Cellular powerhouse

Professor David Hood, Canada Research Chair in Cell Physiology, discusses how mitochondrial dysfunction contributes to the cellular basis of ageing

How does studying mitochondrial biogenesis in health and disease contribute to an understanding of the mechanisms of ageing?

The topic of ageing and mitochondria is not new. It has a long history. There are mitochondrial theories of ageing which have been discussed for several decades about the fact that in ageing tissue, not just muscle, mitochondria produce excessive amounts of reactive oxygen species (ROS). These cause damage to macromolecules like DNA, proteins and lipids, leading to progressive ageing. Our work focuses on skeletal muscle and the consequences of excessive ROS formation on apoptosis (cell death), muscle atrophy, aerobic energy supply and the adaptation of the muscle to exercise and/or atrophy-provoking conditions like nerve injury. We have found that whilst ageing muscle can adapt to these situations, the magnitude of the adaptation is considerably less than what might be found in young muscle.

Is mitochondrial biogenesis reactive to changes in the need of muscular tissue and how does this responsiveness alter with ageing?

Mitochondrial biogenesis responds readily to changes in energy demand, in all species of animal. Think of the dark meat and the white meat in a chicken or turkey. Dark meat is dark because it has more mitochondria. This is found in the highly motive leg muscles. White meat is found in the turkey breast, which is relatively inactive. The same can be said about the heart, which is always beating and therefore always requires mitochondrial energy supply. The heart is very red, reflecting a high mitochondrial content. Mitochondrial responsiveness to changing energy needs is reduced in ageing muscle.

In what ways is the use of animal models beneficial for the study of mitochondrial biogenesis?

Animal models are critical for our work. In ageing, we use the Fischer Brown Norway rat as a model, which is well accepted around the world because these animals live long lives without much pathology. Our transgenic and knockout mouse models help us to understand the role of specific proteins in mitochondrial biogenesis, either with exercise or in conditions of muscle disuse.

Does transcriptional and post-transcriptional regulation of proteins have an impact on mitochondria?

Transcription is very important for the synthesis of the majority of mitochondrial proteins. Once transcribed, the proteins are translated in the cytoplasm before being post-translationally imported into mitochondria via the protein import machinery. We have shown that the import process is accelerated by exercise in muscle from both young and old animals, providing an excellent safety factor in the event of disease processes that might tend to reduce the function of the import pathway.

Can you elaborate on some of the advanced methodologies that you use for your work? How do the facilities available at York University and the Muscle Health Research Centre (MHRC) help you achieve your research goals?

Our laboratory and the facilities found within the MHRC allow us to advance the study of muscle development, disease, metabolism and adaptation to exercise at the highest level. We have space and equipment which permits us to study muscle cells in culture; animal models of exercise and disease – including genetic models; and facilities for human trials and tissue analyses. Analytical equipment such as flow cytometers, real-time polymerase chain reaction (PCR) instruments, molecular biology equipment, tissue culture and core facility areas all support the research programmes of MHRC members and their graduate students. The MHRC is a unique facility which should be sought after by individuals interested in continuing their training in 'muscle health' research.

How does the MHRC facilitate the formation of important collaborations?

Several MHRC members are involved in collaborative research projects with other scientists. Being part of the MHRC allows us to achieve national and international visibility and this facilitates the collaboration process. Our multidisciplinary approaches are also appealing to investigators who wish to look beyond one single aspect and reach for a broader approach to muscle health.

Muscle ageing

Research from the Muscle Health Research Centre at York University, Canada, is investigating the molecular mechanisms underlying the plasticity of muscle and the adaptation of mitochondria

MITOCHONDRIA ARE LARGE, complex organelles found within most eukaryotic cells. They are the main site of a cell's adenosine triphosphate (ATP) production – the most significant source of energy for cellular work functions. Mitochondria have two layers of membrane. The first, the outer membrane, contains many transport channels which allow the movement of large molecules across the membrane. The second inner membrane is the site of ATP synthesis – highly folded to increase its surface area and maximise its efficiency.

The size and number of these organelles is responsive to the varying needs of different tissue types. Cells in the skin, for example, have low energy requirements, so have proportionally less mitochondria than cells in cardiac or skeletal muscle that require lots of energy to power their constant contractile activity. Not only are there differences in mitochondrial mass between tissue types, some cells, such as skeletal muscle, are highly 'plastic', or adaptable. The mass of mitochondria can therefore change quite dramatically in response to variations in muscle use. For example, chronic disuse brought about by illness, disability or cellular pathology reduces mitochondrial mass and brings about diminished endurance and ability to perform regular activities.

The molecular mechanisms that underlie this plasticity remain poorly understood. These include the regulation of gene expression, the signals that regulate transcription, the translocation of proteins into the mitochondria and the organelle's assembly and degradation. A group of researchers, led by Professor David Hood at York University in Toronto, Canada, is studying the molecular mechanisms underlying mitochondrial regulation and biosynthesis to contribute to the elucidation of these unknown pathways.

MITOCHONDRIA AND DISEASE

The broad research programme of Hood's group involves the study of mitochondria in health and disease. "Mitochondria metabolise fat, so disturbances in mitochondrial function or reduced mitochondrial content can lead to an accumulation of lipid metabolites in tissue like muscle. This can, for example, inhibit insulin action and lead to insulin resistance and Type II diabetes," explains Hood, emphasising how the effectiveness of mitochondrial function can influence the development of disease. Similarly, because heart tissue has such high energy demands, mitochondrial defects in cardiac cells can lead to insufficient energy supply, cell death and heart failure.

AGEING

The researchers at York University focus on skeletal muscle as the main regulator of whole body metabolic rate and the largest human organ. Mitochondrial biogenesis is highly adaptable and, in muscle, cells can increase their mitochondrial content by 50-100 per cent in response to regularly performed exercise. By studying how the rate of mitochondrial biogenesis responds to changes in activity levels they hope to understand more about the underlying regulatory mechanisms. Currently, they are particularly interested in elucidating how differences between the responses of mitochondria in the muscle of young people, in contrast to the elderly, lead to reduced mitochondrial content in aged muscle.

Aged muscle is characterised by a loss of muscle mass – termed sarcopenia – which leads to muscle wasting, increased frailty, loss of strength and increased susceptibility to falls and fractures. Increasingly, muscle mass loss is being attributed to mitochondria. Indeed, evidence from studying aged tissue has shown it to be characterised by a decline in mitochondria cell content, organelle fragmentation, functional disruption and the production of damaging reactive oxygen species (ROS).

The group's work has also demonstrated that older muscle is less efficient than younger muscle at adapting to changes in exercise habits. Older muscle is less able to activate signalling pathways which lead to the synthesis of productive mitochondria, and it also appears to remove damaged and worn out mitochondria less efficiently, a process termed 'mitophagy'.

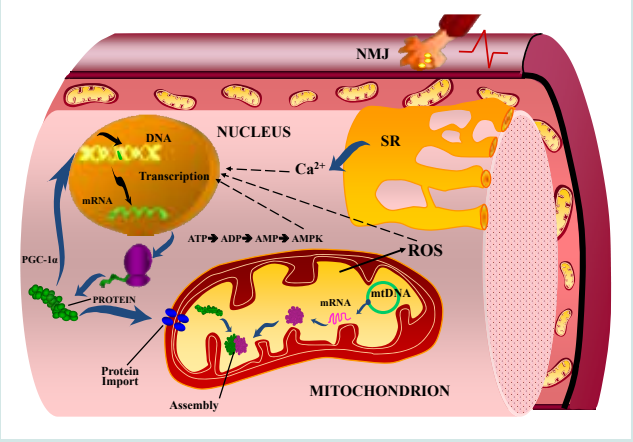
Hood's research group including their research focus (from left to right): Heather Carter (Biogenesis), David Hood, Sobia Iqbal (Morphology) and Anna Vainshtein (Mitophagy)

ELUCIDATING MECHANISMS

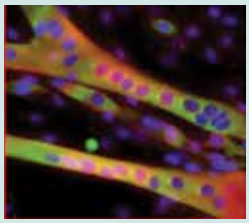
The regulation of mitochondria biogenesis resulting from exercise is multifaceted. Firstly, it is dependent on changes to the levels of cytosolic calcium that occur on muscle contraction, along with increased ROS production, and the activation of an enzyme, adenosine monophosphate (AMP) kinase due to exercise-induced breakdown of ATP to AMP. "These three signals lead to the activation of transcription factors in the nucleus, which turn on the expression of genes encoding mitochondrial proteins, and turn off genes encoding glycolytic enzymes, thereby making the muscle cell more 'aerobic' in nature," explains Hood.

At the molecular level, the researchers have studied how mitochondrial biogenesis is elevated as a result of exercise via increased activity of PGC-1α and SirT1, which are involved in activating the transcription of nuclear genes that encode the necessary mitochondrial proteins. These proteins are then imported into the mitochondria via import receptors and channels within the inner and outer membranes of the organelle. This process is vital for proper mitochondrial biogenesis and function as only 13 out of 1,500 mitochondrial proteins are synthesised from mitochondrial DNA (mtDNA) within the organelle. Transcription of this small group of genes within mtDNA is modulated by mitochondrial transcription factor A (Tfam). Regular exercise can also increase mitochondrial biogenesis by increasing the expression and action of Tfam, resulting in increased translation of important mitochondrial proteins.

Hood's research has shown that these signalling pathways are less highly activated in ageing muscle, even when subjected to the same exercise stimulus. This has led him to deduce that the reduced adaptation response is due to a lessened response to exercise.



Signals for mitochondrial biogenesis as result of exercise include calcium released from sarcoplasmic reticulum (SR), ROS produced by mitochondria and the activation of AMP-activated protein kinase via the breakdown of ATP. These signals affect transcription, leading to the production of proteins which can be imported into mitochondria and assembled into multi-protein complexes to make ATP Exercise-induced signalling is reduced in ageing muscle.



Muscle cells grown in cell culture can be electrically stimulated to contract, producing an experimental model of 'exercise-in-dish'.

Anatomy of a muscle fiber, showing multiple nuclei (blue) and internal myofibrils containing actin and myosin, and surrounded by mitochondria.

MUSCLE HEALTH RESEARCH CENTRE

Alongside leading this groundbreaking research and promoting his mitochondrial work at international meetings and science communication events, Hood has also founded the Muscle Health Research Centre (MHRC) at York University. This represents the largest agglomeration of skeletal muscle researchers in Canada, whose points of focus include muscle blood supply, relationship to other important organs like adipose tissue, and role in health, ageing, exercise and disease. Still in its infancy and thus rapidly growing, the Centre is currently made up of 15 faculty members leading their own teams of graduate students in the areas of kinesiology, health science and biology. "This research focus is both timely and vitally important, given our increasingly aged demographic, as well as our society that is characterised by physical inactivity, overweight/obesity and metabolic diseases, such as Type II diabetes," elaborates Hood.

A great motivating factor for the researchers within the MHRC is that many of the atrophy and metabolic dysfunctional processes that affect skeletal muscle can be reversed or attenuated by physical activity, to the benefit of patients, especially if the underlying mechanisms of muscle conditions can be elucidated. To maximise the research output, the Centre employs a multidisciplinary approach, studying muscle at all levels of organisation from molecules and cells, to organ function and whole body metabolism. Through collaboration, knowledge gleaned from these different levels can be combined to increase understanding of the muscle system as a whole.

The Muscle Health Research Centre facilitates the integrated and broad study of muscle biology, including muscle development, disease, metabolism, blood supply, injury and regeneration, and adaptation to acute and chronic exercise. Approaches used by faculty and graduate students include molecular, cellular and whole-body techniques

Hood envisions that "the Muscle Health Research Centre will become Canada's leading research centre for the study of muscle health and disease". The united goal of its researchers is to help people maintain a good quality of life and functional independence by generating a greater understanding of skeletal muscle function.

Skeletal muscle accounts for 40 per cent of a human's body mass. It is a unique and large tissue that significantly contributes to an individual's metabolism, locomotion, and overall quality of life

INTELLIGENCE

CANADA RESEARCH CHAIR IN CELL PHYSIOLOGY

OBJECTIVES

To study to role of mitochondrial biogenesis in health and disease with a focus on mammalian skeletal and cardiac muscles. Specific current points of interest include the transcriptional and post-translational regulation of nuclear-encoded mitochondrial genes and how exercise affects mitochondrial morphology.

KEY COLLABORATORS

Members of the Muscle Health Research Centre (see **www.yorku.ca/mhrc**) focusing on research related to muscle development, disease, metabolism, and adaptations to exercise

FUNDING

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DAVID A HOOD is a Professor and Tier I Canada Research Chair at York University, Canada. After completing his Bachelor's degree in Physical and Health Education at Queen's University and his MSc degree at Dalhousie University, he studied his PhD at the State University of New York in Syracuse. He has been a member of both the Canadian Society for Exercise Physiology and the American College of Sports Medicine since being a graduate student. He is also a member of the American Physiological Society. Because he believes in the importance of exposing early career researchers to a broad range of research, as well as meeting other researchers, Hood and the members of his lab regularly organise, attend and present papers at the annual meetings of these societies.

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