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SRF role as a mechano-transductor in response to exercise in cancer cachexia

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Introduction: Recent studies showed that physical activity increased survival in cancer patient and animal models of cancer cachexia. The underlying mechanisms, however, are still largely unknown.

Methods: To identify signalling pathways involved in exercise-dependent maintenance of muscle mass and function in cachexia, we investigated the role of serum response factor (SRF)—a transcription factor playing a pivotal a role in muscular growth, differentiation and regeneration—in C26-bearing mice in the absence or presence of voluntary exercise (wheel running).

Results: SRF levels are decreased at protein level in cachexia. Consistently, a decrease in the expression of SRF target genes such as MyoD and SK-actin occurs in C26-bearing mice, suggesting a decrease of SRF transcriptional activity. These tumour effects were counteracted by wheel running and associated to the rescue of muscle mass and function. However, a minimum amount of exercise (2 km/day) is necessary to keep SRF levels elevated in cachexia over a threshold which is necessary to exert beneficial effects. SRF levels inversely correlate with wasting in mice, suggesting that SRF play a role in maintaining body mass (mostly accounted for by muscle mass). We also observe the recruitment of nuclei within the muscle fibres in response to exercise, which could contribute to muscle homeostasis and is consistent with the previously observed opposite effects of tumour and exercise on MyoD and Pax7 expression.

Conclusions: Our results suggest that physical activity rescues SRF expression as well as its transcriptional activity, highlighting the importance of genetic activation induced by skeletal muscle activity for muscle rescue and homeostasis. These effects could be extended to the fibre microenvironment, including myogenic stem cell activity.

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Toward the identification of receptor for advanced glycation end-products (RAGE) as a muscle biomarker of cancer cachexia

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Introduction: Cachexia is a debilitating syndrome affecting more than 50% of patients with advanced cancer. Its major clinical feature is skeletal muscle atrophy leading to pronounced weight loss, reduced quality of life, and poor prognosis. The identification of valuable biomarkers of early cachexia is of great importance to identify the patients at risk of cachexia and to treat patients in the reversible phase of the disease (Porporato *et al*., *Oncogenesis* 2016, Loumaye-Thissen, *Clin Biochem* 2017). RAGE (receptor for advanced glycation end-products) signalling concurs to skeletal muscle development and homeostasis (Riuzzi *et al., JCSM* 2018); however, in cancer conditions, RAGE hyperstimulated by high levels of its ligands leads to muscle wasting, sustains inflammation, and reduces survival of mice (Chiappalipi *et al*., submitted). Here, we investigated whether RAGE might represent a biomarker of cachexia.

Methods: We analysed RAGE expression in muscle tissue of different tumour-bearing mice in the absence or presence of endurance exercise and correlated it with myofiber CSA and hallmarks of atrophy (body and muscle weights, protein degradation, and activation of the proteolytic systems). We performed RAGE expression analysis in muscle biopsies of cancer patients.

Results: We found that (i) Lewis lung carcinoma (LLC)-bearing C57Bl/6 mice and colon adenocarcinoma (C26-ADK)-bearing BALB/c mice express RAGE in myofibres in coincidence with reduced body and muscle weight and induction of proteolysis; (ii) an inverse relationship exists between RAGE expression in muscles, tumour masses, and the beneficial effects of endurance exercise in LLC-bearing mice; (iii) RAGE expression increases in muscles during cachexia progression; (iv) LLC or melanoma A375 cells injected in athymic-nude mice are not able to induce neither cachexia nor RAGE expression in muscle; and (v) muscles of cachectic patients express higher amounts of RAGE than non-cachectic subjects.

Conclusions: RAGE might represent a muscle biomarker of the cachectic stage.