Possible Novel Drug Targets On Satellite Cells

L. Raimondi

Dept. of NeuroFarBa, University of Florence, Viale G. Pieraccini 6, 50139 Firenze

Skeletal muscle comprises about 40% of the human body mass, and it is well recognized for its robust capacity for regeneration, a feature which progressively declines physiologically with aging (sarcopenia), with disuse, or secondary to other comorbid conditions. Reduction of muscle mass and performance constitutes a risk factor for metabolic diseases and deeply affects drug pharmacokinetic features, thus initiating a shortcut which negatively impacts on patient lifespan. To now, few pharmacological approaches are available to ameliorate primary or secondary degeneration of muscle function.
Skeletal muscle regeneration is a peculiar job of resident mature stem cells, the satellite cells (SC). These cells lie 'sleeping' anchored at the basal lamina of myotubes but ready to respond to injuries or stress stimuli escaping from G0 and entering in asymmetrical growth phase and then differentiating. The mechanisms governing these passages and the reasons why they became inefficient are not completely defined.
Notch and Wnt cross-talking signals represent the main regulators of SC growth differentiation and/or fibrosis controlling the expression/activity of Myostatin and IGF1/growth hormone, two among the main catabolic and anabolic signals at SC. Notch and Wnt timing of activation results in the modulation of the core signaling of SC represented by the Akt-mTORC1 and TORC2 cascades and of their counterpart, the AMPk. On these cascades, metabolic, mitogenic and differentiating signals convey. Because of this, drugs interfering directly or indirectly with such cascades have the potential to trigger or to inhibit SC growth and differentiation, including sex hormones. Accordingly, analogs of testosterone and of ghrelin are currently under clinical evaluation.
Ca^{2+} signals are known to be essential for SC differentiation (Przybylski et al., 1989; Friday et al., 2000), myotube fusions (Bernheim and Bader, 2002) and metabolism. Intracellular Ca^{2+} levels increase secondary to the activation of store-operated or L-type Ca^{2+} channels, each recruited depending on cell potential. Among store operated Ca^{2+} channels are the transient receptor potential canonical**,** TRPC1-6, whose expression change during myogenesis (Zhang et al., 2014). Interestingly enough, TRPC channels are classically controlled by intracellular lipid messengers (PIP2 and diacyl glycerol), thus opening to the possible modulation by G-q coupled receptor activation. In this respect, among the most studied systems is that mediated by angiotensin-II (AT-II). For this latter, controversial effects on SC growth and differentiation *in vitro* have been described (Johnston et al., 2010) Yoshida et al.,2013) while systemic infusion produced sarcopenia and induced muscle fibrosis in mice mainly suppressing IGF1 signaling and activating AT1R-p38MAPK-nitric oxide (Yoshida et al., 2013). To confirm the importance of AT-II system, clinical evidence suggest drugs targeting AT-II are among the long-term treatments more respecting muscle function in frail patients. The mechanism underlying such effects remains to be clarified. Among the possible explanations is the production of bioactive fragments, including Angiotensin (1-7) an endogenous ligand for AT2 and MAS receptor, two proteins of the non-conventional renin angiotensin system (RAS). To now, whether AT2/MAS are expressed in SC and if they have a role in Ca^{2+}-driven myogenesis is unknown. The identification of an AT2 signaling might offer a new key of lecture of AT-II effects opening to novel approaches to the treatment of sarcopenia.

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