Resistance training and hypertrophy

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INTRODUCTION

Muscle mass in power athletes is notably crucial for performance as force (strength) is proportional to the cross-sectional area (CSA) of a muscle. Athletes train to induce skeletal muscle hypertrophy for this reason. For hypertrophy to occur, we have adapted the ability to respond to resistance training. There is compelling evidence seen in resistance training regarding mechanical loading and the relationship of hypertrophy (1, 2). Heavy loading had been suggested to be the key stimulus, but new research suggests lower loads consisting of 30% of a one repetition maximum until fatigue was able to maximize hypertrophy signalling (1). There are numerous mechanical stimuli and sensors that work directly, or indirectly in pathways that are essential for hypertrophy (3). These stimuli are responsible for initiating signal transduction to other regulators such as IGF-1, inducing protein synthesis through mTORC1, and cell proliferation through hippo signalling (3). Ones that will be discussed further include; component and regulatory mechanism in mTORC1 of rapamycin target and filamin-C-bag3 respectively. Some uncompelling evidence of costamere-related mechanism and restricting blood flow during resistance training that are yet to be fully understood. In addition, I will also be discussing the benefits of hypertrophy that are unrelated to preformance but overall human health.

mTORC1 AND PROTEIN SYNTHESIS

Protein synthesis is essential building block in muscle growth. Compelling evidence had suggested that the primary regulator of protein synthesis induced by resistance exercise is mediated by mTORC1 (4, 5). To determine

if this was essential, a study had treated participants with rapamycin, an inhibitor of mTORC1 (6). The participants then preformed various resistance exercises to induce contraction mediated protein synthesis (6). They had seen early (1-2 hours) blockage of protein synthesis, resulting in a 40% reduction (6). Rapamycin had also inhibited translation elongation by blocking downstream signals of S6K1 phosphorylation and eEF2 phosphorylation (6). During recovery rapamycin had further affected protein synthases by decreasing RAPTOR ability to bind within the mTORC1 (6). They had concluded that mTORC1 activation along with ERK1/2 stimulation is essential for maximal protein synthesis (6). Therefore, mTORC1 and ERK1/2 are responsible for stimulating hypertrophy from resistance exercise.

COSTAMERES-RELATED PROTEINS

Costameres are associated with muscle fibre Z-discs and provide structural importance as they permit the connection between the sarcomere and cell membrane (3). Ultimately, this allows force to be transmitted between the two. Myopathies (Duchenne) are commonly associated with mutations seen in costamere genes (DMD gene) and tell us the importance costamere proteins play in normally functioning muscles (7). Which give rise to their muscle equivalents, focal adhesions. Focal adhesions connect the extracellular matrix to the cytoskeleton and facilitate anchor cells to a substrate.

Focal adhesion kinase (FAK) aids in the movement of these focal adhesions to a substrate. Due to evidence found in a previous *in vivo* study concluded that FAK was a requirement for IGF-1 signalling for hypertrophy, a new study

was interested in whether FAK activity could be increased by resistance training (8). Participants had performed eccentric and concentric exercises with the vastus lateralis (4 sets of 10 reps.) (9). There was no evidence to suggest a link between FAK activity and resistance training as FAK activity did not increase during exercise (9). However, FAK did increase an hour post exercise in the eccentric trials (9). Although FAK functions in IGF-1 signalling to induce hypertrophy there may not be any further contributions with resistance exercise.

Phospholipases associated focal adhesions are evidently shown to convert PIP2 to phosphatidic acid this synthesis is catalyzed by C γ1 (10). Which in turn activated effectors in the hippo signalling pathway, Yap and Taz (10). This is responsible for regulating gene expression and cell proliferation through satellite cells (10). Therefore, an increase in Yap induced by resistance exercise is shown to play a role within type II muscle fibres to promote hypertrophy through hippo-signalling (10). In addition, Yap may also play a role in protein synthesis. A study had shown Yap inhibiting an inhibitor of mTORC1, Pten (11). To further mediate protein synthesis Yap also played a role in encoding an amino acid transporter (Lat1) (11). Therefore, not only does resistance training stimulate focal adhesions to cascade events to activate Yap to mediate cell proliferation but also induces mTORC1 activity for protein synthesis. Both cell proliferation through hippo signalling and protein synthesis through mTORC1 are responsible for resistance exercise induced hypertrophy. However, little is known about the underlying mechanism in the increase phospholipases to induce phosphatidic acid.

Phospholipase may be a downstream effect of resistance exercise and not the direct stimulus (10).

Integrins have been shown in mice to be related to an increase in muscle mass (12). Overexpression of α7β1-integrin isoform contributed to larger muscle fibre size after resistance training (12). In addition, it was seen that a downstream mTORC1 target had increased phosphorylation (12). The study concluded that integrins may contribute to hypertrophy in an unknown mechanism and protein synthesis by activating mTORC1 pathways during resistance training (12). However, this evidence may not be enough to conclude a distinct association of integrins stimulated by resistance exercise to increase hypertrophy.

FILAMIN-C BAG3

Mutations within proteins of filamin-C and Bag3 cause muscular diseases (13). This shows the importance of these proteins regarding muscle function (13). Filamin-C and Bag3 are responsible for activating protein synthesis, cell proliferation, and autophagy through mTORC1, effector Yap in hippo-signalling and chaperone-assisted selective autophagy (CASA) to have hypertrophic activity from resistance exercise (14, 15, 16). Studies show an increase in concentration of both filamin-C and Bag3 in the muscle after resistance exercise (14). During resistance training it was shown that Bag3 influences protein synthesis through mTORC1 signalling as its (Bag3) WW domain binds with an inhibitor of mTORC1, TSC1 (14). This leads to the activation of mTORC1 (14). Bag3 has a similar effect on LATs1 and AMOTL1 in hippo signalling (15). The WW domain also binds with these proteins to

sequester their inhibition on Yap, therefore activating hippo-signalling to increase cell proliferation within muscle fibres (16). Lastly, during autophagy when there is damage to the Z-disc proteins (CASA) which is inevitable during resistance training, Bag3 binds to synaptopodin-2 to regulate CASA (16). Studies have shown this to be related to induced autophagy and amino acid accumulation (through the breakdown of proteins) which is essential for hypertrophy in muscle (16). Therefore, filamin C and Bag3 show their role in hypertrophic response due to resistance exercise through protein synthesis, cell proliferation and autophagy.

RESTRICTING BLOOD FLOW DURIING RESISTANCE TRAINING

Compelling studies have shown a low-load resistance training with local restriction of blood flow had induced muscle hypertrophy (17, 18). It is known that blood restriction affects muscle metabolism, and this is thought to lead a metabolite stress that signals anabolic pathways to induce hypertrophy (18). Such as reactive oxidative species that affect mitochondrial biogenesis. A recent study had their participants endure an entire hypoxic body environment during resistance training (18). The study consisting of 14 university males had performed 4 sets of 10 repetitions of elbow extension and flexion at 70% of their one repetition maximum (18). Data showed significant increase in muscle mass of those who trained in hypoxic states than the control group (18). Therefore, this study concluded hypoxia improved hypertrophy during resistance training (18). They had further concluded that accumulation of metabolites seen with hypoxia could be more beneficially in maximizing muscle mass than high load resistance

(18). Additional studies should be performed to conclude optimization of muscle growth through hypoxia.

OVERALL HEALTH

Hypertrophy in response to resistance training is not only beneficially to strength and performance but also seen to be good for human health (19). In a cohort perspective intervention, half a million people were analysed to see if grip strength enhanced overall health by comparing it to occurrence of disease incidence and mortality (19). There was a slight correlation with low grip hand strength and higher risk of disease-specific incidence (19). However, more studies should be performed to distinguish this relationship as this perspective study does not prove causality.

CONCLUSION

In conclusion we can see that there are several mechanical pathways that sensor resistance training to stimulate hypertrophy in skeletal muscle. We also see a fully functioning hypertrophic response can be achieved due to protein synthesis (mTORC1and ERK1/2), cell proliferation and satellite cells (hippo-signalling) and autophagy. Mechanical sensors underlying the first in line steps to hypertrophy include, costamere-related proteins such as FAK, integrin, and phospholipases associated focal adhesions. Filamin-C and Bag3 that increase with resistance training and influence mTORC1, Yap and increases autophagy. Lastly, hypoxic environments were seen to increase hypertrophy in response to resistance exercise.

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