



Editorial Article

Cellular and Molecular Exercise Physiology: Historical Perspective for the Discovery of Mechanisms Contributing to Skeletal Muscle Adaptation

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Abstract

Cellular and molecular exercise physiology is the study of the underlying regulatory mechanisms that underpin physiological adaptation to exercise. In this historical perspective, I explain how the field emerged following advancements in technology within the molecular biology field in general and as a result of some exciting forward thinking by the leading exercise biochemists of the time. I also discuss the important advancements in elucidating the mechanisms underlying physiological adaptation to exercise using genetic knockout, overexpression and compensatory hypertrophy models in animals, that subsequently enabled the translation and future study of key mechanisms that underpin human exercise adaptation. This historical perspective also helps decipher the important studies that pioneered the investigation of the cellular signaling networks controlling gene expression in response to acute and chronic exercise, the role of satellite cells in repair of skeletal muscle after exercise and finally how the important topic of exercise genetics/genomics emerged within the cellular and molecular exercise physiology field. Finally, the manuscript identifies that the integration of epigenetics and proteomics to compliment current genome-wide approaches (profiling of heritable genetic variants and gene expression) are likely to play an important role in uncovering the cellular and molecular regulation of exercise adaptation into the next generation.

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Introduction

Cellular and molecular exercise physiology is the study of the regulatory molecular mechanisms that lead to physiological adaptation following exercise. The field is focused particularly at the level of the molecule/cell and investigates how the microscopic responses to exercise ultimately lead to adaptation at the whole tissue and systems level. Broadly, three common themes have emerged within this field and include: 1) How the environmental 'stressor' of exercise modulates the abundance and activity of extra- and intra-cellular signaling networks, leading to the turning on/off of genes (e.g. mRNA levels) and their proteins and culminating in phenotypic changes at the cellular or tissue level. 2) The role of heritable genetic traits and their associated influence on the physiological response to exercise, and; 3) The role of the satellite cells in the repair and regeneration of muscle after exercise induced damage. The majority of these regulatory mechanisms are studied in blood and skeletal muscle tissue and/or isolated satellite cells and sometimes adipose tissue, albeit to a lesser extent than muscle tissue. This is due to the relative ease of sampling of blood and the ever-increasing availability of skeletal muscle biopsy

sampling in human participants and/or patients. Therefore, this editorial provides a historical perspective of the major research that has contributed to the emergence of cellular and molecular physiology as a field, with a particular focus on the discovery of mechanisms that lead to skeletal muscle adaptation.

History of exercise biochemistry and origins of cellular and molecular exercise physiology

The first use of human skeletal muscle biopsy techniques to study exercise adaptation in humans at the biochemical level was by Bergstrom in 1962, publishing the paper 'Electrolytes in Man' (Bergström, 1962). In 1966 Bergstrom and Hultman were the first to measure glycogen synthesis from human muscle after exercise to exhaustion (Ahlborg et al., 1967; Bergström and Hultman, 1966). Bergstrom and Saltin in 1967 also assessed muscle glycogen in the quadriceps of both trained and untrained males and after different starting nutritional backgrounds (e.g. high carbohydrate/high protein) (Bergström et al., 1967; Hermansen et al., 1967). This work was followed by Costill in 1971, who extended biopsy measurements for muscle glycogen to the gastrocnemius and soleus (as well as



quadriceps) after exhaustive running and following multiple bouts of exercise (Costill et al., 1971a; Costill et al., 1971b). Exercise biochemistry was therefore the first discipline attempting to understand some of the changes to biochemical parameters following acute and repeated exercise. In this era, exercise biochemistry was primarily the study of metabolites and protein activity using, exciting novel methodologies that are now taken for granted, such as; enzyme based assays, spectrophotometric and fluorometric analyses together with histological measurements. However, even prior to this work in human muscle, Gollnick's seminal work in 1961 applied exercise biochemistry in rodent model systems to investigate the regulation of ATP and LDH activity in heart and skeletal muscle tissue following exercise (Gollnick and Hearn, 1961; Hearn and Gollnick, 1961). Holloszy also pioneered the early exercise biochemistry field by looking at biochemical enzyme activity associated with mitochondrial adaptation to aerobic exercise in rats (Holloszy, 1967). Booth together with Holloszy (Baldwin et al., 1975; Booth and Holloszy, 1977; Holloszy and Booth, 1976) extended this earlier work in more detail over the ensuing decade, studying in detail the biochemical adaptation to exercise (Booth, 1978; Krieger et al., 1980; Morrison et al., 1989; Tucker et al., 1981). Pertinent examples came from Watson, Stein and Booth who undertook the first work into changes at the gene (mRNA) expression (predating polymerase chain reaction methods) investigating alpha-actin mRNA after muscle immobilization using dot-blot hybridization of radioactive p³²-labelled plasmids containing the alpha actin cDNA on nitrocellulose membranes (Watson et al., 1984). They subsequently went on to investigate alpha-actin and cytochrome C mRNA expression following both exercise and immobilization in rats (Booth et al., 1987; Booth and Watson, 1985; Morrison et al., 1989; Morrison et al., 1987). Frank Booth also undertook some of the first work on muscle protein synthesis (Booth and Seider, 1979) and degradation (Seider et al., 1980) later combining these with adaptation at the biochemical and gene expression level (Wong and Booth, 1990a; Wong and Booth, 1990b). It was here that early exercise biochemists laid the basis for a field that would soon emerge, leading Booth to his postulation within the literature of a specific field called 'cellular and molecular exercise physiology' (Babij and Booth, 1988; Booth, 1988; Booth, 1989; Booth and Thomason, 1991). With the advent of polymerase chain reaction (PCR) to amplify RNA and DNA templates by Mullis in the late 1980's (leading to the Nobel prize in chemistry in 1993), this made gene expression analysis more sensitive, rapid, accurate and enabled higher throughput within the molecular biology field (Mullis and Faloona, 1987; Saiki et al., 1985). Importantly, Booth's lab was also one of the first to simultaneously undertake direct gene transfer into the skeletal muscle of live rodents (Thomason and Booth, 1990; Wolff et al., 1990), altering the gene expression of candidate genes enabling a powerful model to mechanistically ratify (or even refute) the role of specific genes in exercise adaptation. Gene knock-down and overexpression models are discussed below in this editorial.

Non-human mammalian models of exercise adaptation kick started our understanding in humans

The majority of work within cellular and molecular exercise physiology in humans is undertaken in skeletal muscle tissue due to the routine use of human skeletal muscle biopsies. However, non-human mammalian models, predominantly using rodents, have paved the way and continue to provide key mechanistic insights to understand molecular adaptation to exercise via the use of gene knock out (KO) and transgenic (overexpression) models that are unavailable in human studies due to ethical reasons. This type of Nobel prize winning work has been available since the 1980s following original pioneering

work by Capecchi, Evans and Smithies for the introduction of customised genetic mutations in rodents (Doetschman et al., 1987; Evans and Kaufman, 1981; Martin, 1981; Robertson et al., 1986; Thomas and Capecchi, 1987). A pertinent example for the use of this technology includes work into the metabolic regulator, PGC1- α , now probably the most common gene/protein to be investigated in skeletal muscle adaptation following aerobic exercise. Using gene knock out technology, following aerobic exercise or cold water therapy, PGC1- α was confirmed as fundamental in the promotion of mitochondrial biogenesis enabling increases in oxidative metabolism in rodent models (Lin et al., 2002). Later it was also shown that exercise performance was impaired following PGC1- α KO (Handschin et al., 2007). Furthermore, in terms of muscle mass regulation, the double muscling phenotype with a naturally occurring myostatin mutation in cattle (McPherron and Lee, 1997), was confirmed using myostatin KO mice (McPherron et al., 1997). PGC1- α and myostatin are discussed in more detail in the section below entitled: 'Exercise induced signal transduction networks.' Other models in rodents that are not possible in humans, but have led to large forward strides in understanding the molecular regulation of muscle growth, include, synergistic ablation (also termed compensatory hypertrophy), which after removal of agonist muscles culminates in rapid muscle hypertrophy and serves as a model to investigate the molecular regulation of muscle growth. This method, was first used by Goldberg in 1967, who demonstrated a rapid hypertrophic response even after only 24 hr after synergistic ablation (Goldberg, 1967).

Exercise induced signal transduction networks

Following exercise and muscle contraction, extracellular molecules such as calcium, adrenaline, epinephrine, growth hormone or even mechanical load are rapidly 'sensed' by skeletal muscle, for example via; ion channels, receptors or matrix proteins such as integrins. This leads to intracellular signal transduction or signaling cascades that are typically activated/inactivated by phosphorylation/dephosphorylation respectively, ultimately leading to altered gene expression and protein abundance, required for functional adaptation at the cellular level. In 1992 the discovery of protein phosphorylation by Fischer and Krebs culminated in the award of the Nobel prize in chemistry. With this discovery, earlier work in gene expression, and the development of Western blotting using phosphorylation specific antibodies, enabled the role of protein phosphorylation/activity after exercise to be determined (Yamaguchi et al., 1985). Below are some of the most important discoveries for the cellular signaling networks controlling adaptation to exercise in skeletal muscle.

AMPK/PGC1- α in endurance exercise adaptation

In 1996, work by Hardie described that activity of an important protein, AMP kinase (AMPK) was elevated in response to endurance exercise (Winder and Hardie, 1996). Later work by Hardie's group consolidated this observation and revealed that this protein was a key component in energy sensing within skeletal muscle in response to exercise. Spiegelman's team subsequently identified the transcriptional co-factor PGC-1 α as the first major regulator of skeletal muscle mitochondrial biogenesis (Puigserver et al., 1998; Wu et al., 1999) which was later shown to be regulated by AMPK and enable subsequent mitochondrial biogenesis (Lin et al., 2002; Puigserver et al., 1998). PGC-1 α is a co-transcriptional regulator and activates a group of transcription factors, including nuclear respiratory factor 1 (NRF1) and nuclear respiratory factor 2 (NRF2), which activate mitochondrial transcription factor A (mtTFA) leading to initiation of the replication and transcription of mitochondrial DNA, and ultimately mitochondrial biogenesis (Scarpulla, 1997;



Virbasius and Scarpulla, 1994). It was later observed that AMPK and p38 MAPK directly phosphorylate PGC-1 α (Knutti et al., 2001) and activation of AMPK was also shown to increase the gene expression of PGC-1 α (Suwa et al., 2003). At around the same time, Baar and Holloszy were the first to show that an acute bout of swimming increased PGC-1 α protein expression and NRF-1 binding to the δ -aminolevulinate synthase (δ -ALAS) gene promoter and NRF-2 binding to the cytochrome *c*-oxidase IV promoter (Baar et al., 2002). It was later confirmed that exercise performance was impaired following PGC-1 α knock out (Handschin et al., 2007). Following this work, it was subsequently observed that a reduction in PGC-1 α acetylation (therefore deacetylation) occurs via AMPK activation of the deacetylase, SIRT1 (Cantó et al., 2009). Where SIRT1 deacetylation of PGC-1 α regulates expression of key glucose and lipid metabolism genes (Nemoto et al., 2005). However, during endurance exercise it was suggested that AMPK activation of SIRT1 may not be the main mediator of PGC-1 α deacetylation, as exercise performance or mitochondrial biogenesis was not impaired under SIRT1 KO conditions. However, exercise induced PGC-1 α deacetylation was thought to be instead mediated via a reduction in the acetyltransferase GCN5, that would function to reduce acetylation of PGC-1 α (thereby causing deacetylation) (Philp et al., 2011). Overall however, it is now well established that AMPK is one of the main regulators of PGC-1 α and exercise induced mitochondrial biogenesis.

mTOR in load induced muscle mass regulation

With respect to signals promoting muscle growth, in the late 90's work by Baar and Esser identified that a major intracellular signaling molecule controlling protein synthesis, mammalian target of rapamycin (mTOR), was indirectly thought to be load or 'mechano' sensitive (via assessment of downstream translation initiator p70s6K). This was observed in rodents following electrical stimulation-evoked contractions (100 Hz) of the triceps surae. This stimulation resulted in a shortening contraction of the plantar flexors and lengthening contractions of the dorsiflexors in single bout session of 6 repetitions that lasted 3 seconds per contraction, with 10 seconds rest between repetitions and 50 seconds rest after every 6 repetitions (Baar and Esser, 1999). The rodents completed a total of 10 sets resulting in 60 repetitions over a 22 minute period in an attempt to mimic a single bout of resistance exercise in humans (Baar and Esser, 1999). Importantly, the magnitude of muscle mass increase following 2 sessions per week over 6 weeks of training correlated highly ($r > 0.9$) with the increases in p70s6K activity post 6 hrs acute exercise. Shortly after, Bodine's group observed that load induced muscle growth could be prevented using the mTOR inhibitor, rapamycin in rodents (Bodine et al., 2001). Eight years later, it was confirmed in human skeletal muscle that mTOR was a fundamental activated signalling molecule following exposure to physiological load (resistance exercise), where 12 mg of rapamycin was administered to subject prior to performing 11 sets of 10 repetitions of leg extension at 70% of the participants 1 repetition maximum. The rapamycin group did not show the increase in muscle protein synthesis normally seen following resistance exercise (Drummond et al., 2009), consolidating its role in resistance exercise induced muscle growth. In a murine experiment that further consolidated mTOR's role in load induced growth, mTOR was mutated so that it was no longer sensitive to inhibition via rapamycin. In these mice, synergistic ablation led to a similar increase in muscle mass as the control group (approx. 42%) and rapamycin was unable to prevent load induced growth in the experimental mice. Indeed, rapamycin was only effective in blocking hypertrophy in the control mice without the mutated, rapamycin insensitive mTOR (Goodman et al., 2011). mTOR is

therefore now considered one of the major regulators of load induced skeletal muscle growth. Despite this, it is notoriously difficult to measure mTOR via western blotting due to its large protein size. Therefore, the majority of studies in human molecular exercise physiology tend to measure phosphorylation of downstream translation initiator, p70s6K and the activity of the protein that is required for translation elongation, 4E-BP1, whereby mTOR activates 4E-BP1, after which 4E-BP1 detaches from eIF4E, and translation elongation can occur in the ribosome and a peptide chain is synthesised on the basis of the mRNA blueprint.

Myostatin/Smad signaling as a negative regulator of muscle mass

In parallel to mTOR, the myostatin-smad pathway emerged in the late 1990s as an important pathway in cellular and molecular exercise physiology. It was first established that cattle displayed a 'double muscling' phenotype if they possessed a natural myostatin mutation (McPherron and Lee, 1997). Furthermore, with the combination of Follistatin related gene (FLRG), an inhibitor of myostatin, muscle mass was quadrupled (Lee, 2007). Myostatin, also known as growth differentiation factor 8 (GDF-8) and a member of the transforming growth factor (TGF) β superfamily of proteins, was identified as a ligand that binds to activin receptors (Lee and McPherron, 2001). Shortly after the initial discovery that identified myostatin as a potent negative regulator of muscle mass, myostatin induced intracellular signalling was determined. This was demonstrated in experiments showing that suppression of Smad transcriptional activity (using transcriptional repressor SKI) evoked an approximate 2-fold increase in muscle mass (Sutrave et al., 1990), confirming the role for the myostatin ligand in the binding to activin receptors that subsequently controlled the activity of the downstream Smad proteins. Despite this, at present it is unclear whether myostatin is important for exercise adaptation and/or if it is important to try to manipulate its expression with different types/modes/intensities of exercise regime. This is because, myostatin knockout mice possess an increase in maximal tetanic muscle force but the specific force (also termed muscle quality/force relative to the cross-sectional area of the muscle) is lower. Suggesting that reductions in myostatin may produce more muscle, yet at the expense of functional performance (Mendias et al., 2006). The role for myostatin in exercise adaptation is further confused after evidence has suggested that although myostatin gene expression is reduced following resistance exercise, this reduction has also been observed after endurance exercise where muscle mass is not considerably affected. Others have also observed this decrease at the gene and protein level but this effect was also shown not to be related to training induced changes in muscle mass (Hulmi et al., 2009; Kim et al., 2007). Conversely, myostatin has been observed to increase at the mRNA level after chronic resistance exercise (Willoughby, 2004). Interestingly, however, it is perhaps more likely that changes in myostatin could also be involved in inhibiting protein synthesis via Akt/mTOR/p70S6k pathways and therefore have an important role in exercise induced adaptation in skeletal muscle. Indeed, increases in myostatin administered to skeletal muscle cells *in-vitro* have been shown to reduce the phosphorylation of Akt and p70s6K by 50% upstream and downstream of mTOR respectively (Trendelenburg et al., 2009). Also, Smad2 or Smad3 knockdown (via small interference RNA's/siRNA) has been observed to restore Akt activation in the presence of myostatin, suggesting that Smad2 or Smad3 regulate Akt activity, upstream of mTOR/p70s6k. An *in-vivo* study by Sartori et al. (2009) published simultaneously with that of Trendelenburg et al. (2009) showed that activation of the Smad2 and Smad3 pathway induced myofibre atrophy, and that



this effect could be reversed using small hairpin RNAs (shRNAs) blocking Smad2 and Smad3 (Sartori et al., 2009). Importantly in this study, constitutive overexpression of Akt also prevented muscle fibre atrophy induced by Smad2 or Smad3 activation. Myostatin has also been shown to increase FOXO signalling that functions to block Akt (McFarlane et al., 2006), and increase protein degradation via control of ubiquitin ligases MuRF1 and MAFbx (Cong et al., 2011; Sartori et al., 2009). Finally, in an impressive set of experiments by Baar's group using the same electrical stimulation regime used in the original studies to identify mTOR/p70s6K as load-dependent signalling, discussed above (Baar and Esser, 1999). It was demonstrated that reductions in myostatin following exercise were responsible for an 82% increase transcriptional activity of a gene called *Mighty*, that also correlated with muscle growth. The authors suggested, that this was not due to the reduction in myostatin per se, rather an increase in Notch, a known inhibitor of TGF β (one of the main members of the TGF superfamily that myostatin belongs to). Impressively, to confirm this mechanism the group used electroporation of Notch (method for muscle tissue specific gene overexpression) and this was shown to reduce myostatin transcriptional activity and increase *Mighty* gene expression (MacKenzie et al., 2013). Therefore, the TGF family members such as myostatin and their associated signalling and transcriptional targets do seem to be important in adaptation to resistance exercise.

Ca⁺/Calcineurin/NFAT signaling in fibre type specification following exercise

In the late 90's Chin within the group of Williams paved the way for understanding regulators of calcium release from the sarcoplasmic reticulum, following muscle contraction and the subsequent regulation of the calcium-camodulin-calcineurin pathway and its control of the transcription factor NFAT that regulated the switching on and off of 'slow' / 'fast' muscle fibre genes (Chin et al., 1998). They used both gene overexpression of calcineurin *in-vitro* that evoked the expression of slow troponin and myoglobin genes and pharmacological inhibitors of calcineurin, cyclosporine A *in-vivo*, that increased the number of fast type-II fibres by 50%. Taken together, they suggested that there was a fundamental mechanism whereby increases in calcineurin promoted slow fibre formation and that inhibition promoted fast fibre formation. This was later confirmed in KO mice in 2000 (Naya et al., 2000). In the same year it was then also determined that the upstream MAPK (ERK) pathway was important in this fibre type transition by work of the Schiaffino group (Murgia et al., 2000).

Gene expression microarray analysis

Following exercise and signal transduction, transcription factors are activated/inactivated and lead to an increase/decrease in gene expression (mRNA) via binding to the promoter regions on the DNA of target genes. The technological and methodological advancements in the assessment of RNA and DNA particularly in the late 70s and early 80s with the use of pulsed-field gel electrophoresis (Schwartz and Cantor, 1984), early sequencing (Anderson, 1981; Beck and Pohl, 1984; Maxam and Gilbert, 1977; Sanger et al., 1977; Smith et al., 1986), restriction fragment-length polymorphisms (Saiki et al., 1985), polymerase chain reaction (Mullis and Faloona, 1987; Saiki et al., 1985) and the use of bacterial and yeast artificial chromosomes to enable 'chromosome walking' (Hsiao and Carbon, 1979; O'Connor et al., 1989) enabled early progress into DNA and gene sequencing. Subsequently, the first human genome linkage map was produced in 1987 (Donis-Keller et al., 1987) and significant advances in fully automated DNA sequencing (Adams et al., 1991; Prober et al., 1987) allowed the yeast genome to be

sequenced in 1994 (Feldmann et al., 1994), *c. elegans* in 1998 (1998), with the draft of the human genome in Feb 2001 (Lander et al., 2001) using whole genome shotgun sequencing (Weber and Myers, 1997). Following this, the mouse genome was sequenced in 2002 (Waterston et al., 2002) and finally in 2003 the fully completed human genome (Human Genome Sequencing, 2004; Venter et al., 2001) with the rat genome also completed shortly after (Gibbs et al., 2004). These advances importantly revealed 26,588 protein-encoding gene transcripts in the human genome meaning scientists could begin work on what regulated these genes in response to human adaptation (Human Genome Sequencing, 2004; Venter et al., 2001). In the early 2000's, Booth's lab in collaboration with Hoffman were the first use more extensive genome/transcriptome wide gene expression techniques via the use of gene expression microarrays. At that time 'genome-wide' for this technology meant the coverage of around 3000-4000 gene transcripts, as well as around 3,000 expressed sequence tags (ESTs) as the method just predated the full publication of the human and mouse genome sequences and the technology for these arrays were in their relatively early stages. In this study they compared the gene expression profile of approximately 3000 genes and 3000 EST's in both the fast twitch vastus lateralis and the mixed soleus muscles (Campbell et al., 2001). They demonstrated that there were 59 differentially regulated genes between the two muscle fibre types. A year later in 2002, Esser's group undertook the first work into the transcriptome following muscle contraction. Electrical stimulation protocols in rodents were conducted in regimes that mimicked resistance exercise [as discussed previously above (Baar and Esser, 1999; MacKenzie et al., 2013)], with corresponding gene microarrays being performed. These arrays (Affymetrix Rat U34A GeneChips) included around 7000 genes and 1000 ESTs. Importantly, a small subset of 18 genes were identified that were expressed 1 hr after exercise and around 70 genes after 6 hours of exercise (Chen et al., 2002). Also, in 2002, 9 weeks of resistance exercise in humans was undertaken and skeletal muscle biopsies obtained and profiled for around 4000 genes, from otherwise sedentary young males and females as well as older men and women (5 in each group). Almost 100 genes were significantly differentially expressed across all groups in response to chronic resistance exercise. Interestingly, there were a large number of genes that demonstrated stark regulation in male versus female as well as between young adult and elderly (Roth et al., 2002). With gene array technology rapidly advancing, research by Chen et al., (2003) profiled over 12,000 gene transcripts following an acute bout of resistance exercise in males (albeit only 3 individuals) (Chen et al., 2003). Each individual performed 300 concentric contractions with one leg and 300 eccentric contractions with the other. In this study 50% of the genes identified were also identified in their earlier rodent studies following electrical stimulation, discussed above (Chen et al., 2002). They also identified 6 gene transcripts that were related specifically to eccentric muscle contractions. Due to the full mouse genome sequencing in 2002 (Waterston et al., 2002) and finally in 2003 the fully completed human genome (Human Genome Sequencing, 2004; Venter et al., 2001) and rat genome shortly after (Gibbs et al., 2004), and with the knowledge of the 26,588 protein-encoding gene transcripts in the human genome, it was soon possible to undertake gene arrays for more than 23,000 gene transcripts. A study in 2007 performed Illumina microarrays, and out of 23,000 genes identified nearly 600 genes that were differentially regulated in the basal state in elderly versus young adult skeletal muscle. Interestingly, after 6 months of resistance exercise in young versus elderly adults (men and women), resistance exercise enabled the return of gene expression for the majority of these genes back towards levels observed in the young adult group (Melov et al., 2007). In 2007 the first rat transcriptome was



profiled following an acute bout of aerobic exercise and suggested that 52 genes were differentially expressed post 1 hr of exercise (McKenzie and Goldfarb, 2007). In 2011 Timmons and Bouchard, using gene microarrays showed that $\dot{V}O_{2\max}$ responses to chronic endurance training could be predicted by a 29-gene expression signature or 'training-responsive transcriptome' using baseline/pre-exercise skeletal muscle biopsies. With current microarrays, it is now possible to investigate over 47,000 transcripts (i.e. known protein coding transcripts but also their variants). In 2012 using these powerful arrays an investigation found that 661 genes were affected by both an acute bout and chronic (12 weeks resistance training) exercise in young and elderly women and correlated with gains in muscle size and strength. Interestingly, the most pronounced changes in gene expression occurred in fast-twitch (MHC IIa) muscle fibres (Raue et al., 2012). These studies have laid the foundation for investigating in more detail the specific genes important in exercise adaptation, as without such powerful types of analysis these genes may never have been identified using a candidate, one-gene at a time approach.

Exercise Genetics/ Genomics

As well as work on the turning on/off of genes following exercise, molecular exercise physiologists were also interested in how genetic inheritance affected exercise performance and adaptation. Research led by Claude Bouchard in the 1980's first identified that aerobic capacity and aspects of physical fitness could be attributed in part by genetic inheritance (Bouchard et al., 1986; Bouchard et al., 1984; Perusse et al., 1987). Bouchard began to genotype humans within field of sport and exercise science in 1989 (Bouchard et al., 1989). Soon after this both mitochondrial and nuclear DNA sequence variants were studied (Deriaz et al., 1994; Dionne et al., 1991). Bouchard, together with Malina and Pérusse, wrote the first and widely appreciated textbook within the sport and exercise genetics field entitled: *Genetics of Fitness and Physical Performance* (Bouchard et al., 1997). The book was a fundamental tool for academics, scientists and students within sport and exercise science as its content covered both classical and novel molecular genetics theories relevant to exercise scientists. In 1998, Montgomery in a paper in *Nature* reported that the 'I' polymorphism of the human ACE gene was associated with increased duration of repetitive biceps flexion after a program of general physical training. This I allele was also increased in frequency within a population of elite mountaineers (Montgomery et al., 1998). His team later showed that an increased frequency of the I allele was observed in elite 5000 metre British runners versus both 200 and 400-3000 metre runners, suggesting an important role for this particular genotype in endurance performance. In 2000 Williams, in a study led by Montgomery, reported again in the journal *Nature*, that the presence of this ACE allele also conferred an enhanced mechanical efficiency in trained muscle (Williams et al., 2000). After these initial studies in the early 2000s, and the final version of the human genome reported in 2003 that identified the location of 2.1 million mutations (single nucleotide polymorphisms) (Human Genome Sequencing, 2004; Lander et al., 2001; Venter et al., 2001), there was exponential growth in the uncovering of genetic polymorphisms associated with sport performance, where in 2005 there were only 8 polymorphisms associated with sport performance, yet by 2015 there was a staggering 155 polymorphisms identified (93 endurance-related and 62 power/strength-related genetic markers) (Ahmetov et al., 2016b). To date there are just under 160 genetic markers that are linked to elite athlete status (reviewed in (Ahmetov et al., 2016a; Ahmetov and Fedotovskaya, 2012). However, approximately 80% of the studies have not yet been replicated in independent samples (Ahmetov et al., 2016a; Ahmetov and

Fedotovskaya, 2012). For example, only 31 genetic markers have shown positive associations with athlete status in at least 2 studies and only 12 genotypes in 3 or more studies (Ahmetov et al., 2016a). Therefore, despite an increase in the number of potential genetic associations with performance, studies seem to focus on popular associations such as ACE and ACTN3, due to different alleles within these genes being associated with somewhat classically opposing physiological traits such as endurance versus strength/power performance. Also, out of the approximate 160 genetic markers found to date, 29 of them have not been replicated by at least 1 other study, therefore previous authors have suggested that perhaps some of the findings may lack reproducibility or are potentially false positives (Ahmetov et al., 2016a). It is also worth noting that the different geographical populations included in these studies may further increase genetic variability. Also, because single genes are unlikely to influence adaptation to exercise, or the physiological variation observed in the multi-faceted traits that are required for human performance, it is generally accepted that hundreds or perhaps even thousands of individuals are required to enable candidate gene studies to have adequate statistical power. Indeed, in 1998, Claude Bouchard identified that genetic heritability accounted for 47% of $\dot{V}O_{2\max}$ /maximal oxygen uptake, an important predictor of maximal aerobic capacity and endurance performance. This was based on the observation that there was 2.5 times more variation in $\dot{V}O_{2\max}$ between families than within families (Bouchard et al., 1999; Bouchard et al., 1998), suggesting that aerobic capacity has a significant genetic component. With the development of high-throughput Single Nucleotide Polymorphism (SNP) genotyping methods, the human genome sequence and an ethnic group inventory of DNA sequence variants (from the *HapMap* and the *1000 Genomes* projects), the first Genome-wide-association-studies (GWAS) were conducted in 2005 (Klein et al., 2005). Four years later in 2009 the first GWAS was conducted that looked at 1.6 million SNPs associated with physical activity levels in 2622 non-related individuals. Despite the strongest association with physical activity levels identified on chromosome 10q23.2 at the 3'-phosphoadenosine 5'-phosphosulfate synthase 2 (*PAPSS2*) gene, there were no SNPs that actually achieved significance at the genome wide level (De Moor et al., 2009). Bouchard together with Timmons (Bouchard et al., 2011; Timmons et al., 2010) were then the first to really progress the knowledge in this area. In their studies, DNA sequence microarrays were used to search for a wide range of known polymorphisms that could explain variations in endurance performance and trainability. In 2010, they also combined DNA microarrays to identify a large number of known common variants with skeletal muscle gene expression arrays to identify genes associated with the $\dot{V}O_{2\max}$ training response (gene expression arrays are discussed above). The investigation identified 11 single nucleotide polymorphisms (SNPs) that explained the variance for increased $\dot{V}O_{2\max}$ in response to training. Interestingly, 7 of the SNPs were located on transcripts identified in gene expression predictor set suggesting a link between DNA variance and gene expression in response to increases in aerobic capacity following exercise training. In the Bouchard study in 2011, they investigated 324,611 single-nucleotide polymorphisms (SNPs) to identify variants associated with improvements in $\dot{V}O_{2\max}$ following 20 weeks of supervised endurance training. 21 SNPs accounted for 49% of the variance of gains in $\dot{V}O_{2\max}$ following training, which was very close to the maximal heritability estimate of 47% reported previously in the HERITAGE Family study described above (Bouchard et al., 1999). Interestingly, it was identified in these studies that if the participants possessed less than or equal to 9 of these SNPs they were able to improve their aerobic capacity by 221 ml/min over the 20 weeks of training. Furthermore, if the participant possessed greater or equal to 19 of these SNPs they improved on average, a



staggering 604 ml/min (Bouchard et al., 2011). These studies therefore were the first to identify some of the most important genetic variations associated with aerobic exercise adaptation and to show the overall contribution of genetics to human performance. However, since these studies there have been few investigations to really extend this work by including higher powered studies via increasing participant number or by increasing the number of genetic variants studied. Indeed, the genotyping microarrays used in the above studies identify only common variants. Yet, 40 million DNA sequence variations have now been identified in the human genome (1000genomes.org). Further, based on the increasing number of personalised genomes, the number of variants a given individual carries are between 3-4 million, and rare variants carried by any one individuals ranges from 200,000 to 500,000 variants. There are therefore millions of common and rare SNPs between individuals that could contribute to exercise adaptation that have not yet been investigated. However, to identify genetic variants for a given trait it is clear that a large number of people and a large number of SNPs need to be investigated. Rare genetic variants associated with certain traits are extremely difficult to identify as it would be plausible to have to sequence the genome of a large number of people where that particular trait is identified, for example, in families.

With whole genome sequencing becoming increasingly affordable then this approach could be the way to make progress within cellular and molecular exercise physiology. Despite the increasing affordability of genome sequencing, the costs of running adequately powered studies across large groups allowing comparison e.g. between elite and non-elite are still financially out of reach of most exercise science research institutes. Where more avenues for funding these types of studies are more widely available if the focus is human health related. Furthermore, in future these types of studies may also rely on employment of bioinformatician and computational facilities to analyze the DNA sequences to identify variations in DNA between individuals. Finally, there are ethical questions to consider when undertaking genome wide analysis for human performance traits or an individual's ability to adapt to exercise, as it may provide information on increased disease risk or provide information that may be associated with negatively perceived connotations towards an individual's genetic ability to perform well in certain performance measure or sports (Wackerhage et al., 2009). However, on the contrary understanding the different genetic variations between elite, non-elite and diseased individuals and their performance traits may enable important genetic variations to be identified that could lead to therapeutic strategies to improve muscular function in metabolic diseases such as type II diabetes, obesity or muscle loss with age. Therefore, studies conducted within this area of research within the sport, exercise and health sciences require more investment by research councils and charities.

Satellite cells role in repair and regeneration of skeletal muscle tissue following exercise

A fundamental discovery of the regenerative muscle 'stem cell,' or satellite cell by Mauro in 1961 (Mauro, 1961) initiated a growing research programme into the role of this fascinating cell type in muscle mass maintenance and repair. Just over 40 years later the first studies to investigate the role of the satellite cell in exercise adaptation emerged. Because adult human skeletal muscle fibres are terminally differentiated or post mitotic (i.e. a muscle fibres cannot replicate themselves due to being multinucleated structures), and fibre number is set *in-utero*, it is thought creation of new fibres or adequate repair cellular components of the fibres in adult skeletal muscle is not possible

without a resident cell type that does have mitotic potential. The satellite cell was identified as having the capacity to proliferate, migrate and differentiate to enable cellular activation following damage, division (proliferation), movement to the site of injury (migration) and then fusion with the existing fibre to enable repair of the fibre (differentiation). In the early 1970s (around the same Era as Booth's initial work in exercise biochemistry and gene expression), Schiaffino was undertaking pioneering work into characterizing the role of fibre type alterations via enzymatic/histochemical analysis following compensatory hypertrophy/synergistic ablation (reviewed in (Gutmann et al., 1971). Importantly, around the same time, Schiaffino also began fundamental cellular work into the role of satellite cell during muscle regeneration and their ability to increase in number (Schiaffino et al., 1972), and fuse with existing muscle fibres after compensatory hypertrophy in order to repair damaged fibres (Schiaffino et al., 1976). Muscle stem cells were first isolated from muscle tissue to investigate the role of these cells in regeneration processes following tissue damage via the analysis of proliferation, migration and differentiation *in-vitro* in cells isolated from chicken muscle, with studies later progressing to cells isolated from human muscle (Cantini et al., 1980; Sartore et al., 1979; Schiaffino et al., 1982). In 1992 fascinating work by Rosenblatt and Parry, suggested that when satellite cells were lost through irradiation no increase in muscle mass is observed after compensatory hypertrophy, at this stage, suggesting these cells were fundamental in load induced muscle growth (Rosenblatt and Parry, 1992). Work in human muscle stem cells would later pave the work by Stewart and Rotwein to discover the role for ERK and AKT (also known as PKB) in regulating muscle stem cell proliferation, differentiation, survival (Foulstone et al., 2004; Lawlor et al., 2000). Subsequently, following the emergence of gene transfer by Booths lab (discussed above) together with early work by Stewart and Rotwein, these studies would go on to enable investigations into the overexpression of a hyperactive form of the Akt in 2002 that resulted in considerable skeletal muscle fibre hypertrophy (Pallafacchina et al., 2002).

With respect to role for satellite cells *in-vivo* following exercise. It was demonstrated in 2001, using immuno-histological assessment and cross sectional analysis of sectioned and stained muscle tissue that, increased muscle mass following resistance exercise was accompanied by increased myonuclear number (Kadi and Thornell, 2000). After these initial studies, investigators went on to suggest that the number of satellite cells (e.g. immune-histology of the satellite cell marker, Pax7) identified on muscle fibres increases and remains elevated in response to long term training where increased muscle mass was evident (Bruusgaard et al., 2010; Kadi and Thornell, 2000; Petrella et al., 2008). Further research by Smith and Merry (2012) exercised rats for 6 weeks using either resistance type or endurance type exercise, and found similar increases in satellite cell number in both modes of exercise (Smith and Merry, 2012). These data suggested that endurance and resistance training amplify the satellite cell pool to a similar extent. However, it was well known that resistance exercise led to increased mass with myonuclear addition (Bruusgaard et al., 2010; Kadi and Thornell, 2000; Petrella et al., 2008) whereas chronic endurance training does not usually increase muscle mass (Hoppeler et al., 1985; Ingjer, 1979) or myonuclear number (Kurosaka et al., 2012; Verney et al., 2008). At this time, this challenged the field to ask if satellite cells were actually required for resistance exercise-induced muscle growth or whether they were dispensable. Indeed, Type II fibres hypertrophy to a greater extent with resistance exercise vs. type I fibres, where it is also observed that there is an greater response from satellite cells in Type II fibres after exercise (Smith and Merry, 2012; Verdijk et al., 2009) supporting their requirement in load induced growth.



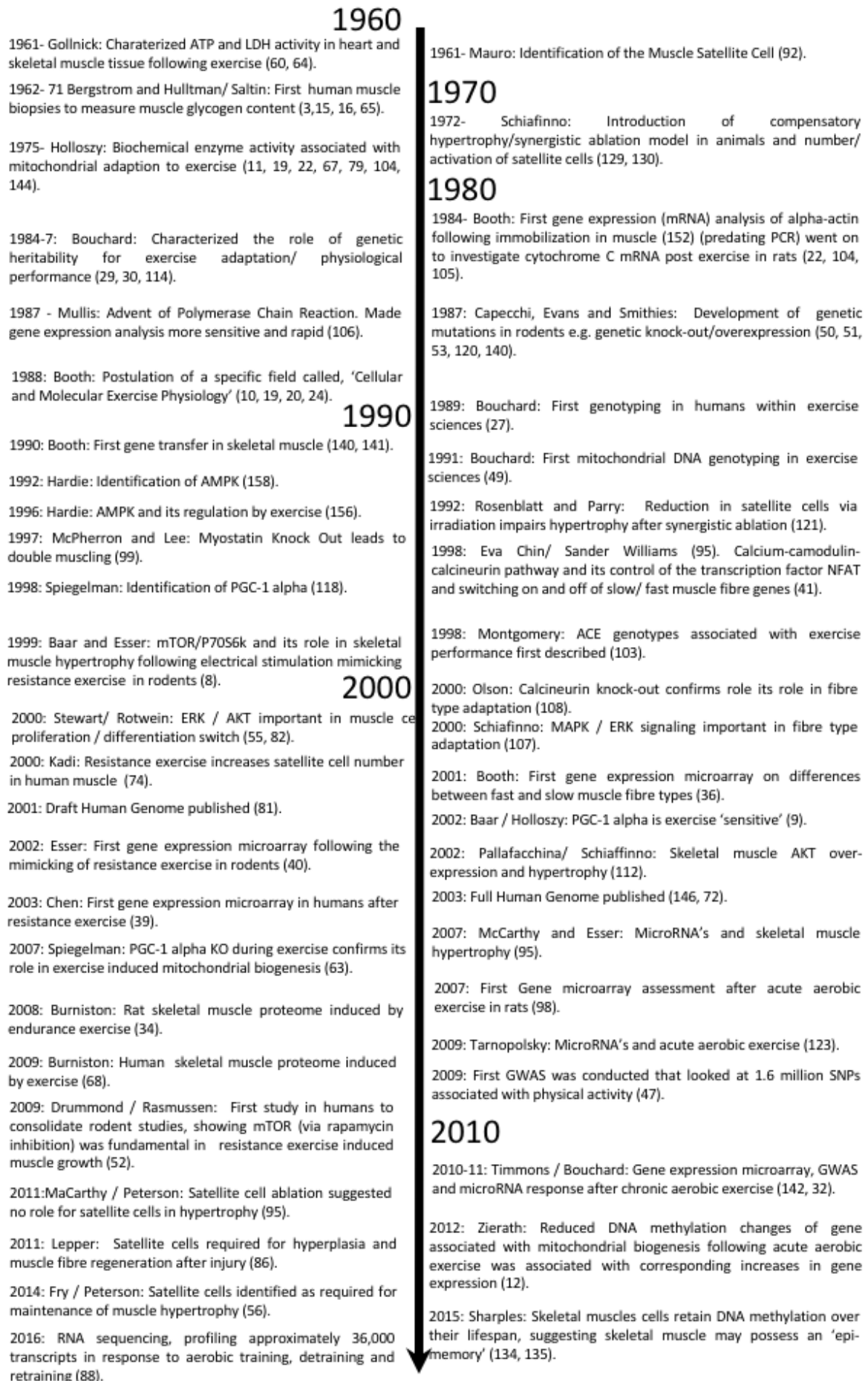


Figure 1: Timeline of major discoveries for the cellular and mechanisms of skeletal muscle adaptation.

Furthermore, after the studies by Rosenblatt and Parry (1992), described above, that suggested if satellite cells were lost through irradiation no increase in muscle mass was observed, in 2011, Peterson's group and researcher McCarthy directly challenged this assumption. They genetically ablated Pax7 in skeletal muscle, essentially removing satellite cells while rodents underwent compensatory hypertrophy (McCarthy et al., 2011). Fascinatingly, it was observed that muscle was still able to hypertrophy without satellite cells (McCarthy et al., 2011). Importantly however, this article did not address whether the lack of satellite cells would affect maintenance of the increase muscle size over longer periods. Where later it was established by Peterson's group that following 8 weeks of load induced growth, hypertrophy is considerably reduced if satellite cells are absent (Fry et al., 2014). Furthermore, satellite cells have also been shown to be fundamental in hyperplasia and new fibre formation after synergistic ablation (Lepper et al., 2011). While new fibre formation does not occur in humans after experiencing physiologically relevant loads, hyperplasia does occur in rodents after supra-physiological load experienced post synergist ablation. Lepper and colleagues (2011) demonstrated that with genetic ablation of Pax7 (same model as McCarthy et al., 2011) new fibre formation was severely impaired suggesting an important role for satellite cells in regeneration after ablation-induced muscle growth (Lepper et al., 2011). Finally, since these studies, it has more recently been confirmed that satellite cells are fundamental to the maintenance of functional muscle over time, where if satellite cells are lost the muscle tissue becomes more fibrotic and therefore less functional (Fry et al., 2015; Lee et al., 2015).

Future: A requirement for combined and integrative proteomic, epigenetic, gene regulatory, and genetic approaches in cellular and molecular physiology

Finally, as we progress into the future, whilst cellular and molecular exercise physiology now uses some of the latest technology available to cellular and molecular biologists, a much more integrative approach is required. Given that proteins within cellular transduction networks are not only phosphorylated/dephosphorylated but also acetylated, deacetylated, sumoylated, ubiquitinated, glycosylated, methylated and demethylated (Consortium, 2012). These other processes are currently understudied in relation to the abundance of studies that investigate phosphorylation and its role in controlling protein activity and cell signaling cascades following exercise. Other than small pockets of the community investigating acetylation/deacetylation such as deacetylation of PGC-1 alpha after exercise, as discussed above (Philp et al., 2011), there are also few wider proteomic approaches being taken. Indeed, the first proteomic studies reporting training-induced adaptations in rat (Burniston, 2008) and human skeletal muscle (Holloway et al., 2009) were only 7-8 years ago. Indeed, in 2009, approximately 2000 proteins from biopsy samples of human skeletal muscle were identified using mass spectrometry. The majority of those identified were abundant myofibrillar proteins, metabolic enzymes and kinases responsible for phosphorylation (Parker et al., 2009). This is because, unlike RNA, it is difficult to isolate all proteins as they cannot be amplified like cDNA (product of mRNA following reverse transcription) via PCR, and the proteome is more diverse than the transcriptome, due to post translational modifications. This is particularly challenging when the identification of proteins following mass spectrometry are based on assessing the unique 'masses' of a skeletal muscle sample in comparison to masses that are predicted within existing gene and protein databases. Current proteomic technology is therefore somewhat behind transcriptomics. However, proteomics is likely to be even more powerful than, for example,

western blotting going forward due to the reliance on the commercial availability of a suitable antibodies. Furthermore, proteins never before identified to play a role in exercise adaptation (e.g. PDIA3- Protein Disulfide Isomerase Family A Member 3 (Burniston et al., 2014)) are beginning to be discovered as regulators of aerobic capacity due to the latest 'mining'/profiling advancements within proteomics as opposed to undertaking western blotting for known kinases.

Furthermore, following the necessary cell signaling response leading to transcription factor recruitment, the switching on/off of genes (gene expression) is an extremely complex process. Indeed, we now know that gene expression can be controlled epigenetically via modifications to DNA e.g. via methylation or histone modification (e.g. acetylation, deacetylation, ubiquitination, methylation) that allows altered chromatin access for transcription factor binding and promotion/suppression of gene expression. The epigenetic regulation of gene expression in exercise has only really been studied since 2009 onwards, as recently reviewed (Sharples et al., 2016). Most notably acute high-intensity cycling exercise evoked increased histone acetylation of Histone 3 in skeletal muscle, a process that is shown to be partly controlled by the removal of the histone deacetylases from the nucleus (McGee et al., 2009). Most notably the first studies to investigate DNA methylation and its control of gene expression in skeletal muscle following exercise was by Zierath's group who showed reduced DNA methylation of PGC-1 alpha, mitochondrial transcription factor A (TFAM) and pyruvate dehydrogenase lipoamide kinase isozyme 4 (PDK4), all associated with mitochondrial biogenesis, immediately post an acute bout of high intensity aerobic exercise. These modifications correlated with reductions in the corresponding gene expression profiles (Barres et al., 2012). Taking this slightly further, it was later established that acute exercise reduced DNA methylation within the PGC-1 alpha promoter A, while methylation of lysine 4 on Histone 3 controlled expression within the PGC-1 alpha promoter B (Lochmann et al., 2015). Importantly, chronic exercise consisting of 6 months supervised aerobic exercise also altered the methylation of several genes associated with metabolism (Nitert et al., 2012). Finally, it has been known for a considerable period of time that skeletal muscle is somewhat programmable/has a memory, where, for example, early life nutrition *in-utero* can affect skeletal muscle metabolism and/or muscle size in later adult life in the offspring, and skeletal muscle cells seemingly remember the environmental niche from which they were derived once isolated *in-vitro* [(reviewed (Sharples et al., 2016))]. These interesting observations have been coupled with recent evidence to suggest that skeletal muscle cells *in-vitro* can retain altered DNA methylation profiles of key myogenic regulatory factors (myoD) if catabolic inflammatory stimuli are encountered early in their proliferative lifespan; an observation that corresponds with an increased susceptibility to a later proliferative encounter with the same catabolic inflammation stimulus. This work is suggestive of an epigenetic mechanism underlying programmable skeletal muscle cells/skeletal muscle cell memory (Sharples et al., 2015). A so called epi-memory (Sharples et al., 2016) and its role in exercise adaptation is of considerable interest to cellular and molecular exercise physiologists with potential to enable the understanding for the role of previous exercise encounters, both acute and chronic, on the ability of skeletal muscle to respond to future exercise. This could enable better periodization of exercise bouts and recovery from injury. However, there are few human exercise studies to investigate the role of epigenetics in controlling the gene regulatory networks in adaptation to training, detraining or retraining, especially in response to skeletal muscle hypertrophy following resistance exercise. A recent study investigated gene expression profiles (via RNA sequencing, profiling



approximately 36,000 transcripts) in response to endurance exercise training, detraining and retraining and found no difference in the gene expression profile in response post training or retraining (following 9 months of detraining). However, 9 months is a considerable period of time i.e. a whole competitive season, and there were altered transcriptional profiles after repeated bouts of exercise with no epigenetic analysis performed (Lindholm et al., 2016). Therefore, these types of studies in endurance exercise and resistance exercise warrant future investigation with respect to the role of epigenetics in the control of gene expression following exercise.

Finally, there are also several post transcriptional modifications to mRNA that can lead to altered protein structure and function. This can occur via small RNA species known as siRNA (small interfering RNA) and miRNA's (micro RNA) (Valencia-Sanchez et al., 2006). Investigations have been conducted in response to both aerobic exercise and resistance exercise and miRNA profiles (McCarthy and Esser, 2007; Safdar et al., 2009) and miRNA expression can differ between high and low responders to exercise adaptation (Davidsen et al., 2011). Work by Timmons' group was really the most comprehensive in this area, as genetic, gene expression and miRNA profiles were undertaken within the same study. Indeed, they found that a gene network associated with the transcription factors Runx1, Pax3 and Sox9 were associated with adaptation to endurance exercise and that the regulatory miRNA's post-transcriptionally regulated these transcription factors (Keller et al., 2011). However, there are few studies that investigate the role that the miRNA's have on the transcribed mRNA sequences and therefore the protein structure and function of the correspondingly translated proteins in response to exercise.

Overall, in the future more extensive investigations using current epigenetic and proteomic analysis in combination with gene expression microarray/RNA sequencing and genetic profiling using the latest technological advancements are required in exercising knock-out, overexpression and compensatory hypertrophy rodent models, as well as human exercise intervention studies. This will enable the field to delve into the deepest regulatory networks and take cellular and molecular exercise physiology into the next generation of research to uncover the mechanistic underpinnings of exercise adaptation.

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