Scientists find off-switch for the mTor complex

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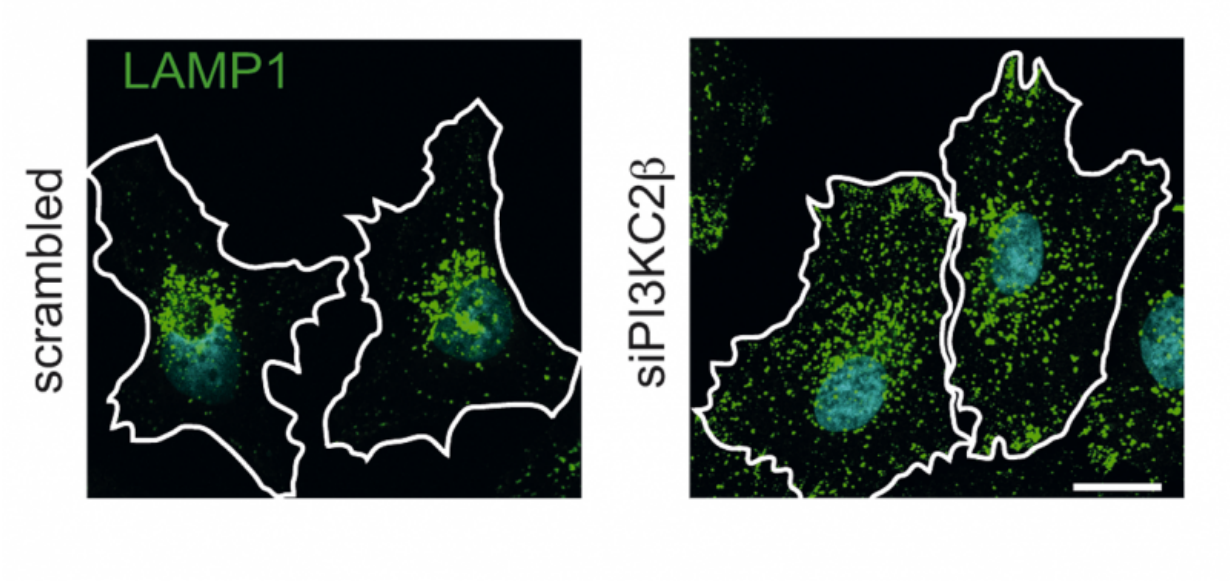

Credit: Forschungsverbund Berlin e.V. (FVB)

As the cell's molecular control center, the mTor kinase regulates cellular metabolism, growth and division. However, in cells affected by pathological change, the regulation goes array. Therefore, it would be helpful if the central control could be simply turned off to suppress insulin resistance or cancerous growth for example. Scientists at the Leibniz–Forschungsinstitut für Molekulare Pharmakologie (FMP) in Berlin (Germany) succeeded in locating a crucial off-switch for the central cell control. Paradoxically, this 'off-switch' is a lipid kinase

producing a product previously known for its role in the activation of mTor. The results just appeared in the high-ranking journal *Science*. They bolster the hopes of patients waiting for new effective therapies against diabetes, obesity, cancer and a rare congenital muscular disease.

The important control functions of the mTor kinase influence cell metabolism, division and growth. For example, the molecular control unit ensures the production of new proteins or the storage of fat and carbohydrates in metabolically active tissue. These processes are stimulated by the influx of sugar and amino acids and by signals initiated by growth factors including the insulin-like growth factor. If this influx does not occur in a starvation period, mTor switches the cell from anabolic to catabolic mode. Instead of synthesizing new proteins from amino acids, the cell now activates clean-up processes to remove damaged proteins, which could become hazardous for the cell or organ. The cleansing effect of interval fasting is attributed to the consequences of deactivating the mTor kinase.

In certain disease states, it would be sensible to shut down the mTor kinase complex. In cases of diabetes and obesity for example, pathological mutations exist in the cellular control center. This also applies to many cancers. This raises the question how and where to switch off such a complex mechanism.

A Surprising Discovery

To find this switch-off mechanism, researchers in the Leibniz–Forschungsinstitut für Molekulare Pharmakologie (FMP) in Berlin kept a keen eye on nature's ways to accomplish this down regulation. According to known facts, the lysosomal mTor kinase complex becomes less active or inactive in extended hunger periods. The lysosome is the regular cell compartment for the mTor kinase complex activity. However, the complex also turns inactive several times during

the day without leaving its membrane-bound place. This happens for example when the stimulating insulin signals do not arrive. Therefore, there has to be a natural mTor brake somewhere in this location. The discovery of this brake is now published in the top journal 'Science'. It came as a surprise even for FMP Director Professor Volker Haucke: "We found a local lipid kinase on the lysosome. This kinase deactivates mTor. Paradoxically, if the lipid product of this kinase is synthesized on the cell surface membrane, it is rather known as growth stimulating lipid, i.e. it has the exact opposite effect."

As the scientist discovered, another scarcely investigated specific class II lipid kinase (PI3KC2ß) exists in the cell, which deactivates the mTor complex on the lysosomal membrane in the absence of stimulating signals from the outside. In the absence of hormonal signals such as insulin or insulin-like growth factor (e.g. at night), the lipid kinase PI3KC2ß becomes active at the lysosomal membrane. The active lysosomal lipid kinase phosphorylates a lipid, which then deactivates the mTor complex. Under these conditions the lysosome mainly functions to degrade cellular proteins.

The discovery of this off-switch for mTor sheds light on one of the riddles in basic cell biology. In addition, the new insights are of the highest relevance for clinical research projects. Doctoral candidate Alexander Wallroth in collaboration with Dr. Andrea Marat (a former postdoctoral researcher now working in New York) discovered the mTor brake. Alexander Wallroth comments: "We set out to discover biomedical applications, and our research is closing in on that goal."

Biomedical Applications are within Reach

The scientists set their immediate sights on practical applications in the treatment of obesity and diabetes. The well-known diabetes drug Metformin already utilizes the mTor repression by activating an enzyme

in the same cascade as the now discovered lipid kinase.

Alexander Wallroth emphasizes: "If we succeed in activating the discovered lipid kinase, we will have another, possibly better shut-off switch for mTor. This will enable us to devise therapies, which influence sugar and fat metabolism. There is even a chance to influence the growth of malignant tumors. It is generally known that patients treated with Metformin are less prone to developing cancer even though obesity actually increases the cancer risk. Right now, our discovery may or may not be applicable to cancer therapies. However, our group considers new approaches within the range of the possible."

Now Underway: The Search for Active Agents

Scientists consider the lipid kinase PI3KC2ß a particularly suitable therapeutic fulcrum because this kinase is not essential for survival. Targeted manipulations from outside the body would therefore be relatively safe. Therefore, scientists working in the screening unit of the FMP are busy hunting down activating and inhibiting substances, which are specific for the lipid kinase.

An activator could be useful for the treatment of diabetes and obesity because it will dampen mTor activity. An inhibitor could possibly be useful in other therapeutic applications: The lipid kinase now identified as an mTor inhibitor also plays a crucial role in myotubular myopathy. So far, there is no treatment for this disease, let alone a cure. Recently, Canadian scientists demonstrated in mouse and zebra fish models that switching off the lipid kinase PI3KC2ß can at least partially cure a rare congenital myotubular myopathy (muscle weakness). So far however, the used inhibitors are unsuitable for use in humans because they also inhibit related enzymes. This alone is a good reason to search for a specific inhibitor.

While the FMP has not developed real drugs, the institute certainly can deliver the 'raw materials' for such development. In view of the started search for active drugs, Volker Haucke promises: "We discovered a new, potentially promising point to attack mTOR and are now pursuing possible therapeutic options. Following up on our work, there is a reasonable chance for our scientists to identify candidate molecules with the desired clinical effects someday."

More information: mTORC1 activity repression by late endosomal phosphatidylinositol 3,4-bisphosphate. *Science* (2017). DOI: 10.1126/science.aaf8310

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