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## Age-Related Sarcopenia: Diabetes of the Muscle?

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### Letter to Editor

Age-related loss of skeletal muscle mass and quality ("Sarcopenia") represents a relevant aspect of the senescent phenotype and a major cause of "frailty", disability and loss of independence of the elderly [1]. Although extremely common, this phenomenon is poorly understood in its causes and mechanisms, which is also reflected by the lack of specific therapeutic approaches except for nutrition and physical activity, often leading to only limited benefit.

The Insulin-IGF (Insulin-like Growth Factor) signaling pathway (IIS) is pivotal to muscle growth and maintenance, mainly through the Akt-FoxO (Forkhead box O), and Akt-mTOR (mammalian Target of Rapamycin) sub-branches, that, respectively, prevent muscle atrophy and promote protein build-up [1]. Evidence exist that IGF content and IIS is reduced in the senescent muscle, because of a combination of reduced fiber volume (and glucose disposal capacity), mitochondrial dysfunction and oxidative stress [2]. Accordingly, sarcopenia has been often found to associate with systemic insulin resistance [3]. However, establishing a causative link between reduced response to IIS and age-related muscle wasting has proven difficult for a number of reasons. First, sarcopenia often develops in combination with obesity ("sarcopenic obesity"), a condition that in turn represents a major cause of insulin resistance in the elderly [4]. Excess adiposity may impair muscle response to insulin by excess release of saturated fatty acids (SFA), or through the establishment of a generalized, subclinical low-grade inflammation (metainflammation) [5], that is known to desensitize insulin responses at a post-receptorial level. Either way, insulin resistance in sarcopenic obesity may not necessarily account for muscle loss, but simply represent a comorbidity induced by excess adiposity or the associated inflammation.

Additionally, muscle represents the major site of glucose disposal in the healthy individual [6], implying that a relative resistance to insulin may well represent a consequence, rather than a cause, of generalized muscle atrophy. Or at least that a mutual relationship between the two phenomena could be envisaged. Importantly, however, studies performed on transgenic animals overexpressing the master inflammation regulator NF- $\kappa$ B in muscle have demonstrated that significant loss of muscle mass can occur without the establishment of systemic glucose intolerance [7]. Instead, primary loss of insulin

response can promote proinflammatory signaling in the muscle [8].

Notwithstanding the above confounding evidence, we stand for the idea that muscle resistance to anabolic IIS signaling represents a major driver of age-related or ("primary") sarcopenia. It is conceivable that loss of mitochondrial mass and oxidative capacity (and the resulting build-up of reactive oxygen species) occurs in the senescent muscle as an early event disrupting of insulin response [9], even in the presence of a preserved muscle mass. Given the role of muscle in glucose disposal, this could result in altered glucohomeostasis, hyperinsulinism and possibly even increased adiposity. In alternative, muscle may develop a "selective insulin resistance", whereby mTOR-dependent protein anabolism, but not glucose internalization and oxidation in the muscle are disrupted [10]. As a further possibility, glucose disposal capacity of liver and adipose may compensate for muscle loss of insulin responsiveness, thus maintaining overall glucose homeostasis within normal limits in sarcopenic individuals. Of note, in the latter two cases, clinical glucose intolerance may not be detected in sarcopenic individuals.

In recent years basic and translational research have established multifaceted connections between nutrient signaling through the IIS pathway and the ageing process [11]. While in model organisms attenuation of systemic insulin action is accompanied by extended lifespan, in mammals tissue specific senescence, as in Alzheimer-like neurodegeneration or endothelial dysfunction, often reflect a defect in response to insulin signaling [12]. Importantly, such defect may involve not only mature cell types, but also stem cells deputed to tissue regeneration and maintenance, and may be due to both cell-intrinsic as well as environmental, blood-born factors [13].

We suggest that age-related sarcopenia may be the result of a tissue-specific impairment of insulin signaling, a form of "muscle-specific diabetes". Systemic evaluation and possibly validation of this hypothesis may entail important consequences for the prevention and therapy of sarcopenia, from the development of diagnostic procedures/biomarkers aimed at specifically addressing muscle response to insulin, to the evaluation of insulin sensitizing drugs (Metformin, Thiazolidinediones) for muscle mass maintenance in the elderly even in the absence of overt diabetes.

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