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Editorial

The role of the estrogen receptor in skeletal muscle mass homeostasis and regeneration

In the manuscript 'Oestrogen-dependent satellite cell activation and proliferation following a running exercise occurs via the PI3K signalling pathway and not IGF-1.' by Mangan *et al.* (2014) sheds new light on the molecular mechanisms involved in the effects of exercise training and estradiol treatment on the activation of satellite cells. The authors focus particularly on the interaction between IGF-1 and estradiol and the role of the PI3K signalling pathway in mediating the effects of estradiol on satellite cell activation. With this work, the authors make a significant contribution to understanding the mechanisms mediating the effects of male and female sex hormones on skeletal muscle satellite cell regulation.

Satellite cells play a major role in the regulation of post-natal muscle growth and regeneration (Ceafalan *et al.* 2014). Age- and disease-dependent loss of muscle mass (muscle wasting) has detrimental consequences for human health, by causing metabolic disturbances and physical frailty in patients. Moreover, skeletal muscle tissue is an important organ for metabolic function. Consequently, muscle wasting is associated with an increased risk of developing metabolic diseases, such as type 2 diabetes or the metabolic syndrome (Koopman *et al.* 2014). Preventing the loss of skeletal muscle mass is therefore an essential aim to prevent the loss of mobility and the development of metabolic diseases. There are numerous reasons responsible for the loss of muscle mass, which may justify the usage of the term 'muscle wasting syndrome'. Disease-associated muscle wasting (cachexia) develops as a consequence of several common diseases, such as cancer, AIDS, heart failure, COPD (chronic obstructive pulmonary disease) and renal failure. Patients suffering from these diseases and developing cachexia have a poor prognosis. Another major reason for muscle wasting is muscle disuse due to an increasingly more sedentary lifestyle (Bogdanis 2012). A scenario of extremely high relevance for public health is the gradual decrease in the ability to maintain skeletal muscle function and mass during ageing (sarcopenia).

There is accumulating evidence suggesting that there are striking sex-based differences with respect to skeletal muscle homoeostasis. Whereas the function of androgens in the regulation of skeletal muscle homoeostasis has been investigate intensively in the past, the role of oestrogens has been largely ignored. The importance of female sex steroids for skeletal muscle health was first identified during muscle regeneration after injury. Twenty years ago, a series of studies by Amelink, Bär, and colleagues have shown that there are sex-based differences in the response of skeletal muscle to injury (Amelink & Bär 1986, Bär *et al.* 1988, 1995, Amelink *et al.* 1990, Koot *et al.* 1991, Bär & Amelink 1997). The finding that creatine kinase (CK) activity was significantly greater in male vs. female rats after muscle-damaging exercise and that ovariectomized (OVX) female rats showed CK elevations similar to those of male rats, first suggested that the female sex hormone 17 beta-estradiol (E2) may play an important role in skeletal muscle damage and repair processes.

E2 attenuates the inflammatory response after muscle-damaging exercise (Tiidus *et al.* 2001) or ischaemia/reperfusion injury (Stupka & Tiidus 2001) by reducing neutrophil invasion into the injured muscles. OVX rats also fail to fully recover skeletal muscle mass after a period of hindlimb unloading followed by a subsequent period of reloading, compared with OVX rats administered E2 (Sitnick *et al.* 2006, Sugiura *et al.* 2006, McClung *et al.* 2007), suggesting that E2 attenuates the rate of disuse atrophy. This is relevant, especially with respect to muscle recovery after injury in older postmenopausal women where sarcopenia rates are higher compared with premenopausal women and the rate of loss of muscle mass can be reduced by hormone replacement therapy (Sørensen *et al.* 2001).

The mechanism(s) behind the influence of E2 on the regenerative responses of skeletal muscle after injury involve satellite cell activation and proliferation in the injured myofibers. This is the aspect mainly addressed in the paper from Peter Tiidus' group. Several years ago, his group was able to demonstrate that treating male rats with E2 resulted in a significantly higher number of satellite cells after a bout of muscle-damaging downhill running exercise compared with sham-treated animals (Tiidus *et al.* 2005). Treating female OVX rats with E2 also resulted in a marked increase in the number of total, activated and proliferating satellite cells in the injured skeletal muscles compared with sham-treated OVX rats (Enns & Tiidus 2008). The E2-mediated effects on satellite cell activity have been shown to be ER mediated involving the oestrogen receptor (ER) alpha (Thomas *et al.* 2010) and/or ER beta (Velders *et al.* 2012).The ER alpha receptor subtype primarily mediates the oestrogenic effects in the reproductive tissues and is involved in the

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development of breast cancer. On the contrary, the ER beta is mostly expressed in the gastrointestinal tract, vascular endothelial cells and the prostate (Matthews *et al*. 2006) without inducing oestrogenic effects in reproductive tissues. Specifically targeting ER beta signalling pathways, either by nutritional supplements or pharmacological tools in combination with training, may prove beneficial for maintaining muscle mass and assisting in the regeneration of skeletal muscle, particularly in the ageing population.

The paper by Mangan *et al*. (2014) provides new data showing that the PIK3/Akt pathway is involved in mediating the oestrogenic effects on satellite cell activation. Taking in account the recent findings with respect to the role of ER beta in skeletal muscle and the controversial discussion regarding the role of ER alpha with respect to proliferation in the reproductive tissues, future studies should focus on investigating the communication between the ER isoforms and the PIK3/Akt pathway. This is of specific interest with respect to pharmaceutical or nutritive intervention concepts for the prevention of loss of muscle mass in postmenopausal females or elderly men. The long-term goal is to find treatment strategies which selectively stimulate oestrogenic effects in skeletal muscle of males and females without inducing oestrogenic effects in reproductive tissues. This is important to prevent the development of breast or uterine cancer in females and feminization in males.

Many phytoestrogens like genistein or other substances identified in plants such as ecdysterone bind selectively to the ER beta. Strategies to maintain muscle mass, involving nutritional supplements containing phytoestrogens in combination with physical training, should be further investigated in terms of muscle mass regulation. Understanding the ER-subtype selective signalling mechanisms responsible for mediating the effects of oestrogens on muscle homoeostasis provides valuable information to assess the effectiveness of oestrogen-based intervention concepts aiming to increase/maintain muscle mass or to stimulate skeletal muscle regeneration in the elderly population.

Conflict of interest

I have nothing to declare.

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