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Press release
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Tightening one's belt
How mitochondria react when energy becomes scarce

Graz, 1 August 2024: Mitochondria are small organelles in our cells that complete an important task. Out of adenosine triphosphate (ATP), they generate the substance that our body uses as energy in a wide variety of processes. They are tiny but essential to life because of their role as chemical powerhouses. The research group of Roland Malli of the Division of Molecular Biology and Biochemistry at the Gottfried Schatz Research Center and Med Uni Graz Core Facility Bioimaging & Flow Cytometry has taken a closer look at organelles and what happens when they are under stress. The research findings show that an enzyme forms ring-like structures around the cell organelles as a protective measure.

When the cell "starves"

To correctly perform their work, mitochondria and the cell need energy in the form of different nutrients. Yet what happens if a certain nutrient deficiency suddenly occurs for some reason, if the flow of food and energy ceases? This is exactly what Johannes Pilic, a PhD student in the team as well as a researcher at ETH Zurich, has explored in a publication appearing in the journal Molecular Cell. The Graz researchers came across an interesting mechanism. An enzyme called hexokinase 1 (HK1) encircles the mitochondrion and constricts it.
According to Roland Malli, this initially unexpected discovery was like so many others a chance finding: "In his dissertation, Johannes Pilic was actually supposed to investigate under which conditions the HK1 in cancer cells migrates from the mitochondria."

Research methodology

The researchers exploited their expertise in visualizing biological processes using so-called fluorescent proteins. An especially bright green fluorescent protein (GFP) is fused to HK1. This method made it possible to observe the redistribution of HK1 when living cells experience energy stress through the use of high-resolution fluorescence microscopy in live cell mode. "Thanks to this modern technology, we were able to understand exactly how the HK1 rings on the mitochondria develop," says Johannes Pilic.

A "life preserver"

This constriction of the mitochondrion has several consequences. First, the HK1 ring around the mitochondrion changes the metabolism of the organelle. Second, the mitochondrion may split at the site of the constriction as soon as all the necessary nutrients are fully available again. Furthermore, it was discovered that these rings mainly form at sites where the mitochondrion has contact with another cell organelle, the endoplasmic reticulum (ER). The ER is involved in the most important cellular processes such as transport or "quality control" of folded proteins.

Johannes Pilic explains: “We were able to show that the HK1 rings form specifically at the contact sites between the mitochondrion and the ER. This could be critical to the efficient control of energy distribution under cellular stress and outward communication of the specific situation.”

Protection against division

Another exciting research finding is that HK1 rings prevent mitochondria from dividing as long as the cell is experiencing energy stress. This is important because the prevention of division may be a protective mechanism in response to an acute deficiency (for example, ischemia in the event of vascular occlusion).

Roland Malli emphasizes: "Our findings indicate that the formation of HK1 rings is a protective measure taken by the cell to protect itself from damage when nutrients are scarce."

Importance of the research and future steps

In the long term, these findings may contribute to the development of new therapeutic approaches to treating diseases caused by an energy deficiency in the cells. For example, they may be useful in treating certain types of cancer characterized by a lack of substrate, where blood vessels do not yet supply a fast-growing tumor sufficiently. In this case, it may be possible to specifically increase the energy deficiency of cancer cells, inducing them to die or enabling the immune system to recognize them. In addition, the new discovery of the HK1 rings during cellular aging that is associated with metabolic change may open up new avenues for slowing down age-related loss of function. These findings are especially pertinent with regard to acute events such as stroke or heart attack during which cells die off due to a lack of oxygen and nutrients. Knowledge of protective mechanisms may help preserve cells during such crises and promote their regeneration.

Outlook on further research

Research now continues as researchers set their sights on further research projects to investigate the physiological and pathological significance of HK1 rings in different medical conditions such as cancer, cellular aging, stroke and heart attack. The objective is to apply the discovery made in the lab to therapy.

“This research project has helped us make particular progress since we have realized that not only is HK1 an enzyme involved in metabolism, which has been well known for a long time, but also that HK1 fulfills a completely different function,” explains Roland Malli. “Under stress, it undergoes polymerization, substantially changing the structure of the mitochondria. Scientists also call this ‘moonlighting,’ which means that HK1 has another ‘job’ in addition to its primary enzymatic function. This is an important knowledge gain for us.”

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Profile: Roland Malli
Roland Malli has been a basic researcher in cell biology and biochemistry at the Medical University of Graz for 25 years. He studied pharmacy in Graz and finished his habilitation in the field of molecular and cellular physiology at a young age. He is well-known and esteemed in the scientific community thanks to his ongoing contributions in the field of biosensor development. He and his team have submitted several patents including ones for biosensors that detect potassium and nitric oxide.
Roland Malli also has a remarkable talent for recruiting young people who are passionate about research and training them so they excel in their careers. Many of his protégés have obtained positions at top universities and research institutions such as Harvard Medical School, Istanbul Medipol University, ETH Zurich, CeMM in Vienna and the University of Tübingen.
A few months ago, Roland Malli joined the Center for Medical Research (ZMF), where he has dedicated himself to sustainable and cutting-edge microscopy, a key method applied in medical research.