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Chronic exercise enhances muscle function and metabolism, contributing to improved quality of life. Exercise affects the basal activity of cellular pathways, modulates the number of cells constituents, and improves both their functioning and turnover (Sanchez *et al.*, 2019). More specifically, resistance training induces several adaptations such as increases of muscle mass and strength associated with myofibrillar adjustments. These adaptations depend on several variables including exercise intensity, volume, rest between sessions, the nutritional statue, recovery, genetic/epigenetic and environmental conditions (Figueiredo *et al.*, 2018; Sanchez *et al.*, 2019). In recent years, several studies have focused on the impact of training volume on adaptations to resistance training and an inverted U-shaped relationship has been hypothesized to exist between training dose and adaptations. However, a graded dose-response relationship between resistance training volume and gains in muscle mass and strength is increasingly suggested (Schoenfeld *et al.*, 2017; Figueiredo *et al.*, 2018). While a discrepancy also exists concerning the most effective method between low and moderate-training volume to induce hypertrophy and health outcomes, recent data seem to be in favor of moderate-training volume (Schoenfeld *et al.*, 2017).

Gains in muscle contractile properties and power are mostly associated with an increase in myofiber cross-sectional area, a shift in the distribution of myosin heavy chains (MHC) to MHC2A and MHC2X, and enhanced myosin ATPase activity. In the last decade, studies have been conducted to improve our knowledge on cellular pathways regulating protein turnover in response to exercise (Sanchez *et al.*, 2019). Among them, the mechanistic/mammalian target of the rapamycin complex 1 (MTORC1) is a critical protein complex that coordinates protein synthesis and contributes to muscle hypertrophy. MTORC1 is sensitive to nutrient availability and growth factors and controls mRNA translation by phosphorylating a myriad of translational regulators. Hence, the enzyme MTOR phosphorylates the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) at Thr-37/46, promoting 4E-BP1 dissociation from the eukaryotic translation initiation factor 4E (eIF4E). This dissociation allows the assembly of the preinitiation complex required for translation. MTOR also phosphorylates the ribosomal protein S6 kinase 1 (S6K1) at Thr-389 and Thr-412 for the isoforms p70-S6K1 and p85-S6K1, respectively. S6K1 activates in turn other translational targets by phosphorylation, such as the ribosomal protein S6 (rpS6) and the eukaryotic translation initiation factor 4B (eIF4B). S6K1 is also phosphorylated at Thr-229 by the phosphoinositide-dependent kinase-1 (PDK1) to induce its full activation and phosphorylates MTOR at Ser-2448. The latest mechanism constitutes a negative feedback leading to inhibition of MTORC1 kinase activity, but also reflects S6K1 activity. Of note, MTORC1 is also an essential regulator of

the autophagy pathway by inhibiting autophagosome formation through phosphorylation of the Unc-51 like autophagy activating kinase 1 (ULK1).

Importantly, it was strongly suggested that the translational capacity of muscle cells is a critical factor for training-induced gains in muscle mass. The abundance of ribosomal RNA (rRNA) and ribosomal biogenesis during resistance training appear as key factors for muscle hypertrophy. Accordingly, Stec and co-workers reported increases in rRNA abundance after resistance training, with a larger effect in high-responders to muscle hypertrophy than in low responders (Stec *et al.*, 2016). The same group have also previously reported that blunted ribosome biogenesis after acute resistance exercise may contribute to the attenuation of training-induced hypertrophy during aging. However, no study has established the impact of training volume on these adaptations to date, especially in humans.

In a recent study published in The Journal of Physiology, Hammarström and coworkers (Hammarström *et al.*, 2019) examined the modulation of protein synthesis and ribosome biogenesis markers in human skeletal muscle during both acute and chronic resistance exercise. The authors investigated the effects of two volume conditions on the modulation of these markers. For this purpose, non-resistance trained participants were recruited and followed 12 weeks of full-body resistance training. They were asked to perform unilaterally leg-resistance exercises consisting of one set (*i.e.* low-training volume) and three sets (*i.e.* moderate-training volume) after their two legs were randomly assigned to one of both conditions. Thus, according to this experimental design, each participant followed both protocols. Several muscle biopsies from vastus lateralis muscles of both legs were performed before the protocol, before and 1 hour after the fifth training session (week two), and at rest after the completion of the training protocol (week 12). Muscle strength (assessed as one repetition-maximum in unilateral leg-press and knee-extension, and isometric/isokinetic knee extension), body composition, muscle CSA were measured, and immunohistochemistry, quantitative real-time reverse transcription polymerase chain reaction (qPCR) and immunoblotting from muscle extracts were assessed.

First, the authors found that both resistance training protocols led to an increase in muscle mass and muscle strength (mean values of both volume conditions were 4.4% and 25%, respectively) with higher gains in muscle strength for multiple-set resistance training. The authors reported that this difference gradually increased over the first nine weeks of the protocol. They also found that multiple-set resistance training led to higher gains in knee extensor muscle CSA. By using immunohistochemistry analyses and mRNA gene-type profiling (*i.e.* GeneFam), the authors demonstrated that multiple-set resistance training also showed more important

conversion of type IIX into type IIA fibres than the single-set training protocol (week 12). However, unexpected higher level of type IIA fibres was observed for single-set training at week two and multiple-set condition showed a higher level of IIX/IIA hybrid fibres and a more pronounced decrease in myosin heavy chain 1 gene expression. Overall, despite this surprising result at week two, these data indicate that higher resistance-training volume led to greater benefits on muscle mass, strength and fibre-type conversion at the end of the training period.

By using immunoblotting analysis, the authors highlighted that both acute resistance protocols induced an increase in the phosphorylation level of the MTOR targets p70-S6K1 (Thr-389) and p85-S6K1 (Thr-412), and the S6K1 target rpS6 (Ser-235/236) within two weeks. Importantly, these changes were significantly more pronounced for multiple-set than single-set resistance training. Even if measurements of protein synthesis rate were not performed, this result strongly suggest a higher activation of protein translation after exercise for moderate volume training. To investigate the effects of both training protocols on ribosomal biogenesis, the authors evaluated the abundance of rested-state total RNA, rRNA and selected mRNA from the vastus lateralis muscles at weeks two and twelve. They found a greater total RNA level at weeks two and twelve for multiple-set training compared to single-set training. Mature rRNA transcripts (18S, 28S and 5.8S) were also more elevated at week two for multiple-set training but not at week twelve where 28S trended to remain higher for single-set training. An increase of the rRNA precursor transcript 45S was found only at week twelve for single-set training when measured per-unit total-RNA. Finally, the authors also found that multiple-set training led to a higher increase of the transcription factor c-Myc which is known to be essential for the initiation of rRNA transcription. Taken together, these data indicate that both protocols led to an increase of ribosomal biogenesis and that multiple-set training promotes higher effects. Collectively, these results support the idea that chronic resistance exercise may enhance protein translation and ribosomal biogenesis in a volume-dependent way. This is the first study to report that moderate-volume is more efficient than low-volume resistance training for inducing the aforementioned adaptations.

Finally, the authors also performed regression analyses to identify determinants of multiple-set benefits. As expected, a strong correlation was found between strength gains and hypertrophy. Analyses also revealed that high baseline percentage of lean body-mass is a predictor of the effects of multiple-set training on muscle hypertrophy. The authors also highlighted that participants showing additional benefits on hypertrophy and strength with multiple-set training have greater total RNA levels at week two. Thus, these analyses reinforce the

hypothesis on the role of ribosomal biogenesis in the volume-dependent effect of resistance training on skeletal muscle mass and strength.

In conclusion, this study conducted in humans highlighted that an increase in ribosomal content contributes to the training-induced development of muscle growth and strength. Importantly, it is also the first investigation to show that the IIX to IIA fibres switch is sensitive to training volume, as it was previously acknowledged for muscle mass and strength. According to the data, ribosomal biogenesis is also volume-sensitive and is now suggested as a key factor in the early phase of resistance training adaptation. Manipulating resistance training volume may be an efficient strategy for individuals that show suboptimal adaptations to resistance training. Thus, studies have to be encouraged to examine the effects of moderate-volume resistance training on muscle hypertrophy low-responders such as ageing people or during diseases. In addition, further studies must investigate the effect of acute/chronic exercise on ribophagy (*i.e.* autophagy-mediated selective engulfment of ribosome for lysosomal degradation) in order to improve our knowledge on the impact of exercise on organelle quality control, especially those implicated in protein synthesis. Because exercise is one of the best approaches to limit atrophy and metabolic diseases, these perspectives are essential in the battle against muscle disorders.

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