# Theory

Resistance training is performed with the purpose to increase performance in sporting competitions or to improve health or well-being in daily life. Specifically, resistance training improves muscular strength, size and power in order to enhance athletic performance as results from morphological and neural adaptations,well as a mean to achieve health improvements through blood pressure, improve glucose tolerance, insulin sensitivity (Folland, Williams, 2007; Kraemer, Raramess, French, 2002). Much of the beneficial effects of resistance training on athletic performance and well-being are due to training-induced muscle hypertrophy. Hypertrophy is affected by protein synthesis and protein breakdown and can only occur through a positive net balance of proteins (Biolo, et at. 1995; Kumar, et al. 2009; Ogawa, et al. 2006; Tipton, Wolfe, 2001). If the net balance is in a negative state, protein breakdown exceeds protein syntheses which lead to muscle loss (Biolo, et at. 1995; Kumar, et al. 2009; Tipton, Wolfe, 2001). This process of breakdown and synthesis of protein structures is determined by protein turnover. Protein turnover is affected by catabolic and anabolic stimuli which respectively controls the rate of breakdown and synthesis. Resistance exercise elevates both mechanism of protein synthesis and protein breakdown and it is the fractional rate between those two that determine an increase or reduction in muscle mass (Philips, et al. 1997; 2002). Ingestion of protein and carbohydrate increases the rate of syntheses and blunt protein breakdown (Biolo, et al. 1995). Co-ingestion of carbohydrates and amino acids surrounding resistance training can blunt protein breakdown (Beelan, et al, 2008; Roy, et al. 1997). MuRF1 is an E3 ligase in the ubiquitin proteasome pathway that is myofibrillar specific and high levels of insulin can blunt E3 ligases through phosphorylation by Akt/PKB.

Hypertrophy and protein turnover

On a cellular level, actin and myosin are the primary proteins that increases in size and results in muscle hypertrophy (Levers, et al. 2015). To induce this response there are two major signaling pathways, insulin-like growth factor 1 (IGF-1), which upregulate phospoinositide-3-kinase-Akt (Akt) and protein kinase B-mammalian target of rapamycin (mTOR) (Schiaffino, et al. 2013). The other pathway that regulates muscle mass is myostain-Smad3 that acts as a negative regulator that works as a co-operator for upregulation of protein breakdown (Peris-Moreno, et al. 2020; Schiaffino, et al. 2013). Protein turnover is an important factor that plays a role in maximizing adaptions to training and muscular growth can only occur through a positive net balance of amino acids (Biolo, et at. 1995; Kumar, et al. 2009; Tipton, Wolfe, 2001). Studies shows that protein synthesis is elevated up to 48 hours as an effect of resistance exercise, while protein breakdown is only elevated for up to 24 hours before returning to baseline values (Philips et al. 1997;2002; Yang, et al. 2006) Proteins supplements is often used to provide sufficient amino acids to ensure this positive net balance (Macnaughton, et al. 2014; Tipton, et al. 1999), but chronic inactivity leads to elevated markers of protein breakdown, even with a normal dietary intake (Ogawa, et al. 2006). This fact demonstrates that nutrition alone cannot improve protein turnover to a positive state. This way, resistance exercise may contribute to protein turnover and nutrition status will determine if the net balance is in favor for synthesis or breakdown (Macnaughton, et al. 2014; Philips, et al. 1997). There has been question if inhibiting protein breakdown during resistance exercise can further increase the net gain of proteins. This might be due to increased insulin levels which acutely activates IGF-1 pathway, upregulate Akt and mTOR, which in turn upregulates protein synthesis but also downregulates pathways for muscle protein breakdown (Peris-Moreno, et al. 2020; Yoon, 2017).

Protein degradation and ubiquitination

Proteolysis is a fundamental biological process providing amino acids for synthesis to vital organs, tissue, repairing and remodeling (Alberts, et al. 2019; Pasiakos, Carbone, 2014). Proteases are enzymes that control proteolysis, which hydrolyze peptide bonds, splitting them into smaller chains and then into individual amino acids (Alberts, et al. 2019; McArdle, Katch, Katch, 2015). Proteasomes are protein complexes that degrades proteins (Alberts, et al. 2019). Proteasomes resides in the cytosol and nucleus within the cell, in a cylindric form made from proteases (Alberts, et al. 2019). Proteasomes unfolds protein complexes marked for degradation by ubiquitin, and cuts them into short peptides (Alberts, et al. 2019). There are three pathways that degrades protein; autophagy, calpain calcium dependent cysteine protease and the ubiquitin proteasomal pathway (Tipton, et al. 2018) In skeletal muscle protein degradation is regulated primarily by the ubiquitin proteasome pathway (UPP) (Myung, Kim, Crews, 2001). The ubiquitin function as a marker that target cytosolic and nuclear proteins for rapid breakdown (Myung, Kim, Crews, 2001). When a protein is tagged with ubiquitin, the ubiquitinated protein enters the proteasome and degrades into smaller peptide units (McArdle, Katch, Katch, 2015). When a protein is set for degrading, tagged with ubiquitin, the ubiquitin conjugating cascade (carboxyl group of Gly-76) is activated by ubiquitin-activating enzyme (E1) (Myung, Kim, Crews, 2001). The activated ubiquitin is then transferred to a thiol group of an activated site Cys residue (E2) by transacylation reaction (Myung, Kim, Crews, 2001). Then the ubiquitin attaches to protein substrate directly by itself, with E2, or together with ubiquitin ligases, (E3) (Myung, Kim, Crews, 2001). It is believed that proteins with specific types E2 and E3 recognize specific proteins set for degradation (Myung, Kim, Crews, 2001).

In 2001, two papers identified two E3 ligases associated with muscle atrophy; Trim63 also known as muscle RING finger 1 (MuRF1) and FBX032 (MAFbx/astrogin 1) (Bodine, 2001; Gomes, et al. 2001). MuRF1 is ligases associate with skeletal muscle atrophy and is believed to be the main regulator for muscle mass through the FoxO families (Ogawa, et al. 2006; Peris-Moreno, et al. 2020). The current belief is that MuRF1 binds to titin located at the M-line where it has access to myosin and actin, to facilitate breakdown of myofibrillas (Peris-Moreno, et al. 2020). In skeletal muscle, MuRF1 is elevated under a fasted or/and physical inactive state and resistance exercise has shown to reduce the mRNA expression of MuRF1 (Mascher, et al. 2008; Ogawa, et al 2006). When FoxO is knocked out in mice, it has shown to lead to muscle sparing and blunting insulin signalling Akt, concluding that MuRF1 is highly important for regulation of muscle mass (O’Neill, et al. 2018). When blood glucose increases, insulin is released and inhibits protein breakdown through Akt and mTOR, which downregulates FoxO families (Peris-Moreno, et al. 2020;). In addition to inhibiting protein breakdown trough Akt, it has been hypothesized that insulin inhibits the activation of AMPK which stimulates the expression of MuRF1 (Deng, et al. 2015).

There seems to be two nutritional ways that lead to muscle hypertrophy, one is to use nutrition and anabolic stimuli to upregulate IGF-1 pathway to maximize protein synthesis, and to use glucose surrounding exercise to increase insulin level maximizing downregulation of protein breakdown.

Nutrition supplements blunts MuRF1.   
Ingestion of amino acids through a protein rich meal or supplement stimulates muscle protein synthesis (Miller, 2007) and ingesting 40 grams (g) of essential amino acids after resistance exercise is sufficient to accelerate protein synthesis (Macnaughton, et al. 2014). When ingesting 100 grams of carbohydrates after resistance training, the net protein balance improves mainly through reduction in breakdown but did not reach positive net balance for synthesis (Børsheim, et al, 2004). With a normal nutrition intake, ingesting carbohydrate and protein supplements during resistance exercise improves whole body protein synthesis (Beelen, et al. 2010). The timing of ingesting carbohydrates may be an important factor to minimize markers for protein breakdown. When co-ingesting supplements after resistance exercise, markers for protein breakdown are only modestly reduced (Glynn, et al. 2010). Ingesting a mixture of amino acids and carbohydrates after resistance exercise decreases the rate of protein breakdown (Beelen, et al. 2008; Borsheim, et al. 2004; Kume, et al. 2020; Roy, et al. 1997) and ingesting supplements right after training has shown to decrease markers for protein breakdown in urinary samples compared to ingesting nutrients before training session (Kume, et al. 2020). When co-ingesting carbohydrates and essential amino acids between exercise sets, markers for protein breakdown in myofibrillas attenuates (Bird, S. P., Tarpenning, K. M., Marino, F. E., 2006).   
Different methods have been used to measure protein breakdown. Urinary 3-methylhistidine can be a good measurement for studies on muscle proteolysis when it is residues from actin and myosin, but participant must be under strict dietary control when measurements of degrading proteins can be from animal meat (Pasiakos, Carbone, 2014). Another method is to measure AV balance and stable isotope tracee release, but it requires trained personnel and equipment less available and does not measure protein degradation per se. (Pasiakos, Carbone, 2014). QRT-PCR and Western blotting is methods used to establish messenger RNA (mRNA) and protein expression, respectively, obtained from muscle biopsies (Pasiakos, Carbone, 2014). While this method does not represent cumulative changes over time and an increase in mRNA expression does not always indicate an increase in the specific pathway (Pasiakos, Carbone, 2014; Tipton, et al. 2018), it can provide snapshots of physiological changes (Pasiakos, Carbone, 2014). This is an important note, when studies have found 1:1 rna-protein.To establish the participants changes in MuRF1 expression in this study, western blotting for protein content in vastus lateralis has been used.

Resistance exercise increases glucose uptake and blood flow

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This study will examine muscle protein breakdown after resistance training while ingesting glucose during training session by measuring MuRF1 content in vastus lateralis.

(Glynn, et al. 2010). Nonetheless, ingesting essential amino acids improve the positive net balance ingested postexercise (Glynn, et al. 2010).). This leads to the question if timing of nutrition can have an impact on protein breakdown.

Co-ingestion of carbohydrates and amino acid supplements surrounding resistance training has the ability to blunt markers of Murf1()

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