PROTEOFIT: healthy, fit muscle cells for exercise and obesity prevention

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Why is our society becoming ‘bigger’ every day?

What makes people put on more weight?

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DISSEMINATION PROTEOFIT

We all know what exercise means. Get up and move. Sometimes it is fun, sometimes hard work, and sometimes we just cannot convince ourselves to get going. Exercise is good for you, and nowadays humankind could use a bit more exercise. The growing global pandemic of obesity is a major public health concern, and exercise can help to prevent weight gain as well as having therapeutic potential. According to the World Health Organization (WHO) the number of obese people has tripled since 1975. The excessive accumulation of fat tissue leads to greater chronic and often fatal diseases such as cardiovascular diseases, diabetes mellitus, metabolic syndrome or certain cancers. In 2017, over 4 million people died because of being obese or overweight (WHO, 2021).

Why is our society becoming ‘bigger’ every day? What makes people put on more weight? The underlying causes for this development are major lifestyle changes in our society over the past decades.

Diets have shifted away from natural products to energy-dense, high fat and high sugar foods, through which people take up more calories than they expend. There is little need for physical activity in many countries across the globe, as we have seen improvements in transportation, automation at workplaces and increasing urbanisation.

Sedentary lifestyles coupled with processed foods with high caloric value meet a human genetic makeup that has developed throughout evolution to expend calories carefully.

Therefore, it is not surprising that this mixture results in efficient weight gain and, more importantly, make it more difficult to lose weight when necessary. It could be so easy, get up and move, lose weight, and improve your metabolism and health. Indeed, increasing physical activity has the impact of reducing the risk of obesity and consequential metabolic diseases, which are remarkable. However, compliance remains an issue.

Exercise as medicine

Using exercise as medicine is not a new concept. Several initiatives and non-governmental organisations (NGOs) promote physical activity to prevent and combat obesity (Haskell *et al.*, 2007). The WHO recommends adults do at least 150–300 minutes of moderate-intensity exercise a week to reduce harmful health threats caused by sedentary behaviour.

However, the ability to be physically active or carry out any voluntary movement does not depend on individual motivation and compliance alone. It should not be neglected that exercise also requires skeletal muscle activity, the tissue that facilitates our body’s movement. The good news is that muscle cells are highly adaptive, and once being used more often, they quickly adapt to the new challenge. Maintaining a healthy muscle apparatus and muscle cells, the myocytes, is very important.

Making up ca. 40 per cent of the body mass in a lean person, the skeletal muscle is not only required for movement but is also a major determinant of whole-body energy expenditure under resting conditions and even more so during physical activity and exercise (Murgia *et al.*, 2015). Therefore, even small everyday exercise breaks or generally implementing more activity in day-to-day schedules impact energy metabolism. Consequently, this will lead to muscle remodelling.

Muscle cell health

On the molecular level, muscle cells respond to training-induced challenges by adjusting metabolic regulation, signalling pathways and protein content and function (Egan and Zierath, 2013). Diet can also significantly affect the outcomes of training and exercise: new muscle tissue requires appropriate building blocks, the proper amino acids composition, some of which are essential and can only be obtained exogenously.

Exercise and skeletal muscle activity require a proper balance of protein synthesis, folding and degradation, which is called proteostasis. In other words,

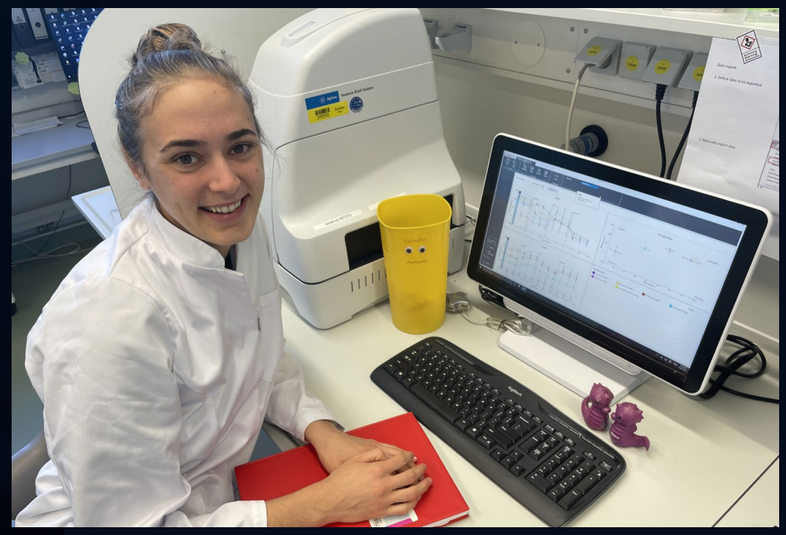

Photo 1: In her PhD project, Imke Lemmer studies the foundations of exercise-related metabolism.

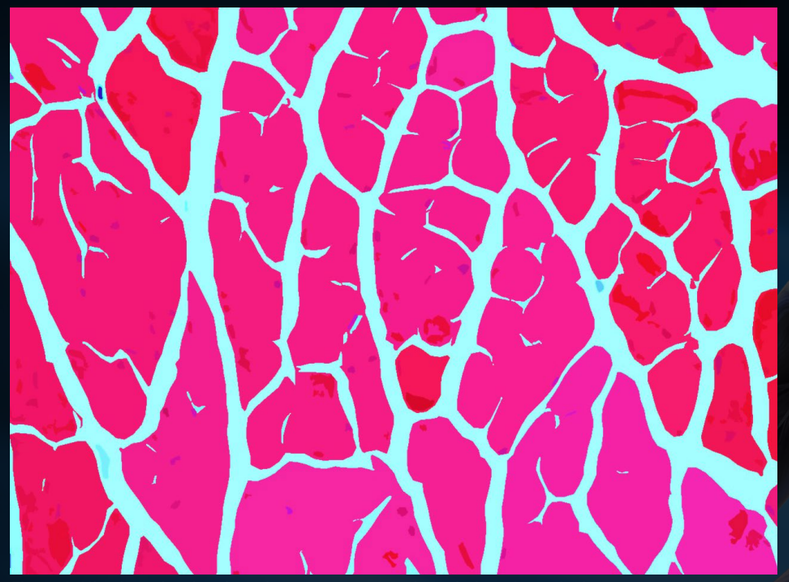

Figure 1: Histology showing the unique structure-function relation of muscle tissue.

Photo 2: Lemmer and Bartelt discussing experiments in the lab.

in addition to making the right proteins correctly, muscle cells also require efficient recycling of protein waste. This increased turnover of proteins, metabolites, as well as synthesis and breakdown of damaged cellular components requires mechanisms that maintain quality control.

Protein degradation

In our ERC project PROTEOFIT, we focus on pathways and regulation of protein degradation, which is a critical but often underestimated process in the cell. Proteins that are misfolded or become obsolete due to changes in environmental strain need to be disposed of. If not, they overload the cell, leading to dysfunction or, in the worst case, cell death—just imagine the trash pick being on strike.

The main degradation pathway in skeletal muscle cells, the myocytes, is the ubiquitin-proteasome system (UPS). In this process, unneeded proteins are tagged with multiple small ubiquitin molecules through a three-step process involving several enzymes. The resulting ubiquitinated proteins are then transported to the proteasome, which is the shredder of the cell. The proteasome is a giant barrel-shaped molecular complex, which has multiple cleavage elements at its core. This complex takes in proteins tagged for degradation and breaks them down into its building blocks, peptides and amino acids, from which new proteins can be synthesised. Therefore, the proteasome represents an internal recycling system, essential to maintaining protein degradation homeostasis and the availability of amino acids for novel protein synthesis. Malfunctions of the UPS are often associated with obesity, neurodegenerative diseases and cystic fibrosis (Goldberg, 2003). This makes the UPS pathway an exciting potential target for new medical therapies.

The objective of our ERC project PROTEOFIT is to investigate the role of Nfe2l1 in muscle-specific adaptation to exercise and obesity.

A recently identified regulator of the proteasomal activity and thereby the UPS is the gene switch nuclear-factor erythroid-2, like-1, or in short: Nfe2l1 (Bartelt *et al.*, 2018).

Under certain environmental conditions, Nfe2l1 has been shown to fine-tune protein degradation to adapt the rates of protein recycling to the amount of unwanted material. This is required to prevent cellular stress and maintain proteostasis (Bartelt *et al.*, 2018). The mechanism behind this gene switch has not been fully understood until now. It is postulated that there is a complex feedback regulation between the proteasome and the activity of Nfe2l1. Ingeniously, Nfe2l1 is degraded by the proteasome under normal conditions, but if the proteasome is 'clogged', the degradation of Nfe2l1 does not take place, and this promotes the production of more proteasomes until a new balance is reached. This adaptive regulatory mechanism couples protein degradation to proteasome function and ensures that the cell is equipped with sufficient proteasome levels. Interestingly, the gene switch Nfe2l1 is also found at high levels in muscle tissue, but its role in muscle function and exercise are unknown.

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Thus far, it is unknown which mechanisms myocytes regulate protein turnover and maintain proteostasis under challenging conditions such as a bout of exercise, whether weightlifting or going for a run. Also, these two challenges may require very different adaptation mechanisms, considering that bodybuilders and marathon runners display different types of athletic performance. Our project aims to understand better the difference between these types of muscle adaptation and how proteostasis is linked to the success or dysfunction of training challenges.

Early (and surprising) findings

Our research has already revealed that Nfe2l1 is a key regulator in isolated muscle cells in the culture dish and in transgenic models that allow studying metabolism in a natural setting. Expectedly, the loss of Nfe2l1 leads to the accumulation of ubiquitinated proteins (the protein trash) caused by hampered degradation by the proteasome.

What is great about research is that sometimes you find what your hypothesis predicted, and then the next thing you know, it is all confusing—this is when the real discovery starts. It is important to realise you are onto something important. Indeed, in our ERC project, we are now entering new shores. Unexpectedly, Nfe2l1 seems to be both friend and foe to muscle cells, and the metabolic outcomes of Nfe2l1 manipulation are beneficial or detrimental, depending on the environmental condition. Just like obesity is a manifestation of a good thing—preservation of energy stores—at the wrong time and in the wrong environment, there seems to be a sweet spot where we can use the mechanism of Nfe2l1 activation to dictate outcomes of exercise and training. It remains to be determined how precisely this affects athletic performance, especially with pre-existing obesity and associated metabolic disorders. However, at this point, it is already safe to say that Nfe2l1 is required for exploiting the full potential of muscle cells and that this ERC project has surfaced a very interesting gene-diet interaction with broad relevance for public health.

In conclusion, our ERC project PROTEOFIT enables us to address an unmet need of understanding the molecular foundations of energy metabolism in a field of growing importance: sedentary lifestyles and the development of obesity-associated disorders in Europe and beyond.

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PROJECT NAME

PROTEOFIT - Adapting protein fate for muscle function and fitness

PROJECT SUMMARY

Physical activity and exercise have beneficial effects on overall fitness and health. However, exercise-induced increases in metabolism require specific molecular adaptation of the muscle cells. This project aims to understand the molecular processes in the muscle during the adaptation to cold, exercise, and obesity, thereby defining novel mechanisms of protein homeostasis with regard to the gene switch Nfe2l1.

PROJECT LEAD

Alexander Bartelt is the Professor of Cardiovascular Metabolism at the Institute for Cardiovascular Prevention, Ludwig-Maximilians-University Munich. He received his diploma in biochemistry in 2007 and his PhD in 2010 from the University of Hamburg, Germany, with honours. After his postdoctoral training at Harvard University, USA. The Bartelt lab is dedicated to understanding the basic principles of metabolic adaptation as well as the molecular pathology of cardiometabolic diseases. Over the years, Dr Bartelt's contributions have been recognised by national and international awards and distinctions.

PROJECT PARTNERS

This project is based at the Institute for Cardiovascular Prevention (IPEK) at the LMU Munich in collaboration with the Helmholtz Diabetes Center Munich.

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