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INVITED REVIEW

The development of skeletal muscle hypertrophy through resistance training: the role of muscle damage and muscle protein synthesis

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Abstract

Resistance training (RT)-induced skeletal muscle hypertrophy is a highly intricate process. Despite substantial advances, we are far from understanding exactly how muscle hypertrophy develops during RT. The aim of the present review is to discuss new insights related to the role of skeletal muscle damage and muscle protein synthesis (MPS) in mediating RT-induced hypertrophy. Specifically, the thesis that in the early phase of RT (≤4 previous RT sessions) increases in muscle cross-sectional area are mostly attributable to muscle damage-induced muscle swelling; then (after ~10 sessions), a modest magnitude of muscle hypertrophy ensues; but only during a latter phase of RT (after ~18 sessions) is true muscle hypertrophy observed. We argue that the initial increases in MPS post-RT are likely directed to muscle repair and remodelling due to damage, and do not correlate with eventual muscle hypertrophy induced by several RT weeks. Increases in MPS post-RT session only contribute to muscle hypertrophy after a progressive attenuation of muscle damage, and even more significantly when damage is minimal. Furthermore, RT protocols that do not promote significant muscle damage still induce similar muscle hypertrophy and strength gains compared to conditions that do promote initial muscle damage. Thus, we conclude that muscle damage is not the process that mediates or potentiates RT-induced muscle hypertrophy.

Keywords Skeletal muscle · Resistance exercise · Myofibrillar protein synthesis · Edema · Soreness · Satellite cells

Abbreviations

AMPK	5′ Adenosine monophosphate activated protein kinase
CSA	Cross-sectional area
CK	Creatine kinase
DOMS	Delayed onset muscle soreness
DXA	Dual-energy X-ray absorptiometry
fCSA	Muscle fibre cross-sectional area
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
Mb	Myoglobin
MPB	Muscle protein breakdown
MPS	Muscle protein synthesis
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
MVIC	Maximum voluntary isometric contraction
MyoPS	Myofibrillar protein synthesis
PGC-1α	Peroxisome proliferator activated receptor gamma coactivator 1 alpha
RE	Resistance exercise
RT	Resistance training
SC	Satellite cells
TNF-α	Tumour necrosis factor alpha
US	Ultrasound

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Introduction

Over the years, science has partially unravelled the mechanisms regulating resistance training (RT)-induced muscle hypertrophy; however, we are still far from understanding the processes and the associated interactions determining how muscle hypertrophy is modulated during RT. Muscle hypertrophy is ultimately the result of cumulative periods of positive net protein balance, i.e. muscle protein synthesis

(MPS) exceeding muscle protein breakdown (MPB). Acute resistance exercise (RE) and protein intake potently stimulate rates of MPS, overcoming rates of MPB (Biolo et al. 1997; Phillips et al. 2002). The increase in rates of MPS post-RE is particularly potent at the onset of a RT regimen, due to the high stress imposed by unaccustomed RE (Damas et al. 2015; Tang et al. 2008). This large overall stress is also reflected in the magnitude of muscle damage, which is significantly higher after the first RT session than following later bouts (Damas et al. 2016b; Gibala et al. 2000; Newton et al. 2008). In fact, the magnitude of muscle damage observed at early phases of RT suggests that a large portion of very early (i.e. 1–3-weeks into RT) increases in muscle cross-sectional area (CSA) may be due to edema-induced muscle swelling (Damas et al. 2016c) and not to 'true' hypertrophy (i.e. accumulation of contractile and structural muscle proteins adding sarcomeres in parallel to muscle fibres). Thus, past reports of increases in muscle size very early into a RT regimen (DeFreitas et al. 2011; Seynnes et al. 2007) could have overestimated the magnitude of muscle hypertrophy, as none of these studies attempted to quantify damage-induced muscle swelling. This topic was discussed in our previous publication (Damas et al. 2016c) and in letters to the Editor (Damas et al. 2016d; DeFreitas et al. 2016). Following these publications, several studies have been published (e.g. Buckner et al. 2017; Counts et al. 2017; Damas et al. 2016b; Jenkins et al. 2016, 2017; Stock et al. 2017), advancing the discussion on the number of RT sessions, or time period, required to assess true muscle hypertrophy, with the contribution of edema-induced muscle swelling from muscle damage on muscle CSA taken into consideration.

Muscle damage as a result of the high stress induced by an unaccustomed RE bout could also be a reason why the potent-mixed MPS increases post-first RT session do not correlate with eventual RT-induced muscle hypertrophy (Mayhew et al. 2009). Intriguingly, even acute RE-induced increases in myofibrillar protein synthesis (MyoPS), while potent in the untrained state, fail to correlate with eventual RT-induced muscle hypertrophy (Damas et al. 2016b; Mitchell et al. 2014). However, as RT progresses the overall magnitude of MPS and MyoPS post-RE and associated muscle damage are attenuated (Damas et al. 2015; Tang et al. 2008) and a correlation between the magnitude of MyoPS and eventual increase in muscle CSA develops (Brook et al. 2015; Damas et al. 2016b). Therefore, we suggest that a significant proportion of the initial MyoPS increase is likely directed toward muscle repair and remodelling, and only after attenuation of muscle damage are post-RE increases in MyoPS focused towards muscle hypertrophy. If this is the case, muscle damage is unlikely to mediate RT-induced muscle hypertrophy, challenging the 'no pain-no gain' paradigm. In addition, we also discuss if muscle damage is necessary to occur previously to muscle hypertrophy, i.e. if muscle damage is required to prepare (remodel) muscles for enduring subsequent RT sessions. We acknowledge that other mechanisms are also involved in these events. For example, RT is not only a stimulus for muscle growth, but also for activation, proliferation and differentiation of muscle stem cells [satellite cells (SC)]. Thus, we will discuss the possible roles of SC in response to exercise stress, muscle repair and hypertrophy (Folland and Williams 2007; McKay et al. 2010; O'Reilly et al. 2008; Petrella et al. 2008).

The purpose of the present review was to critically evaluate current and past literature to discuss how repeated RT sessions contribute to the accumulation of myofibrillar proteins in skeletal muscle as well as the role of muscle damage in mediating skeletal muscle hypertrophy.

Exercise-induced muscle damage

The term muscle damage is per se controversial as it encompasses several physiological processes. Muscle damage phenomenon has been studied for over a century, starting with a seminal study in which Hough (1900) described that exercise-induced muscle soreness did not arise from fatigue but from muscle 'injury', possibly involving rupture and inflammation of muscle, connective or nervous tissues. Even after hundreds of studies on the topic, the physiological processes related to exercise-induced muscle damage and remodelling have not been completely elucidated.

Initial RE-induced stress (i.e. in the untrained state) affects muscle homeostasis promoting changes in muscle morphology, such as disturbances in cytoskeleton (e.g. Z-band streaming), loss of sarcomeric structural proteins (e.g. desmin and dystrophin), muscle fibre segmental necrosis, alterations in connective tissue, as well as in T-tubules and sarcoplasmic reticulum (Beaton et al. 2002a; Damas et al. 2016b; Lauritzen et al. 2009; Paulsen et al. 2012). These changes in muscle morphology may occur as a direct consequence of exercise-induced mechanical stress or later due to activation of calcium sensitive degradation pathways and inflammatory response (Hyldahl and Hubal 2014; Nosaka et al. 2003; Paulsen et al. 2012). To assess time course changes in muscle morphology due to damage, small muscle specimens should be obtained through biopsies performed over the course of hours to days. Sequential muscle biopsies cannot be obtained from a single incision site on repeated occasions due to scar tissue formation and inflammatory response due to the biopsy procedure itself. However, the use of different incision sites along the sampled muscle increases data variability, as damage is non-homogeneous along the muscle volume (Beaton et al. 2002b). Therefore, to adequately characterise the magnitude of exercise-induced muscle damage and recovery process, one should also assess associated symptoms (i.e. indirect

markers) such as loss of functional capacity (e.g. decreased muscle strength), edema-induced muscle swelling, delayed onset muscle soreness (DOMS), and muscle protein leakage.

Indirect markers of muscle damage have been widely studied providing a suitable framework to inform training prescription in the athletic setting. For instance, decrements in muscle function (e.g. muscle strength and/or power) have been extensively used in the literature, and postulated as the best indirect marker of muscle damage (Damas et al. 2016a; Faulkner et al. 1992; Proske and Morgan 2001; Warren et al. 1999). Accordingly, decreases in muscle strength are correlated to the level of Z-band streaming after muscle damage-inducing protocols (Raastad et al. 2010), reflecting the magnitude of myofibrillar disruption, inflammation, and necrosis better than any other indirect marker (Paulsen et al. 2012). Additionally, reduced muscle strength is considered as an indicator of extracellular matrix remodelling or failure in excitation–contraction coupling (Hyldahl et al. 2015; Warren et al. 2002). Thus, the magnitude of changes in force-generating capacity after exercise and into recovery allows inferring the overall status of the muscle tissue, and therefore, the magnitude of muscle damage (Damas et al. 2016a; Paulsen et al. 2012). Edema-induced muscle swelling can be estimated by measuring acute changes in limb circumference, muscle thickness or CSA measured by ultrasound (US) or magnetic resonance imaging (MRI) (Chapman et al. 2011; Clarkson and Hubal 2002; Nosaka and Clarkson 1996; Nosaka and Sakamoto 2001). However, the use of these methodologies does not enable the differentiation of edema-induced swelling from true muscle hypertrophy, as absolute changes in muscle size may encompass both processes. A better indirect estimate of edema is generally obtained by the analysis of muscle echo intensity (obtained from a Fast Fourier Transformation of the pixel intensity of the region of interest—ROI—of US images) and MRI T2 relaxation time of the ROI (Nosaka and Sakamoto 2001). This approach enables the detection of changes in muscle fluid content. Echo intensity evaluation involves analyses in the frequency domain of shades of grey (0: black, 256: white) in US images, where low echogenicity (less white areas) indicates normal muscle areas, and high echogenicity (increased white areas) indicates abnormalities in the muscle tissue, such as edema-induced muscle swelling (Damas et al. 2016c). We acknowledge that other factors such as changes in intramuscular fat, connective and fibrous tissues (Arts et al. 2012; Pillen et al. 2009), and intramuscular glycogen (Hill and Millan 2014) can also affect muscle echo intensity, but not likely in a time course in which muscle damage is often measured (e.g. 24–120-h post RE) (Damas et al. 2016c; Nosaka and Clarkson 1996; Nosaka and Sakamoto 2001). For instance, Nosaka and Sakamoto (2001) showed a 120-h time course after eccentric exercise bouts in which there were significant changes in maximal isometric force, range of motion, DOMS, plasma creatine kinase (CK) activity, upper arm circumference, US echo intensity, and MRI T2 relaxation time. Therefore, if increases in muscle US echo intensity are coupled with changes in other markers of exercise-induced muscle damage, especially at an early stage of RT in which muscle damage is usually more pronounced (Chen et al. 2012b; Damas et al. 2016b; Gibala et al. 2000; Newton et al. 2008; Nosaka et al. 1991), one may account for the occurrence of edema-induced muscle swelling. As such, echo intensity evaluations have been extensively used to assess exercise-induced edema in skeletal muscle tissue (Chen et al. 2012a, 2013, 2009; Chen and Nosaka 2006; Damas et al. 2016c; Gonzalez-Izal et al. 2014; Nosaka and Sakamoto 2001; Rosenberg et al. 2014). DOMS is arguably considered the most practical marker of muscle damage, as it can be easily assessed by visual scales in which participants mark their perceived level of muscle soreness in different conditions (i.e. resting, upon movement, or palpation). Conversely, the validity of DOMS as an index of muscle fibre damage has been questioned (Yu et al. 2004). However, it is well accepted that DOMS indicates the occurrence of damage and inflammation on other muscle structures, such as connective tissue (Abraham 1977; Hyldahl and Hubal 2014; Malm et al. 2004; Nosaka et al. 2002; Warren et al. 1999). In addition, leakage of muscle proteins such as CK and myoglobin (Mb) into the blood stream has also been widely used as a muscle damage indirect marker (Chen et al. 2013; Damas et al. 2016b; Nosaka et al. 2005; Sorichter et al. 1999), reflecting increased exercise-induced sarcolemmal permeability. Finally, post-exercise increased levels of some cytokines in the blood stream, such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6, are indicative of an inflammatory response to exercise-induced muscle damage (Conceicao et al. 2012; Peake et al. 2005; Smith et al. 2000). Overall, assessing changes in morphological variables and symptoms seem to be the best strategy to evaluate exercise-induced muscle damage.

Do early increases in muscle cross-sectional area indicate true hypertrophy or mostly edema-induced muscle swelling?

In this section, we discuss current evidence on the number of RT sessions or time-window required to assess true muscle hypertrophy (i.e. accumulation of contractile and structural muscle proteins adding sarcomeres in parallel to muscle fibres, that eventually increases muscle CSA) over the course of a RT regimen. We recently demonstrated that very early on into RT small increases in muscle CSA (~2.7%) are mainly attributed to edema-induced muscle swelling, and not to true muscle hypertrophy. Specifically, we showed that pre-training session (3rd-week of training,

after 4 RT sessions) Vastus lateralis CSA, and its respective echo intensity, increased from baseline (Damas et al. 2016c). These results indicate the presence of edema-induced muscle swelling likely due to muscle damage. These conclusions were corroborated by the detection of elevated Mb and IL-6 plasma levels pre-training session (Damas et al. 2016c), and the lack of change in muscle fibre cross-sectional area (fCSA) (analysed by laminin-stained immunofluorescence of Vastus lateralis muscle biopsies) in the 3rd-week of RT (Damas et al. 2016b). Furthermore, the latter suggests that RT-induced edema was extracellular. Only during the latter stages of RT (10th-week, after 18 RE bouts) did we observe significant increases in fCSA (Damas et al. 2016b). Accordingly, fCSA assessments at the initial phase of a RT program (~4-weeks of RT, ~12 RT sessions) did not indicate muscle fiber hypertrophy, while significant increases were observed only afterwards (after ~7 to 12-weeks of RT, ~21–38 RT sessions) (Goreham et al. 1999; Green et al. 1999; Kadi et al. 2004). It should be noted that a recent study reported significant increases in type II fCSA (not in type I) after only 6 RT sessions (after 2-weeks of RT), but intriguingly, no significant increase in both type II and type I fCSA compared to baseline was observed after 12 RT sessions (after 4-weeks of RT) (Snijders et al. 2016). Thus, the increase in type II fCSA at week 2 could be a false-positive due to measurement error, as fCSA variability can be considerably high (i.e. ~11 to 20%) (Halkjaer-Kristensen and Ingemann-Hansen 1981; Mahon et al. 1984; Tesch 1980; Young et al. 1982). Conversely, analyses after 24 and 36 RT sessions (at weeks 8 and 12, respectively) in the same study showed significant increases in type II and type I (only at week 12) fCSA (Snijders et al. 2016). Overall, it seems that significant fCSA increases can be consistently observed only after ~18–21 RT sessions, performed through 7 to 10-weeks of RT. Given the variability in fCSA measures, it is our opinion that to have a better representation of muscle hypertrophy responses, fCSA analyses should be coupled with whole muscle CSA assessments.

Previous studies have shown increases in whole muscle CSA very early on into RT, i.e. 1–3-weeks (DeFreitas et al. 2011; Seynnes et al. 2007). At first, such findings seem to be consistent with the robust increase in MPS (and MyoPS) observed post-RE in untrained individuals, and the attenuated increase in MPS and MyoPS post-RE observed in trained individuals (Damas et al. 2015, 2016b; Tang et al. 2008). However, it is possible that a significant proportion of the increase in MyoPS post-RE in untrained persons was directed to muscle repair and remodelling, limiting the amount of shared variance (i.e. low association) between initial MyoPS increases post-RE and muscle hypertrophy (Damas et al. 2016b; Mitchell et al. 2014, 2015). Therefore, as past reports did not estimate the contribution of edema-induced muscle swelling promoted by damage to the increases in muscle CSA (DeFreitas et al. 2011; Seynnes et al. 2007), the number of RT sessions or time-window required to detect true muscle hypertrophy remains to be comprehensively elucidated (Damas et al. 2016c, d).

A recent review attempted to describe the time-frame required to assess true muscle hypertrophy, qualitatively interpreting most current reports (Counts et al. 2017). The authors suggest that data showing muscle growth 2–3 weeks into RT are in fact reflecting true muscle hypertrophy, not edema-induced muscle swelling (Counts et al. 2017). However, we interpret evidence in a different direction. For instance, Counts et al. (2017) indicated that in our previous study (i.e. Lixandrao et al. 2016) increases in muscle CSA were detected after 3-weeks of RT. Actually, we showed significant increases in muscle CSA only after 18 RT sessions over the course of 9-weeks of RT (Lixandrao et al. 2016). Furthermore, it is our understanding that to argue towards very early muscle hypertrophy, Counts et al. (2017) rely on (1) studies in which the contribution of edema-induced muscle swelling to the changes in muscle CSA were not taken into account (DeFreitas et al. 2011; Loenneke et al. 2017; Seynnes et al. 2007); and (2) the suggestion by Buckner et al. (2017) that muscle swelling due to edema might be near baseline values by the end of the 1st-week of RT. We present an alternative interpretation based on three main reasons. First, Buckner et al. (2017) based their conclusions on the changes in US muscle thickness over time. Panels A, B, and C on Fig. 2 (p. 218 of Buckner et al. 2017) show that muscle thickness at 50, 60, and 70% of the arm length, respectively, increased after the first exercise bout and were kept elevated throughout the experimental protocol, not returning to baseline. If exercise-induced muscle edema had been abated, one should expect a return to baseline values. Second, the authors did not perform a thorough assessment of exercise-induced muscle edema such as US echo intensity or MRI T2 relaxation time to rule out the presence of edema. Third, at the end of the experimental week, the maximum voluntary isometric contraction (MVIC) torque (in fact over the course of the entire experimental week) was reduced compared to baseline and was significantly different from the control arm, strongly suggesting the presence of muscle damage. Altogether, it is reasonable to suggest that edema-induced muscle swelling due to muscle damage could have contributed at least partially to the increase in US muscle thickness at the end of the 1st experimental week (after 3 RT sessions) in Buckner et al. (2017). We believe that one approach to help solve the problems associated with defining the time course of early muscle hypertrophy would be to conduct a systematic review coupled with a meta-analytic procedure, which is considered the best level of evidence-based inferences (Ackley et al. 2008; Hess 2004; McKeon et al. 2006; Oxford-CEBM 2009; Puddy and Wilkins 2011). The use of a meta-analytic approach would allow determining the

magnitude of early changes in muscle size amongst studies corrected by the edema-induced muscle swelling. Furthermore, a meta-analysis could account for moderators such as type of RT (concentric, eccentric or isoinertial) and, more importantly, the number of RT sessions performed prior to muscle size assessment (i.e. number of previous RT sessions rather than weeks into RT). However, we acknowledge that a thorough systematic review coupled with an adequate meta-analytic approach may not currently be possible, as the number of studies that have adequately accounted for the impact of edema-induced muscle swelling on muscle CSA is very limited.

Other recent reports also have examined changes in RT-induced muscle hypertrophy by US. Jenkins et al. (2016) showed ~ 3.4% of increase in US muscle thickness after only 5 RT sessions (end of week 2), and Jenkins et al. (2017) showed that ~ 8 to 9 RT bouts (end of the week 3) elicited an increase in US muscle thickness of ~ 3%. In both studies, the authors evaluated echo intensity, depicting no change (despite of a trend for significance, $P = 0.08$) in Jenkins et al. (2016), and a reduction in echo intensity in Jenkins et al. (2017) at week 3 and 6. The reason for a decrease in muscle echo intensity early on into RT is currently unclear. In both studies (Jenkins et al. 2016, 2017) subjects were familiarized with the exercise and testing procedures that could attenuate muscle damage (repeated bout effect) before baseline (pre-training) echo intensity measures. Studies have shown that even low intensity and volume isometric, concentric, and eccentric muscle actions can reduce exercise-induced muscle damage (Chen et al. 2012a, b). Thus, the echo intensity measurements at baseline could be biased by the repeated bout effect. The authors did consider the possibility that edema could have influenced their muscle thickness values (Jenkins et al. 2016). Importantly, the reliability of the assessments depicted a coefficient of variation for muscle thickness ranging from 1.58 to 3.17%, suggesting that the reported increase after only 5 RT bouts (Jenkins et al. 2016), or even after ~ 8–9 RT bouts (Jenkins et al. 2017) could be due to random error. Further into RT, the authors showed that muscle thickness increased ~ 7–9% after 10 RT sessions (end of week 4) (Jenkins et al. 2016) and ~ 6 to 7% after ~ 17 to 18 RT bouts (end of week 6) (Jenkins et al. 2017). Thus, after ~ 10–18 RT sessions (~ 4 to 6-weeks of RT) it is reasonable to consider that a significant portion of the reported increases in US muscle thickness is likely due to true muscle hypertrophy. However, it would still be desirable to include other markers, such as Z-band streaming, DOMS, and muscle proteins levels in blood stream, to get a more complete picture of the presence of muscle damage. It should also be noted that in both studies, when muscle strength increased, it was accompanied by positive neural adaptations, which could account for the improvements in muscle function (Jenkins et al. 2016, 2017). Therefore, it is uncertain if the increases in US muscle thickness reported, when considering the measurement error, are functionally relevant.

A very recent study provides some interesting data on the time course of muscle hypertrophy using isolated concentric training coupled with measures of edema-induced muscle swelling (Stock et al. 2017). The authors showed that significant, although small, changes in muscle hypertrophy were achieved after 7–8 bouts (4-week) of concentric-only RT. While using a minimal damaging-eliciting protocol (i.e. concentric-only) is reasonable, it does not mimic a 'real world RT scenario' including both eccentric and concentric muscle actions. Even so, studies with concentric only exercises do show some degree of muscle damage as indicated by Z-band streaming (Gibala et al. 1995) and indirect markers (e.g. muscle strength, limb circumference and DOMS) (Nosaka and Newton 2002). Unfortunately, Stock et al. (2017) did not perform further assessments at 24–48-h after the exercise protocol, which are time-points more prone to depict even small magnitudes of muscle damage (Paulsen et al. 2012). It should also be noted that the concentric peak torque in Stock et al. (2017), which is, therefore, a similar strength test to the muscle action the individuals trained, have not increased at any point of the analyses. These results suggest that neither neural adaptations nor the magnitude of muscle hypertrophy that they reported contributed to increase concentric torque. We acknowledge that the authors show increases in training load through RT (which can be understood as an even 'more specific' indication of strength increases). However, those increases could be (largely) due to neural adaptations early on RT, as most of the early gains in muscle strength can be attributed to neural adaptations (Kamen and Knight 2004; Moritani and deVries 1979; Sale 1988). Thus, one may argue that the magnitude of muscle hypertrophy was small and did not contribute to increase muscle strength, questioning its functional relevance. Finally, in their article (Fig. 3 of Stock et al. (2017)) only 4–6 subjects [out of 13, thus less than half (30–46%) of their sample size] increased arm lean mass, measured by dual-energy X-ray absorptiometry (DXA), at week 4 (when the authors state that significant muscle hypertrophy occurred). It should also be noted that not all subjects increased muscle mass considering all the methods used to assess muscle hypertrophy, with 8 subjects (i.e. ~ 60% of their sample size) demonstrating changes in muscle hypertrophy by their standards. Therefore, it is possible that individual responsiveness to RT can alter the early time course gains in muscle hypertrophy. Overall, the functional relevance and ecological validity of the results can be questioned, but this study provides interesting information on the early time course of muscle hypertrophy applicable to concentric-only training.

Overall, the minimum time for true muscle hypertrophy in a real-world training scenario remains to be determined.

A randomized controlled trial assessing exercise-induced muscle damage, edema-induced muscle swelling, fCSA, and whole muscle CSA several times over the course of a couple weeks using an intra-subject design could shed some light on the time-window required for the occurrence of true hypertrophy. It is important to emphasize that upcoming randomized controlled trials should assess muscle CSA using highly sensitive methods of measurement, such as the MRI [which is the "gold standard" to measure muscle CSA (Ahtiainen et al. 2010)], or US imaging fitting technique (Lixandrao et al. 2014) and peripheral computed tomography scans (Cramer et al. 2007). DXA scans can also be applied for inferences on limbs or whole body lean mass changes. All these methods should be coupled with an adequate indication of the degree of edema-induced muscle swelling and other muscle damage indices, particularly early on (initial weeks) into RT. In addition to whole muscle CSA assessments, it is also advised that future researchers include muscle biopsies to analyse changes in fCSA. We constructed a schematic illustration regarding what we propose best represents the contribution of edema in response to RT to overall changes in CSA and the development of muscle hypertrophy (Fig. 1). We acknowledge that a small magnitude of true muscle hypertrophy does occur early into RT, but the exact number of RT sessions required and the time-window necessary to actually detect the increase in muscle size using available technologies is unknown. The current body of literature shows that: (1) very early increases in muscle CSA promoted by ~4 previous RE are mostly attributable to swelling; (2) around 8–12 previous RT sessions on, a modest magnitude of muscle hypertrophy (~3 to 4% of true hypertrophy) can be detected; and (3) after ~18 RT sessions, performed over 6–10-weeks of RT, are enough to promote true and functionally meaningful muscle hypertrophy (~7–10%).

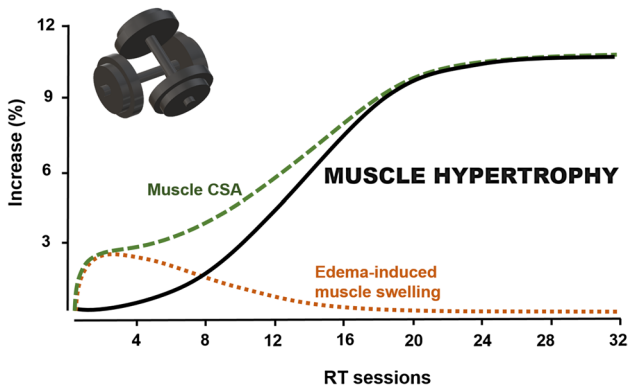

Fig. 1 Schematic representation of the time course of 'true' muscle hypertrophy (i.e. accumulation of contractile and structural muscle proteins adding sarcomeres in parallel to muscle fibres: solid line) with resistance training (RT) practice, considering the increase in muscle cross-sectional area (CSA, dashed line), vs. edema-induced muscle swelling (pointed line)

Modulations on muscle damage and muscle protein synthesis through resistance training and their role determining muscle hypertrophy

Muscle mass is regulated by the net protein balance, i.e. the difference between MPS and MPB. In a resting fasted state, MPB overcomes MPS, resulting in a negative net protein balance. On the other hand, protein ingestion stimulates MPS exceeding MPB, resulting in a positive net protein balance (Biolo et al. 1997; Greenhaff et al. 2008). The dynamic change between post-absorptive and post-prandial rates of MPS/MPB over the day dictates muscle protein turnover, and therefore, the regulation of muscle mass. RE induces acute increases in MPS, but also stimulates MPB (although in a lower extent than MPS), resulting in a still negative net protein balance in a fasted state, but 'less-negative' compared to a rested control (Biolo et al. 1995; Phillips et al. 1997). However, RE when performed prior to protein ingestion potentiates feeding-induced increases in MPS, resulting in a positive state of net protein balance (Biolo et al. 1997; Phillips et al. 2002). As the effect of RE on MPS is much larger than on MPB (Kumar et al. 2009), changes in MPS following RE are considered the primary factor driving protein accretion in muscle tissue (Atherton and Smith 2012; Brook et al. 2015; Glynn et al. 2010; Moore et al. 2009; Phillips et al. 2012). Interestingly, the kinetics of MPS increase after each RT session changes throughout a training program. In an untrained state, MPS peaks later but stays elevated for a longer duration after RE resulting in a greater overall MPS increase post-RE compared to a trained state (Damas et al. 2015; Tang et al. 2008). This greater overall protein synthetic increase in an untrained state could be partially due to the occurrence of muscle damage. Indeed, muscle damage is highest after the 1st RT session but progressively attenuates throughout a RT regimen (Damas et al. 2016b; Gibala et al. 2000; Newton et al. 2008). In fact, one study that assessed muscle damage (i.e. Z-band streaming areas) and MyoPS 4.5- and 8.5-h after performing either eccentric or concentric maximal knee extension exercises matched by total training volume showed that muscle damage elicited by eccentric RE was greater than concentric RE (eccentric: ~ 9.9 areas mm^{-2}, concentric: ~ 1.7 areas mm^{-2}), and promoted a faster increase in MyoPS resulting in a greater overall MyoPS increase post-RE (eccentric: ~ 0.25% and concentric: ~ 0.19%) (Moore et al. 2005). Thus, the greater magnitude of exercise-induced muscle damage was coupled with the larger increase in MyoPS. At first, these results seem to indicate that greater magnitudes of muscle

damage, coupled with higher increases in post-RE MyoPS, would chronically result in larger increases in fCSA (i.e. muscle hypertrophy). Accordingly, one study indicated that fast eccentric exercise promoted a higher magnitude of Z-band streaming when compared to slow eccentric exercise (~185% higher Z-band streaming) after the 1st RT session, and the authors speculated that this difference could be a reason for the greater increase in type II fCSA for the fast vs. the slow group after weeks of RT (Shepstone et al. 2005). However, these speculations were based on muscle damage data obtained after the 1st RT session only, in which muscle damage is the highest. In fact, the magnitude of muscle damage after the 1st RT session could be a reason for disagreement between initial MPS increase and eventual RT-induced muscle hypertrophy (Damas et al. 2016b; Mayhew et al. 2009; Mitchell et al. 2014).

Mayhew et al. (2009) recently showed that the potent increase in mixed MPS after an initial RT bout did not correlate with eventual muscle hypertrophy. Expanding on this work, Wilkinson et al. (2008) demonstrated that both mitochondrial and myofibrillar protein fraction rates increased significantly after the 1st RT session in untrained subjects. It was intriguing that even the increases in MyoPS post-RE in an untrained state did not correlate with eventual muscle hypertrophy after weeks of RT (Damas et al. 2016b; Mitchell et al. 2014). Wilkinson et al. (2008) also demonstrated that after 10-weeks of RT, only MyoPS (not mitochondrial protein synthesis) was elevated post-RE, indicating that protein synthesis response became 'focused' during RT. Similarly, endurance training also results in focused protein synthesis, as only the mitochondrial protein synthesis (not MyoPS) increased post-endurance exercise after 10-weeks of endurance training (Wilkinson et al. 2008). Increased mitochondrial biogenesis seems to be driven by specific signalling transduction pathways, such as increased phosphorylation of 5′ adenosine monophosphate activated protein kinase (AMPK), which in turn stimulates the transcriptional cofactor peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC-1α) (Atherton et al. 2005; Zong et al. 2002). AMPK pathway is triggered by a low ATP:AMP ratio (Aschenbach et al. 2004), which downregulates the activity of the mechanistic target of rapamycin (mTOR) pathway (Bolster et al. 2002). mTOR pathway is related to the activation of protein translation initiation and elongation, key regulatory steps to muscle hypertrophy (Bodine 2006). Altogether, an increased AMPK phosphorylation reduces mTOR activity, which in turn, may dampen muscle hypertrophic response to exercise. However, the relationship between these signalling pathways (AMPK vs. mTOR) is complex and not mutually exclusive. For example, acute endurance exercise increases the phosphorylation not only of AMPK phosphorylation, but also of some down-stream proteins of the mTOR pathway after exercise (Wilkinson et al. 2008). Intriguingly, acute RE can also result in increased phosphorylation of AMPK during and shortly after following exercise. However, ~1-h post-RE, mTOR is up-regulated and ~2-h post-RE, AMPK is down regulated in untrained individuals (Dreyer et al. 2006; Wilkinson et al. 2008). In a trained state, there is evidence that highly RE-trained individuals (9-year of experience) do not increase AMPK phosphorylation after a RE session, a fact also observed in highly trained cyclists (8-year of experience) after an acute bout of cycling exercise. Conversely, when the same trained subjects undertook exercise in their nonfamiliar activity (i.e. cycling exercise for resistance trained subjects, and RE for trained cyclists), AMPK phosphorylation was increased (Coffey et al. 2006). Thus, AMPK phosphorylation seems more related to the impact of exercise stress on muscles rather than exercise mode. More importantly, although endurance exercise was shown to increase phosphorylation of both AMPK and some mTOR pathway proteins, MyoPS did not increase in both the endurance trained (as we commented before) and untrained states (Wilkinson et al. 2008). Thus, an initial RT session can be considered as a more stressful stimulus to muscle stimulating both mitochondrial synthesis and MyoPS [even though, at this point, still not largely contributing to induce muscle hypertrophy (Damas et al. 2016b)]. Nevertheless, with chronic RT, muscle molecular responses to RE become more focused in translating stimulus into training-specific outcomes (e.g. muscle hypertrophy).

Interestingly, muscle adaptation in response to chronic RE stimuli seems to occur early on into RT. We recently demonstrated that after a few RT sessions (i.e. 3rd week of RT), the increase in MyoPS post-RE was attenuated compared to the one found after the 1st RT session, but at this point (week 3), the 48-h integrated MyoPS did correlate with eventual muscle hypertrophy (Damas et al. 2016b). In agreement, Brook et al. (2015) showed that the integrated MyoPS response during the first 3-weeks of RT significantly correlated with muscle hypertrophy. Further into RT (i.e. 10th week), we found strong correlations between the 48-h integrated MyoPS increase post-RE and the chronic increases in fCSA and whole muscle CSA (Damas et al. 2016b). Of note, the focus of MyoPS seems to be concomitant with changes in muscle damage throughout RT. The magnitude of muscle damage is highest after the 1st training bout, but quickly attenuated with RT progression (Chen et al. 2009; Damas et al. 2016b), and virtually non-existent after 10-weeks of RT (Damas et al. 2016b). Thus, we suggest that muscle damage stimulates MyoPS increase post-RE, but requires MyoPS to be directed to muscle repair and remodelling. In fact, when damage was the highest (after the 1st RT session), the level of Z-band streaming tended to correlate with the increase in MyoPS ($r \sim 0.6$, $P = 0.09$) (Damas et al. 2016b). In addition, the potent increase in protein synthetic response in an untrained state is concomitant with an increase in MPB

(Phillips et al. 1999, 2002), which indicates enhanced protein turnover. Increases in protein turnover suggest muscle remodelling due to damage. In fact, Yu et al. (2004) demonstrated that areas of Z-band streaming indicated that new sarcomeres were being added in series to myofibrils. Thus, the potent increase in MyoPS and MPB in the untrained state may mainly be due to a high protein turnover, which contributes to muscle remodelling and the addition of sarcomeres in series (not in parallel, that would result in increased fCSA and muscle CSA). As RT progresses, muscle repair and remodelling diminish, lowering overall protein turnover (Kim et al. 2005; Phillips et al. 1999, 2002; Tang et al. 2008). Accordingly, with the progression of RT, increases in MyoPS and MPB post-RE attenuate, and MyoPS correlates with eventual RT-induced increases in fCSA and muscle CSA, i.e. muscle hypertrophy. Figure 2 provides a theoretical model encompassing the aforementioned processes. Taken together, it is reasonable to suggest that muscle damage neither explains nor potentiates muscle hypertrophic responses [two interesting journal club are recommended to the interested reader on the topic (Keefe and Wright 2016; Smeuninx and McKendry 2016)]. In support of our thesis, several studies have shown no difference in muscle hypertrophy response after weeks of RT between eccentric-only compared with concentric-only RT (Blazevich et al. 2007; Farup et al. 2014b; Moore et al. 2012; Rahbek et al. 2014), despite eccentric RE inducing higher magnitudes of muscle damage after a first RT session (Moore et al. 2005; Nosaka and Newton 2002). We acknowledge that these findings are not universal. There are results showing superior hypertrophy for eccentric-only RT (Farthing and Chilibeck 2003; Hortobagyi et al. 1996), but a study has even reported greater hypertrophy for concentric-only RT (Farup et al. 2014a). A recent systematic review stated that eccentric-only RT is at least as effective in increasing muscle CSA compared to concentric-only or traditional RT (Douglas et al. 2017). Analysing the results of the studies included in Douglas et al. (2017) that measured muscle hypertrophy, the vast majority showed no difference between exercise modes in at least some of the variables used to indicate muscle hypertrophy. Another recent systematic review, which included a meta-analytic approach demonstrated no statistical difference in RT-induced muscle hypertrophy between isolated eccentric and concentric RT (Schoenfeld et al. 2017). Furthermore, despite these contraction modes resulting in distinct muscle damage and MyoPS levels at the onset of RT (Moore et al. 2005), after a small period of exercise habituation (i.e. 3 RT sessions) MyoPS did not differ between eccentric and concentric RE (Rahbek et al. 2014). These results can, at least in part, explain the majority of data pointing to similar RT-induced muscle hypertrophy between contraction modes. Besides muscle hypertrophy, it is worth mentioning that strength gains over weeks of RT are also not potentiated by initial muscle damage (Folland et al. 2001). Overall, we propose that the initial level of muscle damage does not seem to produce significant effects on RT-induced muscle hypertrophy and strength.

Trained individuals require a longer time than untrained ones to produce further relative increases in skeletal muscle size even if the magnitude of MyoPS post-RE was sustained. However, we speculate that even further into training (indicated by 'x', as it is impossible at this point to suggest exactly when) a novel attenuation in MyoPS post-RE may occur (Fig. 2). In this hypothetical model, after several RT

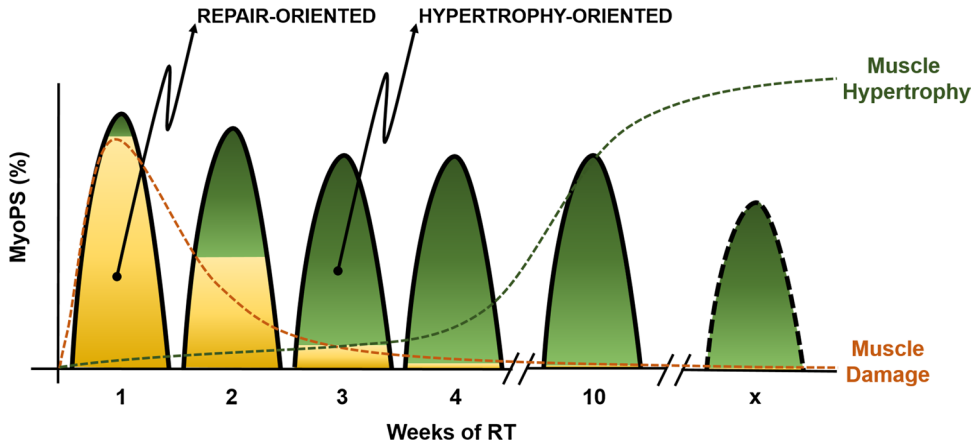

Fig. 2 Schematic representation for the amount of myofibrillar protein synthesis (MyoPS) rate increase post-resistance exercise directed to repair (yellow areas) due to muscle fibre damage (orange dashed line) or to muscle fibre hypertrophy (green areas) throughout resistance training (RT) practice. Cumulative periods of hypertrophy-oriented increases in MyoPS over time results in chronic increase in muscle fibre size (i.e. muscle hypertrophy, green dashed line). Black dashed line at 'x' week of RT: possible new attenuation in MyoPS, which would contribute almost entirely with muscle fibre hypertrophy, but also in line with lower RT-induced hypertrophic adaptations with longer training periods. (Color figure online)

weeks, muscle damage is minimal and MyoPS increase post-RE (though further attenuated) would contribute mostly to muscle hypertrophy. We acknowledge that this model is speculative, as there is no empirical evidence showing a further attenuation in MyoPS with longer RT periods. However, it may partially explain the lower magnitude of muscle hypertrophy observed in trained individuals (Ahtiainen et al. 2005; Brandenburg and Docherty 2002) compared to novice ones (Ahtiainen et al. 2003; Wernbom et al. 2007). For example, Ahtiainen et al. (2003) compared quadriceps CSA increases after 21-weeks of RT in trained and untrained individuals, demonstrating that only the untrained group showed significant muscle hypertrophy, despite the significantly larger training volume of the trained group.

Although muscle damage does not seem to explain or potentiate muscle hypertrophy with RT, it is yet to be determined if muscle damage is necessary to occur to support future gains in muscle mass. In other words, we discuss if muscle damage (in different magnitudes) is required to prepare (remodel) the muscle proteome and architecture to support subsequent RT sessions, which in turn, would promote muscle hypertrophy. Firstly, it should be noted that the occurrence of severe muscle damage, characterized by loss of structural proteins and segmental necrosis, is not required for (actually, it may even jeopardize) muscle hypertrophy. Severe cases of muscle damage impair muscle adaptation to exercise, resulting in delayed recovery of muscle function (in some cases lasting more than 3 to 4-week), necrosis, defective regeneration, incomplete healing, formation of fibrotic scar, or even muscle atrophy (Butterfield 2010; Eriksson et al. 2006; Foley et al. 1999; Lauritzen et al. 2009; Paulsen et al. 2012; Sayers and Clarkson 2001). These highly harmful events can impair athletic performance (as it was shown following several different exercise-induced muscle damage protocols in athletes [e.g. Chen and Nosaka 2006; Doma et al. 2017; Twist and Eston 2009)] and mitigate muscle hypertrophy over time. However, if mild-to-moderate muscle damage is a pre-requisite for future muscle hypertrophy is currently unknown. An interesting study brought some information regarding the importance of DOMS and CK leakage preceding muscle hypertrophy (Flann et al. 2011). Flann et al. (2011) compared muscle hypertrophy after 8-weeks of RT in naive and 'pre-trained' groups (the pre-trained group gradually increased exercise intensity throughout 3 weeks before the 8-weeks RT period). Only the naive group showed increased DOMS and CK levels, especially in response to the 1st RT session, but both groups showed similar muscle hypertrophy after the experimental period. It should be noted that in this experimental design one group trained for 11-weeks (pre-trained) and the other for 8-weeks (naive). The authors attempted to overcome this limitation by adjusting the workloads through the experimental period, to match the final total work between groups. Flann et al. (2011) provide evidence that DOMS and increased CK in the blood are not prerequisites for muscle hypertrophy. Altogether, in a practical standpoint, previous data (Flann et al. 2011) demystify the 'no pain no gain' concept, indicating that 'gain' (muscle hypertrophy), can occur in the absence of 'pain' (DOMS); and our previous data expand this notion showing that actually it is when you feel less 'pain' that you will begin 'gaining' (increases in muscle size) (Damas et al. 2016b). Regarding decreases in muscle strength, Stock et al. (2017) showed that concentric-only training induced a small magnitude of muscle hypertrophy with no decreases in muscle strength measured at 72–96-h after RT sessions. Unfortunately, the aforementioned study did not assess muscle strength at earlier time-points (e.g. 24–48-h) post-RE, which are more prone to present even small levels of muscle damage (Paulsen et al. 2012). Even so, it seems that muscle hypertrophy can occur with minimal or even no disturbance in muscular performance. Altogether, indirect markers of muscle damage such as DOMS, CK leakage to bloodstream or major decreases in strength are not required to precede muscle hypertrophy. Nevertheless, it is currently unknown if changes within muscle fibres (e.g. Z-band streaming) are required to prepare (adapt) muscle to undergo hypertrophy. Data has showed that a small level of Z-band streaming is present when the MyoPS increase post-RE contributes (i.e. correlates) to muscle hypertrophy early into RT, and even in a trained-state (Damas et al. 2016b; Gibala et al. 2000), when MyoPS is mostly directed towards muscle hypertrophy (Damas et al. 2016b). Hence, it is possible that some level of Z-band streaming is necessary to allow adding sarcomeres in series, diminishing stress per sarcomere when muscle lengthens, i.e. preparing (remodelling) muscle tissue to subsequent exercise stress. Nevertheless, as a low-level of remodelling is still present when muscle hypertrophy occurs, it is reasonable to suggest that these processes can happen concomitantly. Even so, this low level of Z-band streaming possibly required to prepare muscle to further stresses, is not necessarily coupled with DOMS, CK leakage into the bloodstream, or large decreases in muscle function. As a comprehensive summary, we constructed a schematic flow chart highlighting main events discussed herein (Fig. 3).

Satellite cells (SC)

Multipotent and mononucleated muscle stem cells, located between the basal lamina and sarcolemma of the muscle are called SC (Mauro 1961). Following stimulation, SC leave the quiescent state, in which 90% of SC express the transcription factor paired-box 7 ($Pax7^+$) and the myogenic factor 5 ($MYF5^+$)—called 'compromised SC'; the remaining 10% are called 'satellite stem cells' ($Pax7^+/MYF5^-$). Compromised SC undergo proliferation expressing myoblast

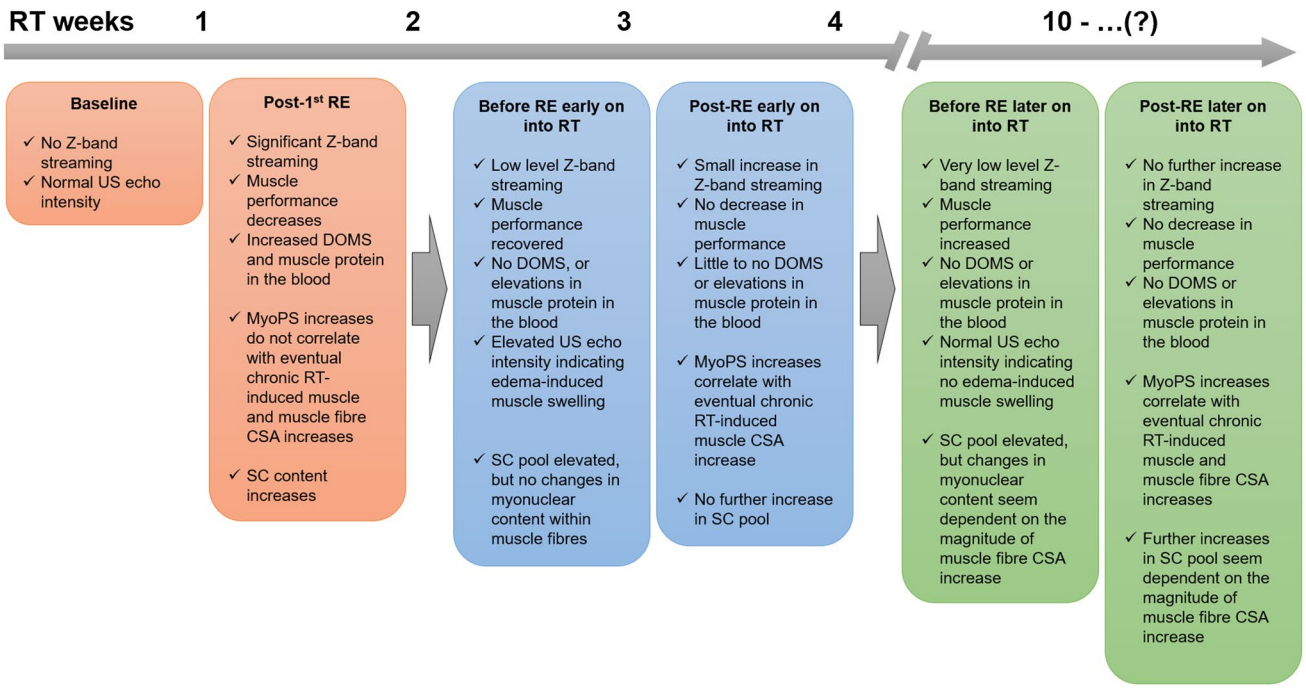

Fig. 3 Flow chart highlighting the main events discussed in this review that are modulated throughout resistance training. *CSA* cross-sectional area, *DOMS* delayed onset muscle soreness, *MyoPS* myofibrillar protein synthesis, *RE* resistance exercise, *RT* resistance training, *SC* satellite cells, *US* ultrasound

determination protein (MyoD) ($Pax7^+/MYF5^+/MYOD^+$) (Wang and Rudnicki 2011). After proliferation, some SC return to a quiescent state ($Pax7^+/MYF5^+/MYOD^-$), replenishing the SC niche (Zammit et al. 2004), or undergo the myogenic cycle, differentiating ($Pax7^-$/myogenin$^+$/myogenic regulatory factor 4, MRF4$^+$) and eventually fuse to muscle fibres, donating their nuclei and increasing transcriptional capacity of muscle fibres (Wang and Rudnicki 2011).

One of the main stimuli to activate SC is muscle damage. Analysing cell cycle using flow cytometry, McKay et al. (2010) showed that 24-h after RE-induced muscle damage there were (1) 32% increase in SC in the G0/G1 phase of the cell cycle (in which SC become active synthesizing mRNA and proteins for subsequent mitosis), (2) 59% increase in SC in the S-phase (synthetic phase, in which SC replicate DNA), and (3) 202% increase in SC number in the G2/M phase of cell cycle (in which protein synthesis and cell growth are highly activated to prepare cells for mitosis, i.e. the last phase of cell cycle before proliferation). RE-induced muscle damage also promotes SC proliferation 24–120-h post-RE (Hyldahl et al. 2014, 2015; McKay et al. 2009; O'Reilly et al. 2008). Expression of differentiation factors (myogenin and MRF4) peaked around 72-h, remaining elevated for at least 120-h after the muscle damaging RE protocols (Beaton et al. 2002a; McKay et al. 2008). The role of SC in severe muscle damage is critical, as SC ablation impairs muscle tissue regeneration after both cardiotoxin-induced (Lepper et al. 2011) and exercise-induced injuries (Sambasivan et al. 2011). However, one possibility is that SC undergo proliferation but do not significantly fuse to muscle fibres, contributing to extracellular matrix deadhesion, disassembly, and remodelling (Hyldahl et al. 2015; Mackey et al. 2011b). SC reside and move inside the extracellular matrix, interacting with connective tissue and fibroblasts (Murphy et al. 2011). In a state of strong extracellular matrix adhesion (e.g. in the absence of muscle damage), SC remain in a quiescent state (Cao et al. 2003), but with extracellular matrix deadhesion [e.g. with exercise-induced muscle damage (Hyldahl et al. 2015)] SC move and proliferate to support tissue remodelling (Murphy-Ullrich 2001; Palecek et al. 1997). Specifically, SC may secrete matrix metalloproteinases and collagens contributing to extracellular matrix deadhesion and remodelling (Alexakis et al. 2007; Guerin and Holland 1995). An interesting study by Hyldahl et al. (2015) demonstrated that immunoreactivity of tenascin-C (protein involved in extracellular matrix deadhesion and remodelling) and SC content increased significantly 48-h after an initial RT session. Before a repeated bout performed 27 days later, collagen I, III and IV (extracellular matrix components) showed increased expression and SC content was maintained, but no further increase in collagens or SC were found 48-h after the repeated bout (Hyldahl et al. 2015). The results suggest that SC play a role in remodelling the extracellular matrix and strengthening the

muscle structure. However, the increased SC content did not result in increased myonuclear content (Hyldahl et al. 2015). Other studies reported maintenance of increased SC pool early on into RT (i.e. 4-weeks) (Kadi et al. 2004), but no increase in myonuclear content during the early phase (2–4-weeks) of RT (Snijders et al. 2016). The reason for the lack of change in myonuclear content early in the RT regimen is uncertain, but may include (1) a small increase in myonuclei that immunohistochemical analyses are not able to detect; (2) a slightly increased myonuclei turnover due to damage; or even (3) SC did not significantly fuse to muscle fibres. Thus, SC pool increase in response to muscle damage possibly supports extracellular matrix remodelling and maintains myonuclei content within muscle fibres. Future studies should confirm these suggestions.

Repeated RE sessions (i.e. RT) maintain an increased SC content over time (Mackey et al. 2011c; Snijders et al. 2016), possibly as an anticipatory mechanism to support future stressful events (Hyldahl et al. 2015; Paulsen et al. 2012; Sambasivan et al. 2011). Nevertheless, whether further acute increases in SC pool occur in a trained state are controversial. While Nederveen et al. (2017) showed that SC content increased acutely post-RE after 16-weeks of RT, recent findings from our group indicate no further acute SC pool expansion after 10-weeks of RT (Damas et al. under review). This disagreement could be due to the magnitude of fCSA increase, as Nederveen et al. (2017) showed ~ 34 and ~ 13% increases in type II and type I fCSA, respectively, whereas we showed ~ 16 and ~ 8% increases in type II and I fCSA, respectively (Damas et al. under review). Thus, it seems that larger magnitudes of muscle fibre hypertrophy are required to induce novel acute increases in SC in a trained state. Large magnitudes of muscle fibre hypertrophy due to continued RT also appear to induce an increase in myonuclear content in muscle fibres donated by differentiated SC. The exact role of SC in muscle hypertrophy has been previously debated (McCarthy and Esser 2007; O'Connor and Pavlath 2007) and revisited more recently (Egner et al. 2016; McCarthy et al. 2017). In humans, there is evidence indicating that at the onset of muscle hypertrophy pre-existing myonuclei would expand transcriptional capacity supporting initial muscle fibre growth, and when the volume of fibre cytoplasm becomes too large to be controlled by previous myonuclei, SC would donate their nuclei to muscle fibres (Andersen et al. 2009; Bamman et al. 2017; Kadi et al. 2004; Mackey et al. 2011a; Petrella et al. 2006). Specifically, studies have proposed that increases in muscle fibre size over ~ 26% (not lower than 15%) require nuclei donation from SC (Kadi et al. 2004), since myonuclei domain [DNA unit (Cheek 1985)] increased beyond a given limit than pre-existing myonuclei can control (Bamman et al. 2017; Petrella et al. 2006). In agreement with this theory, previous reports indicated that increases in fCSA below 26% did not increase myonuclear content (Andersen et al. 2009; Mackey et al. 2011a); while others showed that larger muscle fibre hypertrophy (> 27%) was concomitant with a myonuclear content increase (Petrella et al. 2006, 2008; Snijders et al. 2016). Nonetheless, there are reports showing myonuclei addition with lower than the suggested level of fCSA increase (i.e. 26%). For instance, Bellamy et al. (2014) and Snijders et al. (2016) showed 14–18% increase in type I fCSA after 12–16-weeks of RT concomitantly to increases in myonuclear content. However, considering type II fCSA, it seems that increases in fibre size have to reach ~ 40% to induce changes in myonuclear content (i.e. significant increases in type II fCSA of ~ 18% at week 2 and ~ 25% at week 8 were not accompanied by increases in myonuclear number) (Snijders et al. 2016). To establish whether the limit of 26% is strict or if different types of muscle fibres should be considered separately [both studies that proposed a ceiling limit for myonuclei addition used mixed muscle fibres (Kadi et al. 2004; Petrella et al. 2006)], additional controlled trials and meta-analyses considering the magnitude of RT-induced fCSA increase of different muscle fibre types and myonuclei addition from SC are needed.

Overall, SC are involved in repairing skeletal muscle following exercise-induced damage, and we propose: if damage is severe, SC differentiate and aid tissue regeneration; if damage is mild-to-moderate, SC could contribute to (maybe) slightly elevated myonuclei turnover and muscle extracellular components remodelling. Chronic repetition of RE will maintain SC elevation, replenishing SC niche and enhancing myogenic capacity for future stressful events or muscle fibre hypertrophy. In a trained state, large magnitudes of muscle fibre hypertrophy due to continued RT seem to be required to induce both novel acute increases in SC post-RE and chronic augments in myonuclear content. Figure 3 also includes a summary regarding changes in SC pool and myonuclear content throughout RT.

Conclusions

The precise number of RT sessions or time frame necessary to achieve true hypertrophy is still debatable, but to this date we can infer that (1) increases in muscle CSA promoted by ~ 4 RT sessions are mostly attributable to edema-induced muscle swelling; (2) only after approximately 8–12 RT sessions, a modest magnitude of muscle hypertrophy can be detected; and (3) ~ 18 RT sessions, performed over 6–10-weeks of RT, seem to promote significant muscle hypertrophy.

Initial RT-induced muscle damage possibly drives MyoPS towards muscle remodelling, not hypertrophy. Both muscle damage and MyoPS are attenuated early on into RT, even when considering distinct magnitudes of initial damage.

With the progressive decrease of muscle damage throughout RT (repeated bout effect), the increases in MyoPS after each RT bout may contribute to increases in muscle mass. Especially in a trained state, in which muscle damage is minimal, MyoPS increase post-RE strongly correlates with muscle hypertrophy promoted by weeks of RT. Finally, RE protocols that do not promote significant muscle damage at RT onset, still induces similar muscle hypertrophy and strength gains over time, when compared to conditions that promoted significant initial muscle damage. Thus, although initial muscle damage (if not severe) does not seem to impair muscle hypertrophy induced by weeks of RT, we propose that muscle damage neither explains nor potentiates increases in fCSA and muscle CSA, thus should not be considered as a determinant factor for RT-induced muscle hypertrophy.

SC have a major role in tissue repair after the occurrence of muscle damage, probably with different roles according to the severity of RE-induced muscle damage. RT maintains SC content elevation, replenishing SC niche and enhancing myogenic capacity. Novel acute increases in SC content post-RE in a trained state and chronic augments in myonuclei number within muscle fibres appear to be dependent on the magnitude of RT-induced fCSA increase.

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Author contributions FD, CAL and CU wrote, reviewed and approved the final content of the manuscript.

Compliance with ethical standards

Conflict of interest The authors do not have any conflicts of interest financial or otherwise to declare.

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