Scientific Meeting report: International Biochemistry of Exercise 2022

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Scientific Meeting report: International Biochemistry of Exercise 2022

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Abstract

Exercise is one of the only non-pharmacologic remedies known to counteract genetic and chronic diseases by enhancing health and improving life span. Although the many benefits of regular physical activity have been recognized for some time, the intricate and complex signaling systems triggered at the onset of exercise have only recently begun to be uncovered. Exercising muscles initiate a coordinated, multisystemic, metabolic rewiring which is communicated to distant organs by various molecular mediators. The field of exercise research has been expanding beyond the musculoskeletal system, with interest from industry to provide realistic models and exercise mimetics that evoke a whole-body rejuvenation response. The 18th International Biochemistry of Exercise conference took place in Toronto, Canada, from May 25th to May 28th, 2022, with more than 400 attendees. Here we provide an overview of the most cutting-edge exercise-related research presented by 66 speakers, focusing on new developments in topics ranging from molecular and cellular mechanisms of exercise adaptations to exercise therapy and management of disease and aging. We also describe how the manipulation of these signaling pathways can uncover therapeutic avenues for improving human health and quality of life.

Introduction

The pleiotropic benefits of exercise have been recognized for centuries. However, the cellular and molecular mechanisms mediating exercise-induced adaptations require further elucidation. Knowledge gaps in the molecular foundation that underpins the biochemistry of exercise preclude modern medicine from accepting exercise as a viable and effective therapeutic option, despite its undisputed therapeutic promise. Nevertheless, research on the many facets of exercise continues to forge ahead, and specialists make the case that exercise, if prescribed correctly, can be a safe and effective therapeutic modality for common and rare diseases. Since 1968, the International Biochemistry of Exercise Conference (IBEC) has brought together experts from different sectors and disciplines to discuss and present cutting-edge research in exercise biochemistry. The 18th IBEC conference was held in Toronto, Canada, from May 25th to May 28th, 2022, organized by the Muscle Health Research Center at York University. The 3-day conference commenced with the 13th annual Muscle Health Awareness Day (MHAD13) on May 25th, typically held annually at York University. In sum, the meetings featured presentations from 66 world-leading experts with over 400 attendees, with discussions around the theme of “Exercise for health, adaptation and rejuvenation,” emphasizing biochemical mechanisms of exercise adaptations in health, aging and disease. General descriptions and overviews of these presentations are found in this report.

MHAD Symposium: Skeletal Muscle Signaling and Adaptation

Skeletal muscle signaling is indispensable for muscle-specific and systemic adaptations to exercise and disuse. Ayesha Saleem (University of Manitoba) discussed extracellular vesicles (EVs) that are secreted from muscle to signal to other tissues. When cultured myotubes are electrically stimulated, they release EVs into the surrounding media (1). Although treating myotubes with this media did not appear to impact mitochondrial biogenesis, they could induce an increase in mitochondrial content in cancer cells. The significance of this remains to be determined. Interest in EVs has grown exponentially over the last 10-15 years. Revealing more about their cargo and diversity has generated a greater appreciation for the divergent metabolic effects they can elicit. Val Fajardo (Brock University) then discussed the role of Glycogen Synthase Kinase-3β (GSK-3β) inhibition in ameliorating disuse-induced

atrophy with therapeutic implications for muscle-wasting diseases and sarcopenia (Fig. 1). Any changes in muscle mass can be attributed to the balance between muscle protein synthesis (MPS) and degradation (MPD). Inhibition of GSK-3β with Lithium Chloride improved muscle size and strength, thus preventing muscle atrophy in response to unloading (2). Chris McGlory (Queen's University) discussed that MPS appears to be the dominant determinant of muscle mass in response to exercise and nutrition in humans. Exploiting enhanced MPS through a combination of amino acid feeding with resistance exercise (RE) increases muscle size more than RE alone (3). In contrast, the decline in MPS significantly contributes to the muscle atrophy that occurs during immobilization (4). High doses of essential amino acids only partially protect against loss of muscle mass with aging, while polyunsaturated fatty acids potentiate the MPS response to amino acids and insulin. Changes in retrograde signaling from mitochondria to the nucleus may contribute to these responses, generating avenues for future investigation in nutritional interventions that can influence muscle mass during disuse and aging. In sum, signaling pathways activated by muscle contractile activity or inactivity have significant metabolic implications locally, within the muscle, and at distant organs. Determining the factors that are released from muscle during various metabolic perturbations, and how these factors mediate exercise and disuse-induced metabolic alterations remains an active area of research, raising several questions for future research: How do EVs participate in this process? Can muscle-released factors be harnessed to spare muscle mass with disease and aging? Can dietary supplements be utilized to alter or augment specific signaling pathways to favour an anabolic response?

MHAD Symposium: Muscle Exercise Physiology

The metabolic remodelling induced by physical activity and fasting has significant implications for health and disease. Jenna Gillen (University of Toronto) described how moderate-intensity continuous training (MICT) improves skeletal muscle insulin sensitivity (SMIS). However, the response of SMIS to high-intensity interval training (HIIT) remains controversial. HIIT and MICT yield similar SMIS improvements, although the response appears to be mediated by the acute effects of exercise rather than chronic training (5). Interestingly, increased post-recovery muscle glycogen content was the primary factor

associated with improved SMIS with HIIT. The response of skeletal muscle to fasting was then discussed by Brendon Gurd (Queen's University). Fasting is associated with positive adaptive responses, including enhanced antioxidant defences, mitochondrial biogenesis, autophagy, and control of inflammation. However, since these benefits were identified in rodents, whether fasting can elicit the same effects in humans has been subject to debate. In contrast to what is observed in rodents, humans display only minor changes in body weight, metabolic rate, and glycogen content in response to fasting, resulting in minimal effects as a consequence of fasting (6). Fasting is an effective way to reduce caloric intake, however, in humans, health benefits beyond caloric deficit remain to be demonstrated. Rebecca MacPherson (Brock University) reviewed the novel roles of exercise-inducible brain-derived neurotrophic factor (BDNF) in exercise and brain health. An acute bout of exercise enhances BDNF expression, reducing beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) activity in the pre-frontal cortex and hippocampus (7). Given the importance of BACE1 in β-amyloid plaque formation, this can potentially slow the amyloidogenic pathway in the brain, suggesting a neuroprotective role for acute exercise (Fig. 2). Collectively, this symposium highlighted the diversity of metabolic flexibility induced by acute physical activity, exercise training, and fasting on skeletal muscle and brain function and metabolism. Future studies should focus on dissecting the physiological and biological complexity of human metabolic plasticity over a range of acute physical activity and chronic training conditions.

MHAD Symposium: Muscle Bioenergetics in Aging and Diabetes

Skeletal muscle is a metabolically plastic tissue that can rapidly and effectively adapt to environmental changes, bearing significant consequences for aging and diabetes. Yan Burelle (University of Ottawa) discussed mitochondrial quality control in muscle stem cells as a determinant of cell fate decisions and tissue repair capacity, with mitophagy being critical for stem cell commitment and activation (8). Satellite cells lacking PINK1 and Pax7/Parkin double knockouts (KO) undergo premature commitment with increased differentiation and fusion. This generates a maladaptive response to stressful stimuli, manifesting in impaired muscle regeneration following cardiotoxin injury. Sex differences in

mitochondrial quality in the context of Type 1 Diabetes (T1D) were discussed by Thomas Hawke (McMaster University). Although there are no differences in mitochondrial content between healthy and diabetic subjects, T1D organelles exhibit altered morphology as they are swollen with disorganized cristae and functional impairments manifesting as reductions in oxygen consumption and ATP synthesis. Furthermore, sexual dimorphisms in mitochondrial bioenergetics are present, with women appearing to be better protected from losses in mitochondrial volume that accompany T1D (9). These findings highlight the importance of considering sex as a variable when generating exercise prescription regimens for the treatment of patients with T1D. Mitochondrial bioenergetics with insulin resistance in the context of white adipose tissue (WAT) was discussed by Graham Holloway (University of Guelph). Mitochondrial creatine kinase 1 uses mitochondrial ATP to phosphorylate creatine, generating phosphocreatine (PCr). This results in the liberation of ADP, which then serves as a powerful respiratory stimulus that can dissipate reactive oxygen species (ROS). Knockdown of CKmt1 in animals fed a high-fat diet did not exacerbate HFD-induced insulin resistance, indicating that it is dispensable for high-fat diet-induced insulin resistance. However, CKmt1 is not the predominant creatine kinase in WAT, thus putting into question the relevance of these results. This symposium demonstrated the importance of mitochondrial bioenergetics in metabolic health. Mitochondrial morphology and turnover are vital for organelle function in satellite cells, myofibers, and fat, where impairment in either process carries devastating consequences for organismal metabolic health. How alternations in mitochondrial bioenergetics in one cell type impact organismal metabolism and exercise capacity, and whether augmenting these processes bares metabolic benefits for diseases such as diabetes, remains to be fully elucidated.

Poortmans Lecture (IBEC Honor Award – Presented to Mark Hargreaves): Exercise, Muscle and CHO Metabolism: an IBEC Journey

Jacques R. Poortmans was a dedicated exercise physiologist and a founding father of IBEC. He organized the first meeting, which was held in Belgium in 1968. For over 50 years, IBEC has hosted the leaders in the field and provided opportunities to incite collaboration and innovation. Since the passing of Dr. Poortmans on February 26, 2022, he has left a remarkable legacy. As a tribute, the IBEC Honor

Award will henceforth be entitled the Poortmans Lecture. Mark Hargreaves (University of Melbourne) gave the first Poortmans lecture in Toronto, where he discussed his research journey, including the many individuals he crossed paths with and those who helped him get to where he is today. Throughout his doctoral work, Dr. Hargreaves focused on carbohydrate metabolism, specifically investigating muscle glycogen utilization and exercise performance (10). He demonstrated that glucose transporter type 4 (*Glut4*) expression increased following training but is subject to reductions during detraining (11) (Fig. 1 & 2). More recently, his work has shown that histone acetylation on the *Glut4* gene increases post-exercise as a result of the nuclear export of histone deacetylase 5 (HDAC5), thereby increasing *Glut4* gene expression through myocyte enhancer factor-2 (MEF2) (12). This lecture served as a reminder of the importance and over-arching goals of IBEC. These include bringing like-minded individuals together to foster new connections, share information, and for new ideas to be formulated to help future generations in the quest to enhance human health and performance.

IBEC Young Investigator Award: Illuminating the Role of Compartmentalized Redox Signals in Skeletal Muscle Stress-Adaptations

The 2022 IBEC meeting brought about a record number of applicants competing for the illustrious Young Investigator Award, with no shortage of worthy, emerging scientists up for consideration. Many previous winners of this award have become leaders in the field. Carlos Henríquez-Olguin (University of Copenhagen) was named the 13th recipient of the award for his achievements in studying the role of intracellular redox signaling and its connection to skeletal muscle metabolism in the context of exercise and metabolic diseases. His work identified NOX2 as the predominant myocellular source of ROS during moderate-intensity exercise. Combining human and mouse models, the use of fluorescent dyes and genetically-encoded biosensors, NOX2 was established as a key regulator of GLUT4-dependent glucose transport in skeletal muscle via production of cytosolic ROS (13) (Fig. 2). He next focused on the diffusion and compartmentalization of H_2O_2, a facet of redox control that is regulated by peroxiredoxins (PRDXs) and is subject to disruptions with age and metabolic diseases. Indeed, both mitochondrial, PRDX3, and cytosolic, PRDX2, expression are induced with exercise training in both mouse and human muscle, and the oxidation state of PRDX2 is reduced with 12 weeks of training.

Additionally, PRDX deletion impairs physical performance and reduces lifespan in a *Drosophila* model. Understanding the regulation of ROS production, compartmentalization in muscle, and influence on metabolism is of considerable interest, raising some intriguing questions for future research: How do these processes contribute to age and disease-related muscle pathology? At what threshold do ROS become detrimental? Can nutritional or lifestyle interventions help keep ROS in check?

IBEC Plenary Lecture I:

The PGC-1α-Irisin Pathway: Linking Exercise to Cognitive Function and Neurodegeneration

Bruce Spiegelman (Harvard University) spoke about the cognitive benefits of exercise and the realization of its therapeutic potential for neurodegeneration. The gravity of his work is highlighted by discoveries of proteins that have a profound impact on metabolism, including peroxisome proliferator-activated receptor-gamma (PPARγ), PPARγ-coactivator 1-alpha (PGC-1α), PR domain containing 16 (PRDM16), and more recently, the myokine Irisin (14). In pursuit of circulating mediators of PGC-1α, his laboratory identified Irisin, a muscle-secreted protein (myokine) that communicates to distant organs and potentiates the beneficial effects of exercise. Irisin is a cleaved form of Fibronectin type 3 domain-containing protein 5 (FNDC5), a transmembrane protein that is regulated by PGC-1α and has been shown to cross the blood-brain barrier. Small doses of Irisin have been shown to induce adipose tissue browning and improve cognition in various murine models of neurodegeneration (15). This is likely mediated by a reduction in neuroinflammation and enhanced clearance of aggregated proteins in the brain. Irisin appears to act through the αVβ5, a major integrin receptor, in a process which requires the presence of heat-shock protein 90α (HSP90α) to induce the “open” conformation of integrin and facilitate Irisin binding (Fig. 2). In sum, much has yet to be uncovered about Irisin’s mechanism of action in different organs and tissues. Moreover, the propagation of the beneficial effects of exercise is likely carried out by various secreted molecules that have yet to be identified.

IBEC Plenary Lecture II:

Should Women Exercise During Pregnancy? Discovery of Novel Mechanisms Mediating the Effects of Maternal Exercise on Offspring Health

Laurie Goodyear (Joslin Diabetes centre, Harvard University) described how improvements in glucose tolerance achieved with voluntary wheel running of pregnant rodent mothers (dams) was observed in the offspring one year following birth (16), especially when the mothers were fed a high fat diet. This generational effect of exercise was mediated by maternal exercise-induced cross talk between placenta-derived superoxide dismutase 3 (SOD3) and the offspring's liver (17). Increased placental SOD3 enhances the activation of TET (ten-eleven translocation) proteins, a family of enzymes that demethylates 5-methylcytosine to activate glucose metabolic gene expression in the offspring's liver (Fig. 2). Even more remarkable, exercise-trained grandmother mice were able to pass along epigenetic modifications to the second generation of offspring, thus bestowing their grandchildren with increased insulin sensitivity (16). These data strongly support exercise training during pregnancy as a mitigator of metabolic disease transmission to future generations.

IBEC Plenary Lecture III

Interactions Between Metabolism, Ca^{2+} and Redox Signaling in Skeletal Muscle Fatigue, Recovery and Training Response

Håkan Westerblad (Karolinska Institute) presented discoveries that were fundamental for our understanding of skeletal muscle fatigue, recovery, and training-induced adaptations (18). Decreased Ca^{2+} release from the SR is a key mechanism underlying acute muscle fatigue, a discovery made possible by the pioneering measurements of force production and concentrations of free Ca^{2+} in mechanically dissected single muscle fibers. Three main mechanisms underly the decrease in SR Ca^{2+} release during acute fatigue: 1) impaired sarcolemmal/t-tubular action potential propagation, 2) inhibition of SR Ca^{2+} release by low [ATP] or increased [Mg^{2+}], 3) SR Ca^{2+}-Pi precipitation that reduces the releasable Ca^{2+} in the SR. All three mechanisms can be explained by metabolic factors such as localized glycogen depletion. Moreover, Ca^{2+} and ROS contribute to both the slow recovery from exercise-induced fatigue and beneficial adaptations from endurance training. Specifically, sprint-interval exercise causes ROS-related RyR1 modifications, which can delay recovery but also act as an important trigger of mitochondrial biogenesis. Therefore, cellular Ca^{2+} handling and ROS play an integral role in skeletal muscle fatigue, recovery, and adaptations (18) (Fig. 2).

IBEC Symposium: Epigenetic and Transcriptional Control of Adaptation to Exercise

Recent years have seen substantial progress in uncovering the molecular mechanisms controlling specific facets of exercise-induced adaptations in muscle, including epigenetic memory and the diurnal control of metabolism. Using omics-based approaches, Christoph Handschin (University of Basel) demonstrated that transcriptional responses differ considerably in trained and naïve muscle following acute exercise, in both the type of enriched transcripts and the magnitude of the response (19). Adam Sharples (Norwegian School of Sport Science) addressed the concept of epigenetic memory in skeletal muscle and how it exerts anti-aging effects. Previously trained muscle retains hypomethylated hypertrophic genes, allowing even greater enrichment and thus, adaptation with retraining (20) (Fig. 1). Karyn Esser (University of Florida) discussed the intrinsic circadian clock within muscle, regulated by the key players *Clock*, and brain and muscle ARNT-Like 1 (*Bmal1*) (21). The interaction between training time and the circadian clock suggests that temporal administration of exercise and other therapies should be considered to optimize results. Juleen Zierath (Karolinska Institutet, and the University of Copenhagen) continued the discussion on the diurnal control of signal transduction, substrate metabolism, and the influence of the time of day in the molecular response to exercise. Metabolomic analysis revealed that early morning versus late afternoon training had differential effects on metabolism and glucose control, whereby morning exercise favoured carbohydrate metabolism and afternoon training preferred fat oxidation (22). Altogether, this symposium showcased the latest findings in the molecular mechanisms controlling exercise-induced adaptations in trained and untrained muscles. The genetic and temporal complexity of exercise-induced adaptations raises further questions regarding the potential for epigenetic memory in muscle, interactions between the muscle circadian clock and exercise adaptations, and the impact of energetic stressors and the diurnal control of metabolism.

IBEC Symposium: Redox Signaling During Muscle Use and Disuse

Reactive oxygen species and redox buffers play an active role in regulating muscle metabolism and health, with signaling being highly sensitive to both muscle use and disuse. Darrell Neufer (East Carolina University) presented a theoretical model that applies principles of mitochondrial bioenergetics

to understanding mechanisms of anti-diabetic drug action (23). The organic cationic nature of these compounds increases positively charged molecules in the matrix, thus, decreasing mitochondrial membrane potential and attenuating the efficiency of oxidative phosphorylation. This requires more glucose and fatty acids to generate the same amount of energy, thereby reducing the circulating concentrations of these substrates and improving insulin sensitivity. Malcolm Jackson (University of Liverpool) presented new evidence that hydrogen peroxide (H_2O_2) increases in exercising muscle. However, the concentration of H_2O_2 during contractions is insufficient to activate redox-sensitive signaling pathways directly (24), but instead may act through peroxiredoxin-mediated signaling relays. Scott Powers (Stetson University), described the importance of calpains in inducing mechanical ventilation (MV)-induced diaphragm atrophy (25). Overexpression of the calpain inhibitor, calpastatin, preserved protein synthesis in the diaphragm during MV, a mechanism that seems to involve aminoacyl-tRNA synthetase and is independent of the Akt-mechanistic target of rapamycin (mTOR) pathway. Holly Van Remmen (Oklahoma Medical Research Foundation) then demonstrated how oxidized lipid mediators, including hydroperoxides, act as effectors of muscle atrophy and weakness in response to denervation (Fig. 1). Inhibitors of this pathway, or lipid hydroperoxide scavengers, reduce their content and attenuate denervation-induced muscle atrophy. For example, overexpression of glutathione in murine muscle reduces lipid hydroperoxides and mitigates atrophy and weakness during denervation. This symposium provided theoretical frameworks for modeling the integration of muscle metabolism, ROS generation, and the roles of specific types of oxidants and redox buffers in regulating muscle function. Collectively, the findings demonstrate how highly sensitive redox biology is to both contraction and physical inactivity and inspires new perspectives for the precise roles of ROS and redox buffers in regulating muscle metabolism and health.

IBEC Symposium: Exercise and Adipose Tissue Browning

Adipose tissue browning is a beneficial metabolic consequence of exercise that can occur through various mechanisms, including alterations in bioenergetic, hormonal, and exerkine/myokine profiles. Kristin Stanford (Ohio State University) presented new findings on brown adipose tissue (BAT) adaptations to exercise and the role of the sphingolipid 12,13-diHOME (Fig. 2). 12,13-diHOME is a

lipokine released from adipose tissue in response to exercise and plays an important role in metabolism and cardiac function by regulating fatty acid uptake and insulin action (26). Lawrence Kazak (McGill University) highlighted new factors involved in adipocyte thermogenesis. Focusing on the futile creatine cycle (FCC) in BAT, his laboratory identified creatine kinase B (CKB), a kinase involved in the liberation of ADP in the presence of creatine (27). David Wright (University of Guelph) discussed exercise and temperature-mediated regulation of adipose tissue and systemic metabolism, highlighting the importance of inguinal adipose tissue depots to exercise- and cold-induced metabolic benefits. Topical menthol treatment mimics cold exposure leading to an increase in energy expenditure in BAT through a norepinephrine and transient receptor potential cation channel subfamily M (melastatin) member 8 (TRPM8)-dependent mechanism (28). Rolando Ceddia (York University) questioned the purpose of white adipose tissue browning in the context of exercise. He presented convincing evidence that adipose tissue browning is more likely a metabolic remodelling process rather than a thermogenic one. WAT browning involves the enhanced capacity to break down, export, and resynthesize triglycerides. This remodelling leads to the activation of energy-consuming pathways, such as futile cycles, rather than energy dissipation through mitochondrial uncoupling by uncoupling protein 1 (UCP1) (29). Altogether, this symposium illustrated the complexity of metabolic plasticity in adipose tissue in response to exercise and changes in temperature raising questions for future research: Are there divergent mechanisms which govern thermogenic pathways versus those that mediate metabolic adaptations? What are the factors involved in these adaptations? Can chemo-genetic models be used to identify new exercise-inducible thermogenic pathways?

IBEC Symposium: Mitochondrial Turnover with Exercise in Muscle

Mitochondrial dysfunction lies at the epicentre of many metabolic and aging-related diseases. Thus, adequate mitochondrial turnover is necessary to replenish the mitochondrial pool and prevent excessive damage imposed by dysfunctional organelles in these pathological contexts. Exercise has been shown to stimulate mitochondrial recycling through mitophagy, a selective mitochondrial autophagic process (Fig. 2). Andrew Philp (Centenary Institute) described a biphasic mitophagy response to exercise, wherein exercise-stimulated mitophagy returns to basal levels during acute

recovery and increases again in late recovery. Chronic training also enhances mitophagy, which can rescue the mitophagic decline observed with age (30). Zhen Yan (University of Virginia) reported similar findings, where mitophagy was enhanced 6 hours post-exercise, regulated by Unc-51 autophagy activating kinase 1 (ULK1) and AMP-activated protein kinase (AMPK) (31). Dr. Yan also reported novel findings on the localization of AMPK to the mitochondrial outer membrane during mitophagy, although the mechanism remains unclear (32). Giles Gouspillou (Université du Québec à Montréal) then discussed aging and mitophagy (Fig. 1). He reported that the overexpression of Parkin, an E3 ubiquitin ligase and critical component of mitophagy, in 18 month-old mice mitigates atrophy and declines in muscle strength at 24 months (33). Andrea Hevener (UCLA Medicine) discussed the Hybrid Mouse Diversity Panel (HMDP), a tool that was recently developed to facilitate the identification of genetic correlations, mapping, and statistical modeling methods to address various metabolic research questions. This database compiles RNA-seq data of multiple tissues from over 100 strains of male and female mice that underwent 30 days of voluntary wheel running and will be available on an open-access web-based app. Using this tool, positive correlations were observed between dynamin-related protein 1 (*Drp1*), DNA polymerase subunit gamma 1 (*Polg1*), and estrogen receptor 1 (*Esr1*). Deletion of *Esr1* in skeletal muscle results in hyperfused mitochondria and declines in newly synthesized mtDNA, likely due to decreased expression of *Drp1* and *Polg1*, respectively (34). In contrast, overexpression of *Esr1* confers protection against feeding with a high-fat diet, along with greater mitochondrial content and enhanced running capacity. In sum, this symposium highlighted the importance of exercise-stimulated mitochondrial turnover under various physiological and disease states, while displaying the regulatory complexity of the mechanisms involved. These data provide a strong rationale for further exploring the therapeutic potential of enhancing mitochondrial turnover, through exercise and pharmaceuticals, for the treatment of various diseases and aging.

IBEC Symposium: Stem Cells, Regeneration and Neuromuscular Disease

Muscle growth and regeneration is supported by the myonuclear domain (MND) and muscle niche resident cells, such as satellite cells (SCs) and pericytes. Gianni Parise (McMaster University) uncovered that SCs residing closer to capillaries are more readily activated in response to resistance

exercise (35). He surmised that the age-related atrophy that predominantly occurs in Type II fibers is due to an increase in the distance to capillaries and loss of SCs, both of which are restored with resistance exercise. Indeed, enhancing capillarization with aerobic preconditioning promotes greater increases in muscle mass following resistance training. Charlotte Peterson (University of Kentucky) demonstrated that increases in myonuclear number precede hypertrophy with PoWeR (progressive weighted wheel running) training (36). Interestingly, mice devoid of SCs display a blunted hypertrophic response to training, due to the presence of “cryptic myonuclei” (37). The depletion of satellite cells throughout the lifespan did not exacerbate age-related losses in muscle cross sectional area (CSA), suggesting that SCs may not influence the development of sarcopenia in aging muscle at baseline (38). Douglas Millay (Cincinnati Children's Hospital Medical Center) demonstrated that diversity exists within newly acquired nuclei during post-natal development and with aging, but not during homeostasis. He suggested that muscle fibers with large MNDs require accretion to grow during development, whereas those with small MNDs exhibit hypertrophy prior to accretion (39). Marni Boppart (University of Illinois at Urbana-Champaign) discussed the role of pericytes in muscle mass maintenance and in the incomplete recovery that occurs with remobilization (40). Her group uncovered that pericytes isolated from immobilized limbs fail to upregulate antioxidants in response to an oxidative insult by ROS, but an injection of healthy pericyte-derived EVs into immobilized limbs prior to remobilization promotes enhanced recovery in mice (Fig. 1). Taken together, multiple processes converge to promote muscle growth. Based on the findings discussed in this symposium, future studies may aim to 1) test the efficacy of aerobic preconditioning in clinical populations; 2) understand how myonuclear localization may dictate their functional contribution to muscle; and 3) the impact of harnessing extrinsic factors to promote muscle growth and slow muscle atrophy.

IBEC Symposium: Muscle Protein Turnover and Translational Control of Muscle Mass

The balance between protein synthesis and degradation determines muscle mass, and these processes are subject to alterations in disuse atrophy and cancer cachexia. Marco Sandri (University of Padova) highlighted the role of mitochondrial dynamics in muscle atrophy, where deletion of the fusion protein optic atrophy type 1 (OPA1) causes loss of muscle mass and weakness (41). Cachectic and

pre-cachectic muscles display altered mitochondrial dynamics and increased oxidative stress, inducing interleukin-6 (IL-6) and Noggin expression (Fig. 1). Taken together these maladaptations lead to neuromuscular junction (NMJ) instability, enhanced protein degradation, weakness, and fatigue (42). Furthermore, the E3 ubiquitin ligase Musa1 seems to play an active role in muscle atrophy by promoting the degradation of sarcomeric proteins. Sue Bodine (University of Iowa) outlined the roles of the E3-ligases muscle RING finger 1 (MuRF1; *Trim63*) and Muscle atrophy F-box gene (MAFbx; Atrogin 1; *Fbxo32*) in muscle unloading and reloading in adult and old animals. Despite exhibiting similar levels of atrophy, aged animals experienced a greater loss in force production during unloading (43). Dr. Bodine explained the concept that MuRF1 and MAFbx are great markers of muscle atrophy but not good predictors of proteasome activity. Furthermore, ubiquitination by MuRF1 may act as a priming signal influencing the stability of targets rather than their degradation (44). Troy Hornberger (University of Wisconsin – Madison) answered a long-debated question regarding muscle growth (45). His laboratory used BONCAT (BioOrthogonal Non-Canonical Amino acid Tagging), a novel system to visualize the accumulation of newly synthesized proteins during skeletal muscle growth, to demonstrate that muscle overload-induced increases in myofiber number are mediated by myofiber lengthening in muscle structures known as “sphenodes”. Unlike myofiber hypertrophy, this process is mediated by an mTOR-independent pathway. Stuart Phillips (McMaster University) argued that loss of muscle mass in “simple” disuse atrophy induced by unloading occurs predominantly through reductions in MPS rather than increased proteolysis (46). This is likely mediated by decreased mitochondrial ATP production as a result of reductions in mitochondrial gene expression that accompanies atrophy. Supplementation with omega-3 fatty acids, essential amino acids, or mitochondrially-targeted therapeutics may help combat “simple” disuse atrophy. Therefore, muscle mass is regulated by protein turnover, which is mediated by an intricate and complex web of both short-term signaling pathways and longer-term genetic programs. The interplay between MPS and MPD under various physiological and pathological conditions and their contribution to net muscle loss or gain remains to be better clarified and will likely require a close examination under each physiological and pathological condition, as pathway activation appears to be stimulus specific.

IBEC Symposium: Role of Calcium in Muscle Fatigue, Function and Adaptation

Calcium is a key messenger implicated in proper muscle function, fatigue, and exercise-induced, adaptations. Robyn Murphy (Latrobe University) described the importance of homeostatic control of cytosolic calcium regulation in different muscle fibre types (47). She focused on the ratios of the sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA), phospholamban (PLN), and sarcolipin (SLN) proteins in muscle fibres expressing MyHC I, MyHC IIa, or MyHC Iix. She further discussed the importance of examining muscle at the single fibre level, facilitating the acquisition of meaningful, mechanistic data about the function of ATPases and their regulatory properties. Russ Tupling (University of Waterloo) discussed the role of the SERCA pump in human neuromuscular fatigue (Fig. 2). Exercise to fatigue causes a prolonged depression in SERCA function, whereas exercise preconditioning increases heat shock protein (*Hsp70*) expression and prevents subsequent exercise-induced inactivation of SERCA, thus, attenuating fatigue. Genetic models of SERCA dysfunction (Brody's Disease, SERCA1 KO, PLN overexpression) demonstrate how slowing the rate of SR Ca^{2+} uptake impairs skeletal muscle performance and can cause disease (48). Arthur Cheng (York University) provided insights on CK-2066260, a pharmacological agent that activates troponin in fast-twitch fibers, and its influence on skeletal muscle fatigue caused by impaired SR Ca^{2+} handling. CK-2066260 mitigates fatigue by reducing the energetic demand required by SERCA to produce a given force, and improves force recovery post-exercise (49). The role of calcium in muscle adaptations following sprint interval training (SIT) was discussed by Nicholas Place (University of Lausanne). SIT, in contrast to MICT, results in increased calcium leakage as a consequence of oxidative stress-induced calstabin-1 oxidation and dissociation from the ryanodine receptor (RyR). Interestingly, the calcium leak that arises from SIT results in an increase in mitochondrial content (50). This symposium further cemented the importance of calcium in the regulation of muscle function, fatigue, and exercise-induced adaptations, particularly highlighting the divergent role of calcium in different fibre types. Therefore, future studies should carefully evaluate the role of calcium in the functional regulation of different fibre

types, and vice versa, the impact of fibre type on calcium signaling should be examined under different exercise, physiological, and pathological conditions.

IBEC Symposium: Diabetes and Glucose Metabolism with Exercise

Diabetes has a profound impact on muscle glucose uptake and systemic glucose metabolism with exercise. Exercise, in turn, impacts glycemic control and the management of diabetes. Michael Riddell (York University) described how technological advancements and new insulin formulations have improved clinical outcomes and patient quality of life. However, glycemic control with exercise remains a challenge, as all forms of exercise tend to cause drops in glucose levels, with aerobic exercise promoting the greatest drop in glycemia (~20 mg/dL). Variability in glucose response can be explained by event-level (e.g., exercise type, time of day etc.) and patient-level (e.g., sex, fitness, age, HbA1c level, etc.) variables that could be incorporated into an artificial pancreas device algorithm, thus, making exercise safer by eliminating exercise-associated hypoglycemia (51). Sreekumaran Nair (Mayo Clinic) highlighted the many beneficial effects of regular exercise on diabetes, aging, and mitochondrial health, all of which are linked to reductions in mitochondrial ROS production. Regular exercise offsets high fat diet-induced insulin resistance in hippocampal neurons of aged and insulin-resistant rodents. Similarly, both aerobic and resistance exercise enhance skeletal muscle insulin sensitivity, protein synthesis, and improve mitochondrial function in humans, at least in part by stimulating PGC-1α1 and α4, respectively (52) (Fig. 2). Lykke Sylow (University of Copenhagen) highlighted the critical role of Rho GTPases, such as Ras-related C3 botulinum toxin substrate 1 (Rac1), in skeletal muscle signaling and glucose transport (53). This effect may be linked to mechanical stress on the plasma membrane, ROS production, and mTOR-independent regulation of muscle gains with exercise. Interestingly, Rac1 and AMPK double KO mice have dramatically attenuated exercise-mediated glucose uptake (54). Gregory Cartee (University of Michigan) presented data on exercise-induced GLUT4 translocation to the plasma membrane, involving the phosphorylation of Akt substrate of 160 kDa (AS160). AS160 KO rats are glucose intolerant, insulin resistant, and have lower total GLUT4 abundance. Furthermore, the overexpression of GLUT4 in AS160 KO animals is not sufficient to restore post-exercise insulin-stimulated glucose uptake, suggesting that AS160 is critical for enhancing insulin sensitivity post-

exercise (55). Altogether this symposium focused on the unique metabolic effects that diabetes has on skeletal muscle health, function, and energy metabolism. Despite major progress in the treatment of diabetes, glycemic control remains a challenge for patients and clinicians. Continuing to unravel insulin-independent pathways that enhance glucose uptake could further improve treatment options for patients with diabetes.

IBEC Symposium: Molecular Basis of Exercise-Induced Angiogenesis

Adult skeletal muscle displays an exceptional capacity to induce capillary growth (angiogenesis) in response to the metabolic and biophysical stimuli associated with exercise. Katrien de Bock (ETH Zürich) provided evidence that only a subset of skeletal muscle capillary endothelial cells responds to an angiogenic stimulus. This sub-population was identified by high expression of Activating Transcription Factor (ATF)3/4 (Fig. 2). Her research showed that these transcription factors control the production of amino acid transporters and are required for exercise-induced angiogenesis (56). These findings challenge the long-standing dogma that all skeletal muscle capillary endothelial cells possess the same potential to respond to a given angiogenic stimulus. Ellen Breen (University of California San Diego) presented data supporting the concept that myocyte-derived vascular endothelial cell growth factor (VEGF)-A is required for exercise-induced angiogenesis but is not essential for sustaining capillary number in adult limb skeletal muscle (57). Cigarette smoke extract impaired endogenous VEGF-A production in muscle (58), implicating smoke exposure as an environmental repressor of exercise-induced angiogenesis. Emilie Roudier (York University) introduced the concept that epigenetic regulation of chromatin accessibility dictates angiogenic responsiveness. She presented evidence that the E3 ubiquitin ligase Mdm2 is a multi-faceted regulator of skeletal muscle angiogenesis through controlling transcription factors (59), machinery for microRNA (angiomiR) (60), and potentially through coordinating the redistribution of repressive chromatin marks on angiogenesis-related genes during exercise. Mark Olfert (University of West Virginia) discussed the fate of newly formed capillaries following cessation of exercise training. A substantial decrease in capillary number was detected in mouse muscles after just one week of detraining (61) (Fig. 1). This regression of capillaries coincided with an increase in the angiogenic repressor Thrombospondin-1 (TSP1). In sum, this symposium

highlighted multiple distinct molecular pathways that influence capillary growth and stabilization, reflecting the complexity of skeletal muscle angiogenesis and raising provocative questions for future research: Can the angiogenic population of endothelial cells be expanded to provide more potential for capillary growth? Can exercise improve this angiogenic potential or capillary maintenance by reshaping the endothelial chromatin?

IBEC Symposium: Cancer and Exercise

Cancer cachexia is the loss of skeletal muscle mass and fitness that accompanies many cancers and is a known predictor of poor prognosis. James Carson (University of Tennessee) discussed the role of disuse in skeletal muscle-specific and systemic metabolic dysfunction, and how physical activity can preserve muscle health (62). Voluntary wheel running restores some disruptions in diurnal metabolic flexibility exhibited by tumour-bearing mice, while treadmill exercise improves recovery from fatigue. Andrew Judge (University of Florida) demonstrated that cachectic muscle from both mice and humans presents a downregulation of genes involved in muscle structure and function. While several of these genes are improved with exercise, they are also identified as downstream targets of the nuclear receptor MEF2, a critical factor whose function antagonizes the loss of muscle mass and function in tumour-bearing mice (63) (Fig. 1). Michael De Lisio (University of Ottawa) demonstrated that radiation induces pathological muscle remodeling by enhancing the differentiation of fibroadipogenic progenitor (FAP) cells into pro-fibrotic cells while impairing their secretome, facilitating fibrosis. Interestingly, exercise training can reduce fibrotic and inflammatory gene expression while increasing that of regenerative genes in a rodent model of juvenile cancer. This points to an exercise-induced immunological response that mediates muscle preservation (64). Erin Talbert (University of Iowa) described that reductions in muscle mass are strongly correlated with decreased survival, compromised quality of life, and lower treatment tolerance in pancreatic cancer patients (65). A variety of circulating inflammatory cytokines are associated with muscle wasting during cancer, with considerable heterogeneity in their concentrations. Moreover, mounting evidence suggests that a compromised extracellular matrix and collagen I may play a role in regulating muscle weakness and cancer pathogenesis, generating a new avenue for therapeutic intervention. However, while exercise reduces inflammation, counters catabolism, and stimulates anabolism, there is limited clinical evidence of this in incurable cancers. Collectively, speakers in this symposium highlighted pathways underlying muscle dysfunction during cancer and conventional cancer treatments that have the potential to be modifiable by exercise therapy. Understanding these mechanisms, and how cancer impacts muscle health could

lead to the identification of new therapeutic modalities, including exercise, that preserve muscle function and improve the quality of life of patients.

IBEC Symposium: Symposium: Inter-organ communication with exercise

Metabolic organs including muscle, adipose tissue and the liver communicate through a spectrum of bioactive molecules released into circulation during exercise, together termed “exerkines” (Fig. 2). Mark Tarnopolsky (McMaster Children’s Hospital) discussed EVs and their role in aging, exercise, and fatty liver disease. Acute exercise induces the release of EVs into the blood, returning to baseline with recovery, an effect that is attenuated in trained and aged subjects. The strong therapeutic potential of EVs in mitochondrial DNA disease was also discussed. EVs can be utilized to transfer healthy mtDNA to pathological cells and improve heteroplasmic ratios (66). The discussion of EVs in disease contexts was furthered by Mark Febbraio (Monash University). Analysis of the myokinome following acute exercise indicates an increase in the plasma abundance of approximately 1190 proteins, including proteins that compose extracellular vesicles (67). These myokines may contribute to the attenuated severity of non-alcoholic steatohepatitis (NASH) elicited by exercise training, as purified EVs from trained animals transferred into those with NASH improve hepatic fibrosis, inflammation, and insulin sensitivity. Changhan Lee (University of Southern California) discussed the role of MOTS-c peptide in inter-organ communication. Encoded within 12S ribosomal RNA locus of mitochondrial DNA, MOTS-c is exercise-inducible and promotes metabolic homeostasis during feeding with a high fat diet, likely through AMPK. Furthermore, MOTS-c treatment improved running distance and insulin sensitivity in aged mice, as well as cell survival and proliferation in serum-starved muscle cells, an effect that may be mediated by heat shock factor-1 (HSF-1) (68). John McCarthy (University of Kentucky) then dissected the role of satellite cells in mediating intercellular communication during exercise (69). Fibrosis in the absence of satellite cells is mediated by the loss of miR-206 from satellite cell EVs that inhibits fibrogenic cell collagen synthesis. Moreover, levels of microRNA-1 (miR-1), a factor known to regulate lipolysis and the expression of mtDNA-derived transcripts, are reduced in muscle during mechanical overload, but abundant in serum EVs. miR-1 containing EVs are transported to distant adipose tissue and promote lipolysis. This symposium demonstrated the importance of inter-organ signaling through

various exerkines and EVs in mediating exercise-induced adaptations. However, this field is still in its infancy with many controversies surrounding EVs including divergent isolation methodologies, inconsistencies in findings, and uncertain treatment efficacy. Strong, consistent, and transparent study design as well as reproducibility will be key for the future progress of this field.

IBEC Symposium: Exercise and Immune Function

The effects of exercise on immune responses have been well documented over the past three decades. With recent seminal advancements in our understanding of the intricate interplay between immune responses and metabolism, emerging research is exploring the link between exercise, metabolism, and immune responses. Ali Abdul-Sater (York University) presented insights into achieving a balanced inflammatory response following exercise. Long-term moderate exercise alters inflammatory responses in mouse bone marrow-derived macrophages by reducing the activation of pro-inflammatory transcription factor (NF-κB), expression of pro-inflammatory cytokines (IL-1β, TNF-α), and activation of inflammatory signaling pathways (iNOS, HIF-1α) (Fig. 2). Conversely, moderate exercise increases the expression of anti-inflammatory markers and signaling pathways (IL-10, Arginase-1, Hmox1, Irg1). These effects are mediated by changes in chromatin accessibility in regions that are important for the induction of inflammation, controlling metabolism and oxidative stress (70). Frank Mooren (University of Witten/Herdecke) discussed the role of circulating miRs in exercise immunology, highlighting their role in regulating exercise-induced changes in mRNA and protein expression. miRs specific to heart, skeletal muscle, and those involved in inflammation present different circulatory profiles following exercise, acting as useful biomarkers of exercise capacity and adaptations to endurance training (71). Jorge Ruas (Karolinska Institutet) discussed how novel proteins that mediate signaling between muscle and the immune system impact energy homeostasis and muscle regeneration. The metabolite of kynurenine, kynurenic acid, is released from skeletal muscle during aerobic exercise and can activate G protein-coupled receptor 35 (GPR35) in immune and adipose cells, to regulate both immune cell function and adipose tissue energy expenditure (72). Richard Simpson (University of Arizona) presented therapeutic applications of the effector lymphocyte response to exercise, demonstrating that acute exercise preferentially mobilizes effector lymphocytes such as natural killer-cells, gamma-delta

(γ/δ) T cells, and cytotoxic (CD8+) T cells, while increasing lymphatic transportation of neutralizing antibodies. Intriguingly, the frequent mobilization and redistribution of these cells with every exercise bout has been purported to increase immune surveillance and protect the host from malignancy and viral infections (73). This symposium demonstrated that exercise-mobilized immune cells may have therapeutic benefits for cancer patients. Indeed, mobilized cells have been shown to extend survival and reduce leukemic burden in xenogeneic mice. This could have clinical implications for treatment of various cancers, however, many questions regarding specific exercise prescriptions, patient selection, and mechanisms of action remain to be addressed before this can become an accepted treatment modality.

IBEC Symposium: Aging Muscle and Neuromuscular Diseases – Response to Exercise

The efficacy of exercise as medicine for neuromuscular diseases and aging has been demonstrated time and again but has not been universally adopted by physicians. Vladimir Ljubicic (McMaster University) evaluated the use of a single dose of exercise as molecular medicine for myotonic dystrophy type 1 (DM1), a multisystemic neuromuscular disorder. A single bout of exercise stimulated mitochondrial dynamics and turnover in the skeletal muscle of a mouse model of DM1, thus, highlighting the potential therapeutic benefits of exercise as mitochondrial medicine (74). Mark Tarnopolsky (McMaster University) discussed exercise biochemistry in mitochondrial myopathy patients and aging, suggesting that exercise is the most beneficial therapy available for patients since there are currently no, or limited, pharmacological therapies (75). Beth Phillips (University of Nottingham) discussed the impact of high-intensity interval (HIIT) training on octogenarians with disease. She demonstrated that HIIT training is safe and effective at improving body composition, cardiorespiratory fitness, and protein synthesis (FSR), and that these improvements are likely mediated, at least in part, by an increase in mitochondrial capacity (76). Aymeric Ravel-Chapuis (University of Ottawa) presented promising data on combining exercise with the pharmacological augmentation of AMPK to treat DM1. Exercise appears to potentiate the drug-induced activation of AMPK and improve alternative splicing in DM1 mice (77). This symposium highlighted the far-reaching potential of acute and chronic exercise for the treatment of genetic and geriatric disease. Exercise should therefore be further investigated as part

of a comprehensive therapeutic strategy for age-related as well as neuromuscular and mitochondrial diseases.

IBEC Industry Innovation Workshop: Aurora Scientific

Aurora scientific demonstrated a methodology-focused overview of three main experimental techniques for assessing contractility of murine muscle. Experimental practices were highlighted for the in-vivo (footplate), in-situ, and in-vitro techniques. This was supported by video of the experimental surgeries, animal manipulation and preparation, electrode placement and experimental setup.

Conclusions

Exercise science is a multifaceted and multidisciplinary area of research, combining cellular, murine, and human research in the spectrum of biology, physiology, genetics, and biochemistry. Continuing to unravel the mechanisms of exercise signaling and its many downstream health benefits has implications for our understanding of a spectrum of pathological conditions and diseases, including aging, disuse atrophy, diabetes, obesity, mitochondrial DNA, and neuromuscular diseases. IBEC 2022 highlighted the importance and effectiveness of exercise as a therapeutic strategy for a multitude of diseases as well as its utility as a model for studying systemic metabolism, angiogenesis, proteostasis, mitochondrial quality and inter-organ communications. The information presented at this conference will undoubtedly generate many projects, collaborations, and formulate new ideas, progressing the field of exercise biochemistry to help future generations live healthier and longer lives.

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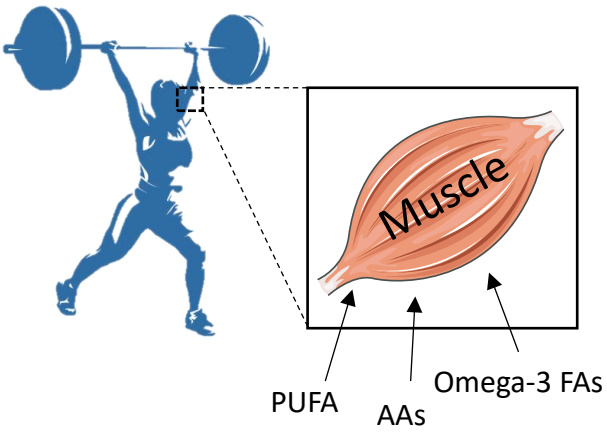
Figure legends

Graphical abstract: The many systemic benefits provided by regular exercise and their impact on health were highlighted at IBEC 2022. The activation of various tissues, organ systems, and their secretomes during exercise leads to improvements in metabolism, cognition, immunity, angiogenesis, and overall vitality.

Figure 1: Skeletal muscle adaptations to resistance exercise and muscle wasting/sarcopenia. During resistance training, skeletal muscle protein synthesis increases beyond protein degradation resulting in muscle hypertrophy, which is further positively influenced by supplementation with PUFAs, AAs and omega-3 FAs. Several effectors that contribute to muscle hypertrophy are listed. During muscle atrophy induced by sarcopenia, disuse or other muscle-wasting conditions, protein degradation outweighs protein synthesis resulting in the net loss of muscle mass. Atrophy is often accompanied by fatigue, inflammation, NMJ instability, oxidative stress, fibrosis, and satellite cell malfunction/depletion. There are many effectors of muscle atrophy (some of those discussed in the symposia are listed), and the inhibition or blockade of some of those could mitigate muscle wasting. PUFA=polyunsaturated fatty acids; AAs= amino acids; FAs= fatty acids; MPS= muscle protein synthesis; SMIS = skeletal muscle insulin sensitivity; MPD=muscle protein degradation; NMJ=neuromuscular junction.

Figure 2: Adaptations to aerobic exercise training. Exercise induces pleiotropic benefits by impacting various tissues, including skeletal muscle, brain, adipose tissue, blood vessels, immune cells and developing fetus. Exercise enhances systemic crosstalk by influencing the factors secreted from several tissues and induces tissue- and cellular- remodeling by altering short-term cellular signaling and longer-term genetic and epigenetic reprogramming. Exercise-induced adaptations and some specific molecular mediators discussed at the various symposia are listed. BDNF**=**brain-derived neurotrophic factor; TET = ten-eleven translocation BACE1=beta-site amyloid precursor protein cleaving enzyme 1; MPS= muscle protein synthesis; SMIS = skeletal muscle insulin sensitivity; WAT= white adipose tissue; BAT=brown adipose tissue; ROS=reactive oxygen species; FCC= Futile creatine cycle; Cr=creatine; PCr= phospho-creatine.

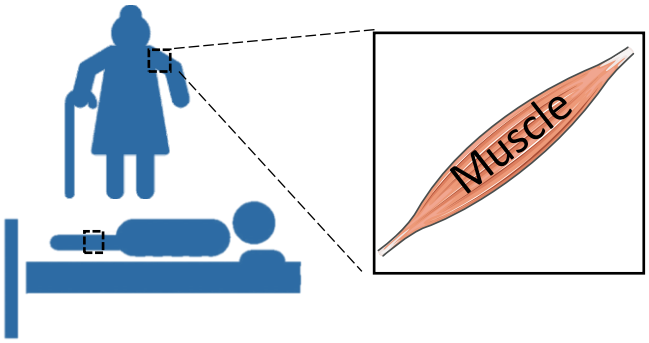
Protein Degradation < Protein Synthesis



Effectors of muscle hypertrophy

- ↑ MPS
- ↓ Methylation hypertrophic genes
- ↑ Capillarization
- ↑ Myonuclei
- ↑ SMIS
- ↑ PGC-1α4

Protein Degradation > Protein Synthesis



Effectors of muscle atrophy

- ↑ GSK-3β
- ↓ MPS
- ↓ Glut4
- ↓ Mitophagy
- ↑ Calpain
- ↑ Oxidative stress (hydroperoxides)
- ↓ OPA1
- ↑ IL-6
- ↑ Noggin
- NMJ instability
- ↑ Fatigue
- ↑ MPD
- ↑ Musa1
- ↑ MuRF1
- ↑ MAFbx
- ↓ Mitochondrial ATP production
- ↓ Capillarization via ↑ TSP1
- ↓ MEF2
- ↑ Inflammation
- ↑ Cytokines
- Compromised extracellular matrix
- ↓ Collagen I
- Pericyte impairments

Figure 1

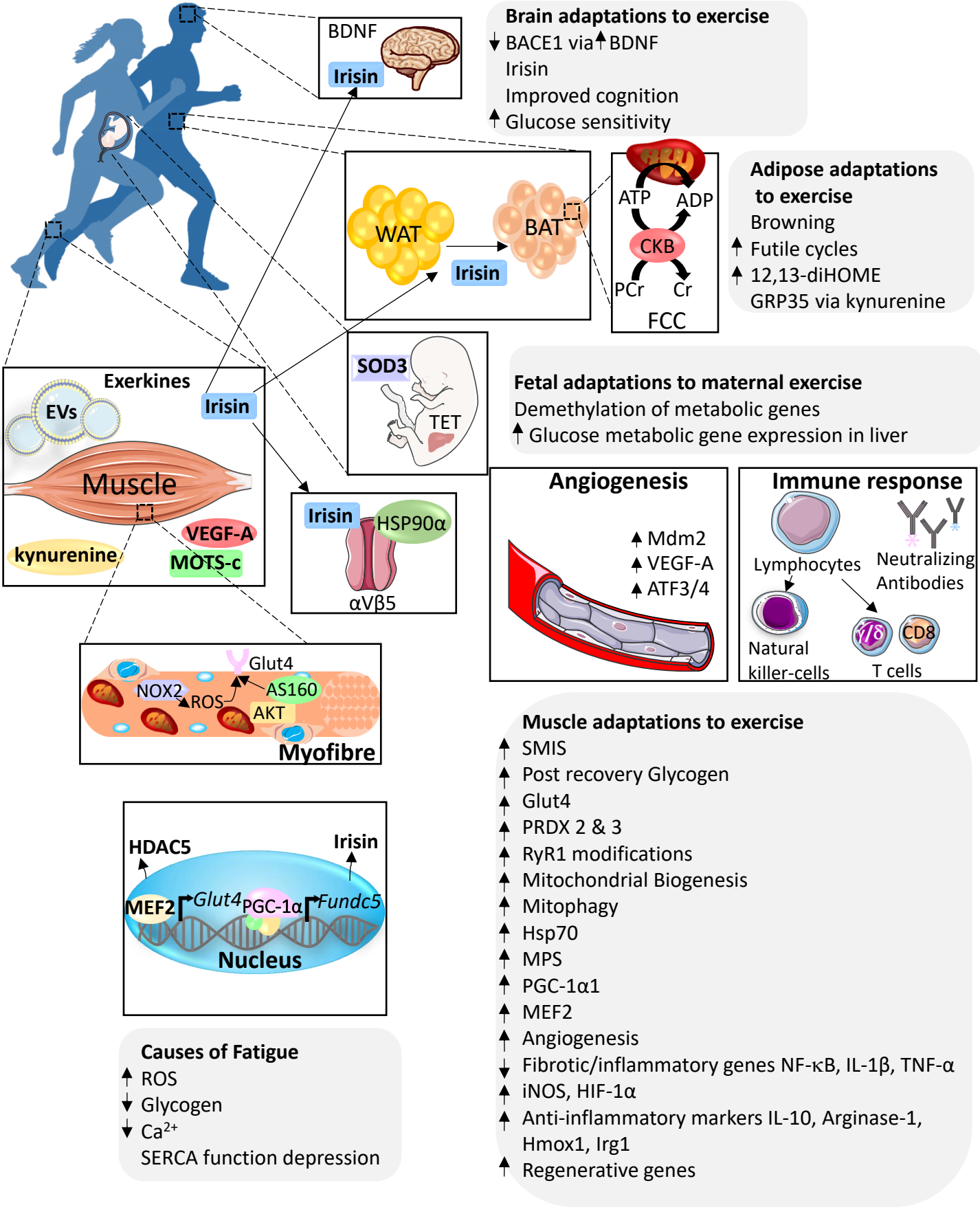
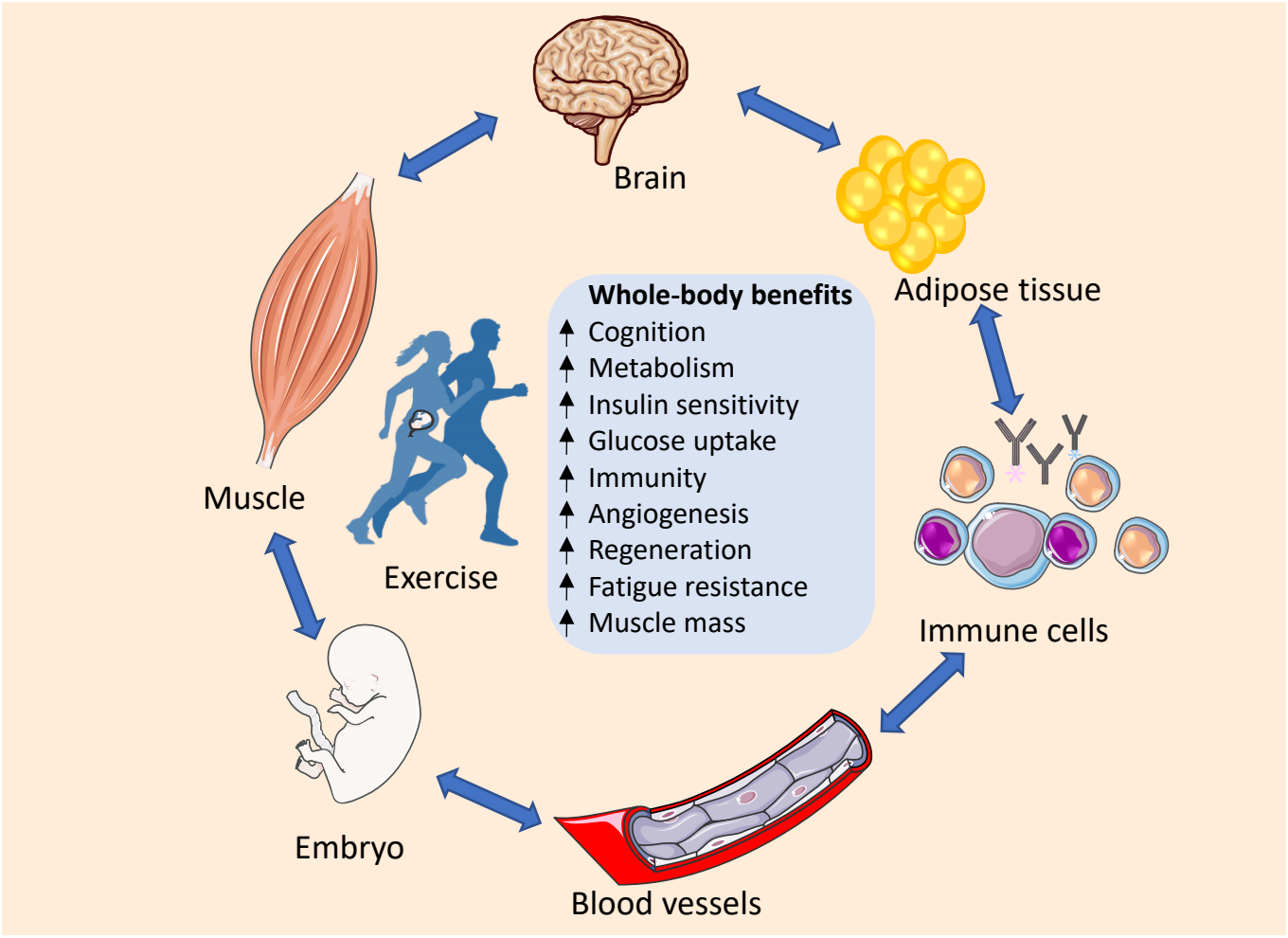


Figure 2

The systemic benefits of regular exercise presented at IBEC 2022



Conclusion: The many systemic benefits provided by regular exercise and their impact on health were highlighted at IBEC 2022. The activation of various tissues, organ systems, and their secretomes during exercise leads to improvements in metabolism, cognition, immunity, angiogenesis, and overall vitality.