

Nitration/dysfunction of myogenic stem satellite cell activator HGF: the physiological impact on age-related muscle atrophy with impaired regeneration

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(筋幹細胞活性化因子 HGF のニトロ化による不活化 : 加齢性筋萎縮・再生不全に対する生理学的インパクト)

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Thesis Summary

Satellite cells, resident myogenic stem cells found between the basement membrane and the sarcolemma in post-natal skeletal muscle, are normally quiescent (or dormant) most of the time in adult muscles; hence activation of quiescent satellite cells to enter the cell cycle is an initial and crucial step for muscle growth, maintenance, and regeneration after injury. Recent studies showed that mechanical perturbation triggers activation of quiescent satellite cells through a cascade of events including NO radical-dependent release of hepatocyte growth factor (HGF) from its extracellular tethering and its subsequent presentation to signaling receptor c-met.

This Ph.D. thesis provided an iconic evidence that extracellular HGF undergoes tyrosine-residue (Y) nitration to lose c-met binding activity with aging, therefore possibly mediating age-related muscle atrophy and impaired regeneration. This study was originally raised by high-frequency stretch experiments in cultures, which revealed an inhibitory mechanism centered on nitration/dysfunction of released HGF. The subsequent biochemical study demonstrated that nitration/dysfunction is specific to HGF among the major growth factors examined (FGF2, IGF1, and TGF- β 3) and characterized by peroxynitrite (ONOO⁻)-induced physiological modification at Y198, Y250 in the K1, 2 domains. Importantly, direct-immunofluorescence microscopy of rat lower hind-limb muscles from three aged-groups provided direct *in vivo* evidence for progressive nitration of ECM-bound HGF with aging, by showing that fast Ila, IIX myofibers were exclusively positive for anti-nitrated Y198 and Y250 HGF antibodies raised in-house.

Overall, findings highlight an inhibitory impact of HGF nitration/dysfunction on “activation—proliferation—self-renewal axis” of myogenic stem cells, as a possible key for understanding age-related muscle atrophy with impaired regeneration. Consequently, this potent inhibitory mechanism may emerge as a crucial key in enabling the design of innovative therapies not only to prevent or delay aging-related muscle atrophy and improve the care of patients with a variety of myopathies and severe muscle trauma victims but also can contribute to livestock and veterinary medicines through the improvement of meat productivity and animal welfare.