PRESS RELEASE

Signal transduction in cells: Researchers describe new model for regulation

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In their recent study, Thomas Leonard and his group at the Max F. Perutz Laboratories (MFPL) of the University of Vienna and the Medical University of Vienna have shown that the cellular activity of the enzyme ROCK is controlled by a 'molecular ruler'. ROCK is a protein kinase. These enzymes transmit signals and regulate complex processes in cells. Their findings, representing a completely new model in kinase regulation, have recently been published in the prestigious scientific journal *Nature Communications*.

In order to adapt to changing environments and eventually to survive, cells have to change their shape constantly: they bend, stretch, and move. In doing so, the cells depend on a network of filaments called the cytoskeleton just beneath the plasma membrane, which surrounds the cells. One key regulator of the cytoskeleton is the protein ROCK, which is crucial from embryonic development on. However, while the biological roles of ROCK have been studied extensively, the structure and the mechanisms by which its activity is controlled are not well understood.

Size and position matter

The group of Thomas Leonard has now determined the structure of ROCK, showing that a 107 nm long coiled-coil tether links the kinase domain, which is responsible for the enzymatic activity of the protein, and the membrane-binding domain. As a reference, the diameter of the smallest known unicellular organism is just 200 nm. Postdoc Linda Truebestein and her colleagues show that ROCK activity in cells depends on the length of this coiled-coil tether, which therefore acts like a "molecular ruler". This mechanism represents a completely new type of spatial control.

Similarities to a car engine

"Our findings indicate that the activity of the Rho kinases is regulated by the spatial positioning of the kinase domain and substrate in the cell, much like the clutch in a car engine determines whether the car is in gear or not. The engine, or kinase, is always running, but the car, or cell, doesn't move unless the clutch, or substrate, is engaged. This represents a hitherto unknown mechanism in the regulation of protein kinases such as ROCK, whereby substrate specificity and corresponding activity are simply governed by the precise spatial positioning of enzyme and substrate," says MFPL group leader Thomas Leonard.

Challenges for the future

The future challenges of the MFPL researchers are to find out what this "molecular ruler" is actually bridging and whether there are additional functions of the ruler beyond its role in positioning the kinase domains – the part of the molecule that carries out its function. "We could show that the molecular ruler is conserved throughout evolution, but we don't know yet if the ruler is truly sequence independent," says Linda Trübestein, who conducted the studies together with PhD student Daniel Elsner.

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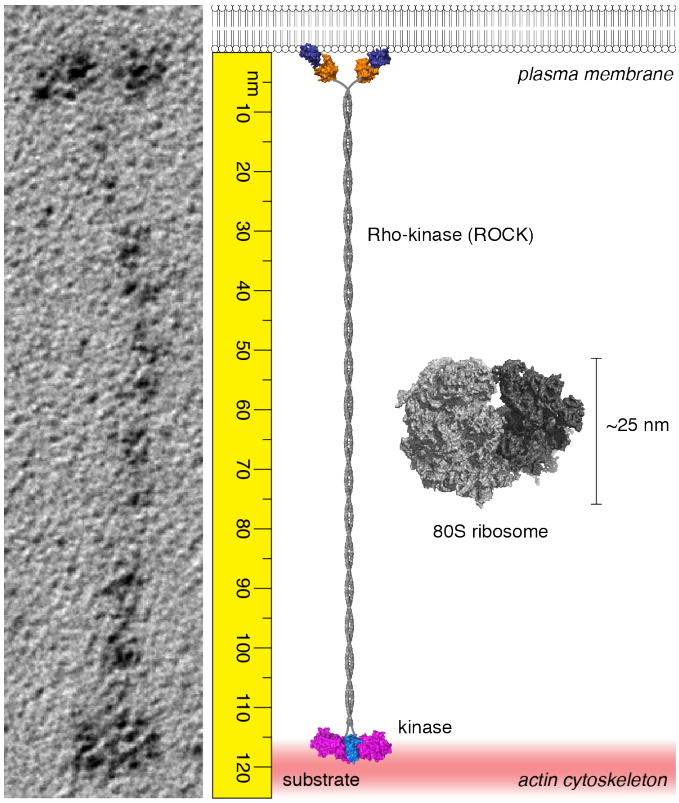
The Max F. Perutz Laboratories (MFPL) are a center established by the University of Vienna and the Medical University of Vienna to provide an environment for excellent, internationally recognized research and education in the field of Molecular Biology. On average, the MFPL host 60 independent research groups, involving more than 500 people from 40 nations.

Thomas Leonard and his group at the Max F. Perutz Laboratories have shown that the activity of the enzyme ROCK depends on a "molecular ruler", which represents a new paradigm for kinase regulation. ©K.C./Fotolia.com



Dimeric Rho-kinase (ROCK) comprises N-terminal kinase domains and C-terminal membrane-binding domains joined by a long, parallel coiled-coil of 107 nm. For comparison, the 80S eukaryotic ribosome is drawn to scale alongside. Removal of the membrane-binding domains or truncation of the coiled-coil has no effect on ROCK activity in vitro, but truncation of the coiled-coil blocks stress fiber formation in cells. Truebestein et al. propose that the coiled-coil of ROCK functions like a molecular ruler, bridging the membrane to ROCK substrates in the actin cytoskeleton. ©2015 Truebestein et al. Nature Communications. doi: http://dx.doi.org/10.1038/ncomms10029