozen for further analysis. **RESULTS**: Data of protein abundance by western blotting revealed that elevated Nox2 complex marker (p67 phox), and Nox4 are decreased in the GHSR -/- groups in both middle and old-age mice. RANKL levels are significantly increased in the old group compared to the middle age. Furthermore, knocking out the GHSR mitigate the elevated RANKL levels. Markers for the damage, inflammation, Ca2+ overload, and sarcopenia-related sarcolemma-DGC dysregulation are currently being investigated. **CONCLUSION**: In conclusion, we demonstrate the contribution of RANKL, Nox2, and Nox4 in aging-induced sarcopenia. GHSR-dependent ghrelin pathway knockout shows a promising mechanism to mitigate oxidative stress, damage, and inflammation in sarcopenia. Further analysis will be performed to fully understand these underlying mechanisms.