The Renin Angiotensin System in self-renewal and differentiation of human satellite cells

L. Sartiani

C.I.M.M.B.A., Dept. of NeuroFarBa, University of Firenze

Satellite cells are multipotent stem cells that in the healthy skeletal muscle are responsible for physiological growth, homeostasis and regeneration after injuries. They normally lie in highly specified niches, which provide the microenvironment to support the maintenance of cell quiescence and self-renewal or the induction of proliferation and differentiation toward the myogenic lineage. Through these processes skeletal muscles are able to counteract atrophy, limited injuries or excessive growth, and provide satellite cell pool preservation during aging and regeneration. Understanding the microenvironmental cues that control satellite cell fate and the molecular interactions involved in the underlying processes is of utmost importance for the identification of novel druggable targets in the muscle and effective therapies for sarcopenia and wasting disorders.

Recent interest is emerging for the role of Renin-Angiotensin System (RAS) in the skeletal muscle, where the axis acts as master regulator of different physiological functions including perfusion, trophism and regeneration capacity. Accumulating clinical and experimental studies have documented the potential benefits of RAS blockade in different conditions associated with sarcopenia (Sayer AA et al., 2013) and uncovered a crucial role exerted by Angiotensin II (AngII), the main effector molecule of RAS, and derivative peptides. However, the direct effects of AngII in skeletal muscle remain controversial due to divergent results which propose AngII either as promoter or negative regulator of muscle trophism and regeneration capability (Yoshida et al., 2013; Johnston et al., 2010). Our recent findings demonstrate that a complete RAS axis is expressed in proliferating human satellite cells and differentiating myotubes, which mirrors the expression pattern found in the whole human skeletal muscle. The evidence suggest the existence of a local or muscle specific RAS that likely contributes to the microenvironment inside the satellite cell niche in the native muscle, paralleling or complementing the function of systemic RAS. Of note, the local RAS phenotype is functionally expressed in human satellite cells and is directly and dose-dependently modulated by AngII. The peptide promotes satellite cell mitosis and activates a signaling pathway (Akt, ERK1/2, p38) of fundamental importance to drive cell proliferation and differentiation. The effect of AngII passes through activation of AT2 receptors, uncovering a pro-mitotic regulatory function of AT2 receptors that likely counterbalances the detrimental effects of AT1 receptors. To exert this function AngII/AT2 complex requires the contribution of Transient Receptor Potential Canonical (TRPC) channels, a family of voltage independent, nonselective cation channels that mediate calcium entrance into the cells, a crucial signal to modulate plasma membrane bioelectricity, and to promote cell cycle progression and cell fate decision of precursors (Bernheim et al., 2002). Future investigations will clarify the impact of AngII/AT2/TRPC-channel complex as pharmacological target(s) potentially useful to preserve satellite cell/muscle homeostasis and regeneration potential and to promote skeletal muscle repair after injuries or muscle diseases.

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