



# Investigating the properties of satellite cells

**Dr Thomas Hawke** explains his research into the control of satellite cells during physiological stresses. In an illuminating discussion, he outlines the lab's most recent discoveries linking skeletal muscle health to the prevention and recovery of myopathic diseases

## Why are you focusing on the role and regulation of satellite cells in disease states?

Understanding the capacity for growth and repair of muscle in healthy and diseased states has been our primary focus. Two disease states of particular interest to us are diabetes mellitus and muscular dystrophy. Defining the role and regulation of satellite cells has an inherent relationship with myopathic diseases, so our work with muscular dystrophy was a natural progression from this. Our investigation of diabetes originated from discussions with Dr Michael Riddell when I was working at York University. As our discussions progressed, I realised that very little was known about skeletal muscle growth and adaptation in the diabetic state. Type 1 diabetes (T1DM) was particularly pertinent to this kind of research as disease onset generally occurs in childhood; a time of robust musculoskeletal growth. My interest in this topic grew from these initial stages and I have been an active researcher in that area ever since.

## Can you outline the group's efforts to date in elucidating the role of Xin protein in muscular dystrophies?

Our studies have demonstrated that Xin is a regulator of satellite cell activity. We have exclusively determined that while Xin protein is undetectable in undamaged skeletal muscle, its expression increases significantly in damaged muscle tissue. In fact, our lab has recently demonstrated that the expression of Xin is highly correlated with the degree of muscle damage. This study was undertaken using more than 45 human biopsy samples from patients with a variety of myopathic conditions, such as inflammatory myopathies

and limb girdle muscular dystrophy. These properties of Xin make it a strong candidate for use in clinical trials that assess muscle damage; for example, statin myopathy trials. Our current studies are focused on further defining expression patterns of Xin in myopathy. We are also working to determine the contribution of Xin mutations in muscular dystrophies of unknown aetiologies.

## Could you expand on these efforts to study the aetiology and effects of diabetes on skeletal muscle growth and repair?

In diabetes, the health of skeletal muscle is often overlooked clinically because of other overwhelming complications. These may include cardiovascular disease, neuropathy and nephropathy. Though skeletal muscle is remarkably resilient and can maintain basic function in diabetes mellitus, this does not equate to 'healthy muscle'. Impairments in skeletal muscle health (decreases in mass, strength and regenerative and metabolic capacity or flexibility) can be observed in very early stages of a T1DM onset. Skeletal muscle is the largest metabolic organ and it is capable of both insulin-mediated and contraction-mediated glucose uptake. An increase in healthy skeletal muscle would allow a greater 'sink' for glucose disposal, thereby reducing the time spent in a hyperglycaemic state.

## Based on your current findings, what does the future hold for your research?

Based on the findings of our work and other research, we have proposed the new hypothesis that impairments to muscle health in diabetes mellitus precede other diabetic complications. In fact, they exacerbate these complications by impairing normal metabolism

and reducing the capacity for glucose uptake. Our current investigations are working towards testing this hypothesis.

## What ultimate impact do you foresee this work having on diabetes-focused clinical research and care?

We have now demonstrated convincingly that while T1DM may begin with a state of hyperglycaemia caused by hypoinsulinaemia, the disease is far more complex than this. Our recent studies have shown that diabetic mice display impaired muscle growth and repair from injury. My team has also made discoveries related to plasminogen activator inhibitor-1 (PAI-1), an enzyme in the blood that regulates clot breakdowns. As in diabetic humans, we have demonstrated that PAI-1 is elevated in the blood of diabetic mice. When we restore the mice's PAI-1 levels to normal, we can rescue their impaired regeneration, even without correcting their diabetic state. These findings strongly suggest that effective treatment of T1DM must develop beyond insulin 'mono-therapy'.

These results led us to screen the blood of diabetic mice and humans to determine other factors which may be dysregulated. The restoration of their expression may aid in delaying other diabetic complications. Moreover, expression levels of various factors are being compared to screenings of diabetic mice with a variety of exercise paradigms in the hope of identifying factors which may be modulated by lifestyle versus pharmacological intervention.

I feel very strongly that the results of these studies will reveal a new important area of clinical research and diabetes care.

# Understanding changes to muscle health in chronic diseases

A research team at **McMaster University**, Ontario, Canada is conducting research into the role and regulation of muscle satellite cells in health and chronic disease. Their findings help alleviate the complications of disease states such as diabetes mellitus and muscular dystrophy

**WHILE IT IS** generally accepted that an unhealthy lifestyle leads to poor skeletal muscle health, strong evidence now links muscle health with morbidity and mortality in a variety of diseases. Grip strength is now used clinically as an indicator of overall muscle health, and in fact studies have demonstrated its effectiveness in gauging mortality risks for the elderly and those suffering from disease (eg. cancer). These positive findings exist independently of other variables, highlighting the importance of a healthy skeletal muscle mass to overall wellbeing.

The relationship between muscle health and overall wellbeing is even more pronounced in metabolic disease states such as diabetes mellitus. Decreased skeletal muscle health limits physical capacities, which in turn negates the positive effects of physical activity. However, there are even more significant implications. Skeletal muscle is the largest metabolic organ, and a decrease in its health may have profound effects upon the basal metabolic rate, insulin sensitivity, blood glucose management and blood lipid control. While skeletal muscle health is now generally understood to be important for the prevention and care of Type 2 diabetes (T2DM), a deeper understanding of its role is still lacking – and its relationship to Type 1 diabetes (T1DM) is virtually unknown.

## SATELLITE CELLS

Skeletal muscle has an impressive capacity for growth and repair from injury. The primary

muscle stem cells, termed satellite cells, play a critical role in these processes. Satellite cells share many characteristics with stem cells; they can divide numerous times, self-renew their population and enter a state of quiescence when not needed. The satellite cells will remain inactive (in quiescence) at the periphery of muscle fibres until a stimulus, such as muscle damage, triggers them to become 'activated'.

Muscle nuclei are post-mitotic (incapable of proliferation), meaning that the inclusion of new nuclei to support muscle growth, maintenance or repair comes from the satellite cell population. Satellite cells 'donate' their nuclei in order to allow for muscle to adapt to a variety of stresses. Upon activation, the satellite cells will migrate to the site of the damage and undergo extensive proliferation. In this way they create progenitor cells, termed myoblasts, which are destined to become muscle. At the appropriate time, these myoblasts will undergo fusion and differentiation to repair damaged muscle, or even generate new muscle fibres if the damage is extensive.

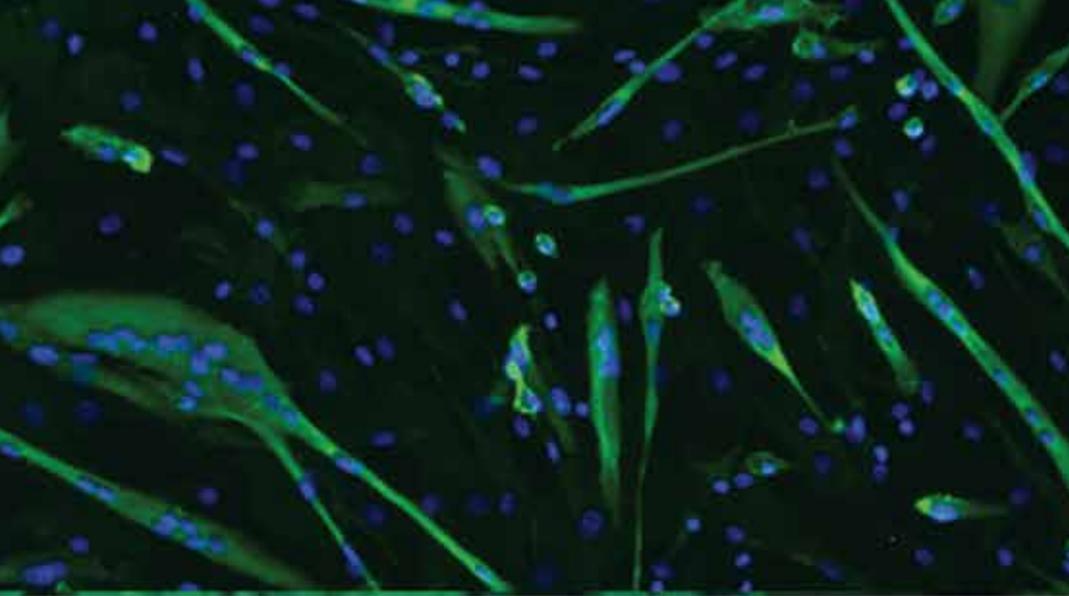
## RESEARCH FOCUS

Hawke and his research team are attempting to define the impact of chronic disease on skeletal muscle health and its primary stem cell population by using a variety of molecular, cellular and physiological techniques. These include histology, immunohistochemistry, protein and RNA assays and the isolation of single fibre and primary myoblast cultures. Currently, his lab is involved in two major

projects: (1) defining the role of Xin in the muscular dystrophies; and (2) understanding the alterations to muscle health in diabetes (ie. diabetic myopathy).

Xin is a muscle specific actin-binding adapter protein. Changes in its expression are currently linked to the remodelling of striated muscles following damage, and in cardiac morphogenesis, though its exact role is still unknown. Hawke's previous investigations have shown that Xin is upregulated during the early phases of mouse skeletal muscle regeneration and his most recent work has demonstrated Xin expression in damaged human skeletal muscle. Importantly, a high correlation between the degree of damage and the expression of Xin exists, suggesting it may be an effective marker for muscle damage in clinical trials with muscle health as a primary outcome. With respect to satellite cells, Hawke's group has shown that Xin plays an important role in the ability of satellite cells to exit quiescence and become activated. Currently, his team are conducting further investigations into the mechanisms underlying Xin's action and defining novel binding partners in these activities.

Regarding his work on diabetic myopathy, Hawke has been focusing on T1DM. This results from the autoimmune mediated destruction of the pancreatic B cells, which leaves the patient in a state of hypoinsulinaemia and hyperglycaemia (T1DM is often referred to as insulin-dependent diabetes). There are many complications associated with T1DM, including retinopathy, nephropathy, neuropathy and



## INTELLIGENCE

### MECHANISMS REGULATING MUSCLE HEALTH IN WELLNESS AND DISEASE

#### OBJECTIVES

- To determine the role and regulation of Xin within the muscle satellite cells and clarify its relationship with other known signalling proteins
- To evaluate the function of Xin within the whole animal in response to exercise or toxin-induced muscle injury
- To elucidate the alterations to skeletal muscle in diabetes and uncover novel therapeutic strategies to alleviate diabetic myopathy

#### KEY COLLABORATORS

**Dr Mark Tarnopolsky**, McMaster University, Canada

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**THOMAS HAWKE** received his PhD in Human Biology and Nutritional Sciences from the University of Guelph, Canada in 2000 and completed a postdoctoral fellowship with Dr Daniel Garry at University of Texas Southwestern Medical Centre Southwestern, Dallas, Texas from 2000-03. Hawke's research focus is on the maintenance of skeletal muscle health, including the regulation of muscle's stem cell population and satellite cells in disease states such as diabetes and muscular dystrophy.

myopathy. The current understanding of the aetiology and effects of diabetes on skeletal muscle growth and repair is limited. Given that muscle biopsies are not ethically feasible in children, much of Hawke's work in this area has used rodent models of T1DM. A series of recent papers from his lab have demonstrated that skeletal muscle growth and repair from damage is significantly attenuated in the diabetic state.

Hawke and his team have contributed numerous research papers which document their findings from both projects. These include: (1) the discovery that Xin expression is highly correlated to the degree of muscle damage; (2) regeneration from muscle injury is delayed by reduction in Xin expression; and (3) the regenerative capacity of skeletal muscle is impaired in the diabetic state and this impairment is related to insulin-independent hormone dysregulation.

#### METHODOLOGY AND APPROACHES TO WORK

The methods adopted by the lab are integrative and span from the molecular to the physiological. The group uses this 'molecular physiology' approach to investigate skeletal muscle and its satellite cell population. Working with rodent models, they have taken findings at molecular and cellular levels and determined their contribution to the overall physiology of the animal. This work is essential to the field, as the results will demonstrate how molecular changes can impact the functionality of an organism as a whole.

The use of rodent models in their work has allowed them freedom to delve deep into the molecular and physiological changes that occur in the skeletal muscle. While these results alone are not directly applicable to human populations, by unravelling selected pathways, Hawke and his colleagues can identify appropriate markers to make their investigations into human samples more focused. This targeted, comprehensive approach improves the significance of their findings for both fundamental scientists and the clinical setting.

#### OUTREACH BEYOND THE RESEARCH COMMUNITY

The dissemination of new findings and research within this field to a more generalised audience has hitherto proven difficult. The work on T1DM has yet to receive attention outside of the core research community due to the fact that the deterioration of skeletal muscle health is not categorised as a 'clinically serious health complication'. Historically, this term has been reserved for complications in other tissues, such as the retina (retinopathy) and the kidney (nephropathy), which lead to blindness and kidney failure respectively.

However, young people with T1DM do display deteriorations in muscle health and this can lead to serious repercussions. Considerable evidence indicates that longstanding T1DM patients who are also physically inactive (and therefore have poor muscle health) have an increased risk of diabetes-related complications and higher mortality rates than those who are active. Furthermore, increased physical activity at a young age can help to prevent long-term T1DM complications. Thus, delineating the role of skeletal muscle health in attenuating other diabetic complications is of paramount importance.

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Overall, Hawke's studies illustrate the benefits of maintaining muscle health in people with chronic diseases and consider the underlying mechanisms that govern these effects. The hope now is that the significance of these studies will be able to impact upon a wider audience, fostering more of an appreciation for the maintenance of healthy muscle mass and a greater understanding of how this may delay and assuage diabetic complications.

