Expert in muscle plasticity Professor Dr Martin Flück is studying the processes that underlie muscle degeneration, a common characteristic of injury and modern sedentary lifestyles. He describes the close link between muscle and fat, and provides a frank insight into the challenges of a career in research.

My work involves clinical and experimental investigations to expose the mechanisms underlying the adaptive processes set in motion in skeletal muscle after musculoskeletal injury and exercise rehabilitation following orthopaedic surgery. The main objective of my investigations is to advance understanding of the processes that underlie muscle degeneration with injury (and inactivity) and characterise countermeasures, with a view to developing therapeutic applications.

Many of your research endeavours have centred on the relationship between muscle and fat tissue. What have you discovered about the mechanisms underlying muscle-to-fat conversion?

My group’s experiments demonstrate that muscle-to-fat conversion takes place in muscles with tonic functions, which are inactive for prolonged periods of time. This conversion resembles the processes in the deconditioning of skeletal muscle observed in bed rest or a sedentary lifestyle. In exercise studies with laboratory species and human subjects, we showed that fat content is reduced when interventions take place that enhance loads to the muscle. We made similar observations with endurance training concerning muscle cells, which are active during daily activity. Conversely, we noticed that muscle unloading negatively affects processes in the powerhouse of skeletal muscle – the mitochondria – which is responsible for the combustion of lipids and carbohydrates. We therefore hypothesise that the muscle-to-fat ratio is related to adhesive processes that modify the mechanical properties of muscle cells.

How do these findings relate to your research into the treatment of rotator cuff tendon tears?

Full or partial tears of rotator cuff tendons initiate degeneration of muscle tissue, which is characterised by permanent muscle retraction and an increase in fat cells. Knowledge of the processes underlying the former pathology is still scarce, but it indicates that the implicated processes involve those the muscle unloading initiates in physiological models. To what extent does this involve the destruction of muscle fibres and the expansion of muscle by internal fat cell precursors? This is the burning question we aim to answer.

You have been quoted as saying ‘inactivity may be the main culprit of the obesity epidemic’. Can you expand upon this statement?

In scientific circles, there is consensus on the importance of activity-induced metabolism for cardiovascular fitness and health – the muscle hypothesis. It reflects the fact that physical exercise places high energy demand on contracting muscle cells, which leads to a considerable increase in aerobic metabolism and blood flow in exercised skeletal muscle to fuel the energetic requirements of contraction. If the stimulus of exercise is repeated during training, skeletal muscle improves its capacity to supply metabolites via quantitative increases in the entities such as capillaries and mitochondria, which set muscle metabolism. At the same time, capacity for storing organic substrates of energy metabolism in muscle cells (intramyocellular lipids and glycogen) is elevated, while lipid deposits outside muscle cells are depleted with regular extensive training and not replenished with a moderate diet.

In general, what have been the main barriers you have had to overcome over the course of your research?

The major limitation I have experienced as a scientist is the regulated possibilities of pursuing a career in academia; bottlenecks created by the limited duration of university posts and funding. This caused considerable strain during my attempt to return to academia after a postdoctoral fellowship in the US, and impacted negatively on my personal relationships. In addition, I think there are a lack of effective options for a PhD-trained scientist to translate his or her research into biomedical applications.

Where do you see your career taking you in the next five to 10 years?

I hope to help explain how training schemes and pharmacological interventions can be applied to improve surgery and the rehabilitation of sports injuries. Therefore, an important task will be to identify clinical syndromes that require such an approach. Beyond this, I see great importance in disseminating the accumulated knowledge on molecular exercise physiology to the public. This will foster the translation of emerging concepts into health benefits for individuals.
Inspired by paradigms of exercise-induced muscle plasticity, researchers from the University of Zurich are tackling the mechanisms of muscle loss. Their work could halt the conversion of skeletal muscle into fat, preventing the degeneration seen in elderly patients, injured athletes, and overweight and obese individuals.

THE MOLECULAR CHANGES that take place in muscle are an important area of medicine that require further research, as they have applications relevant to several health issues, such as obesity, which is an established and growing threat to the developed world. A significant cause of the pandemic boils down to a molecular process in which muscle converts to fat. This process not only occurs in obese individuals, but in any situation where muscle cells are not contracting often enough, including elderly and bedridden patients whose frailty is often caused by fatty atrophy.

Professor Dr Martin Flück, a member of University of Zurich’s Laboratory for Muscle Plasticity, is studying the molecular mechanisms of muscle plasticity in order to understand how this muscle-to-fat conversion process occurs, and he aims to develop pathological mechanisms and therapeutic targets to prevent it.

TENDON TEARS

Flück is particularly interested in examining this molecular process in the scope of injuries to the rotator cuff, a group of muscles that stabilise the shoulder. Tears to tendons within the rotator cuff are relatively common; in fact, they affect 40 per cent of the general population over 60 years of age, and in Switzerland alone, they generate annual costs of CHF 240 million (almost €200 million) every year.

Left untreated, these tendon tears cause irreversible damage to muscle. This includes retraction of the tendon, muscle atrophy and, importantly, fatty infiltration. In clinical terms, fat infiltration is so important that the fat cell content of the affected muscle is the primary predictor for the success of reparative surgery. If intramuscular fat content exceeds 50 per cent of the remaining contractile tissue, tendon repair is considered impossible.

SOPHISTICATED SIGNALLING

Clearly, the cost of this common ailment is high and treatment options are lacking. Flück aims to change this by accumulating knowledge on the mechanisms underlying fatty infiltration. Previous results collected by his group have provided unprecedented molecular detail on the differentiation of muscle tissue into fat, showing that the pathway depends on muscle use, and is controlled by its effects. It also involves costameres, which attach the units of muscle – myofibrils – to the sarcolemma, the muscle cell membrane.

Further, the researchers revealed that reduced muscle use down-regulates focal adhesion kinase (FAK), an enzyme found within costameres, which in turn reduces protein synthesis – the basis for muscle growth. This complex hypothesis is addressed in experiments assessing the infiltration of fat cells (adipocytes) in muscle of sheep and rats after tendon release.

Based on these findings, Flück believes that muscle degeneration following surgery is the result of a decrease in muscle loading. Reduction of force at the interface between inactive muscle fibres leads to the down-regulation of focal adhesions (which transmit mechanical force), due to the breakdown of FAK. In turn, this encourages the differentiation of muscle fibres into adipocytes and aids the down-regulation of protein synthesis. These processes conspire to increase the conversion of muscle to fat and prevent the synthesis of new muscle. The team will sooner test these hypotheses in the well-established sheep model, aiming to describe the factors preventing functional recovery of reattached rotator cuff muscle. Subsequently, they will explore treatment strategies, translating the most promising options into human trials.

EXPRESSION PROFILING

Unsurprisingly, this work is of particular interest for athletes. Following tendon rupture, a common sporting injury, the accumulation of fat cells in skeletal muscle reduces the capacity for an individual to produce and maintain force. The team has expended particular effort to understand the genetic basis of metabolic fitness, and recently published a paper demonstrating the use of gene expression to measure endurance performance.

While traditional physiological measures of exercise performance provide important reference points for physical health and fitness, they cannot reveal the improvements needed to achieve maximal performance. Thus, Flück
Flück hopes to create personalised treatments for athletes with muscle injury

and create personalised exercise interventions could use the results of the laboratory’s studies for athletes with muscle injury: “This constitutes one of our ultimate aims. Considerable overlap exists in the mechanism of how an untrained muscle, or a deconditioned muscle after injury, responds to a phenotypic stimulus”. An injured athlete looking to re-establish performance could use the results of the laboratory’s studies and create personalised exercise interventions during rehabilitation. “However, further investment would be necessary to establish the necessary structures to provide a cost-neutral platform to administer such molecular counselling,” Flück adds with caution.

CONTINUING CLINICAL TRIALS

Beyond sport and muscle science, this project will have particular benefits in all situations where muscle is inactive (unloaded) as a result of injury. Flück is already underway with research to reveal the exact processes involved in converting muscle to fat after tendon rupture, and he is using rotator cuff injuries as a framework. Existing methods to restore a ruptured rotator cuff are limited; they rarely stop, and certainly cannot reverse the degenerative process in the shoulder muscle once fat content exceeds 50 per cent and permanent retraction has established. However, Flück believes that these key processes could feasibly be targeted with drugs to prevent muscle degeneration for a myriad of individuals, from the elderly to athletes: “Through these investigations of its pathogenesis, and the relationship between fatty infiltration and atrophy, we aim to improve understanding of the regulation of muscle integrity, and then develop solutions to its loss”.

The team has a number of promising projects ongoing to investigate tears to the rotator cuff tendons, one of which aims to define the complex pathological process. “We have already initiated approaches in animals aimed at halting the degenerative process with genetic and pharmacological interventions,” Flück comments. Pursuing a more novel research avenue, the group is working to identify human biomarkers associated with successful rehabilitation. “A clinical trial is underway to identify internal molecules and gene variants that underlie individual variability in recovery and the re-rupture of reattached rotator cuff muscle,” he concludes.

MUSCLE AND METABOLIC DISORDERS

The conversion of muscle stem cells into fat cells is of great interest in the context of the obesity epidemic, as the conversion of muscle to fat seen after tendon rupture is similar to the inactivity-induced adiposity of metabolic disorders. In fact, a growing body of evidence suggests that inactivity may be a primary cause for the obesity epidemic.