Kathrin Thedieck – the art of deciphering signalling

The molecule mTOR is one of the most important cellular switch centres; it controls cellular growth in relation to the availability of nutrients and also plays a key role in the pathogenesis of cancer, neurodegenerative diseases and ageing. Dr. Kathrin Thedieck from the Institute of Biology III at the University of Freiburg is interested in solving the question as to how insulin, growth factors or nutrients such as amino acids influence the complex mTOR system and how this effects signalling networks, the growth of human cells and the life span of their model organism C. elegans. Using a systems biology approach, Thedieck and her team have simulated the complex processes of the mTOR signalling network and developed a model that describes the dynamic processes involved rather well.

Dr. Kathrin Thedieck
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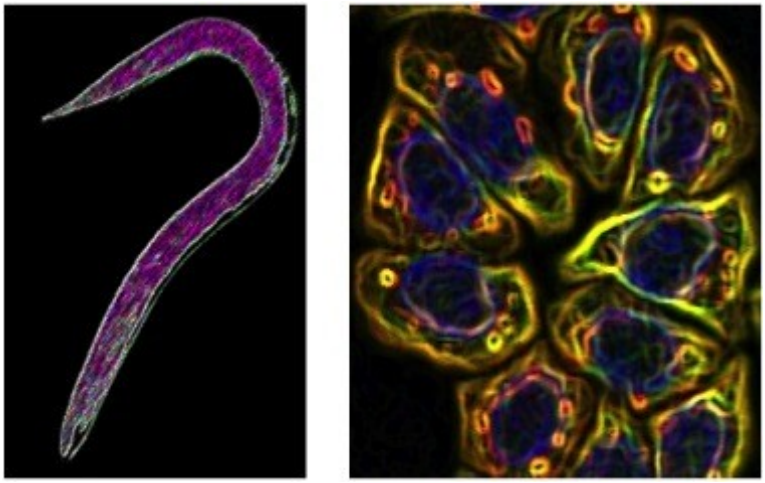
Before starting her university studies, Thedieck was not entirely sure whether she wanted to focus on natural science or on the arts. She now feels that the decision to study biology was the right one, particularly given that the work of a scientist these days is nowadays highly interdisciplinary and not very far removed from how an artist works. "Carrying out experiments requires a lot of dexterity, and thinking out, planning and designing them is a fairly creative process," said Dr. Kathrin Thedieck from the Institute of Biology III at the University of Freiburg. Born in the city of Hamm (Westphalia) in 1977, the scientist is now head of a group of junior researchers in the Department of Bioinformatics and Molecular Genetics led by C. elegans expert Prof. Dr. Ralf Baumeister. Her work involves a

signalling network in human cells and in the C. elegans model which is quite exciting from a clinical perspective and is so complex that finding a solution to the different questions requires enormous creativity.

A sensor for hunger

Thedieck did her biotechnology degree in Strasbourg and started her doctoral degree in the field of signalling research and proteomics at the Helmholtz Centre for Infection Research in Braunschweig in 2001. She then spent her postdoctoral period at the Basle Biocentre in Prof. Dr. Michael N. Hall's group between 2006 and 2008. Her work is still centred on the mTOR (mammalian target of rapamycin) protein discovered by Hall. mTOR is a cellular protein that interacts with rapamycin, a drug that suppresses the immune system and is mainly used for the treatment of cancers. Rapamycin inhibits mTOR, which normally controls proteins that promote the growth of cells, including the synthesis of proteins and ribosomes. mTOR also reacts to nutrients such as amino acids, to the energy currency ATP and to the hormone insulin, which regulates the blood glucose level. "mTOR is a sensor that detects the nutrient situation of a cell, either allowing the cell to grow or preventing it from growing," said Thedieck. This is exactly why rapamycin targets tumours: mTOR is usually hyperactive in cancer cells; the drug inhibits mTOR and hence tumour growth.



Dr. Kathrin Thedieck's research group uses C. elegans (left) and human cell (right) as model systems.
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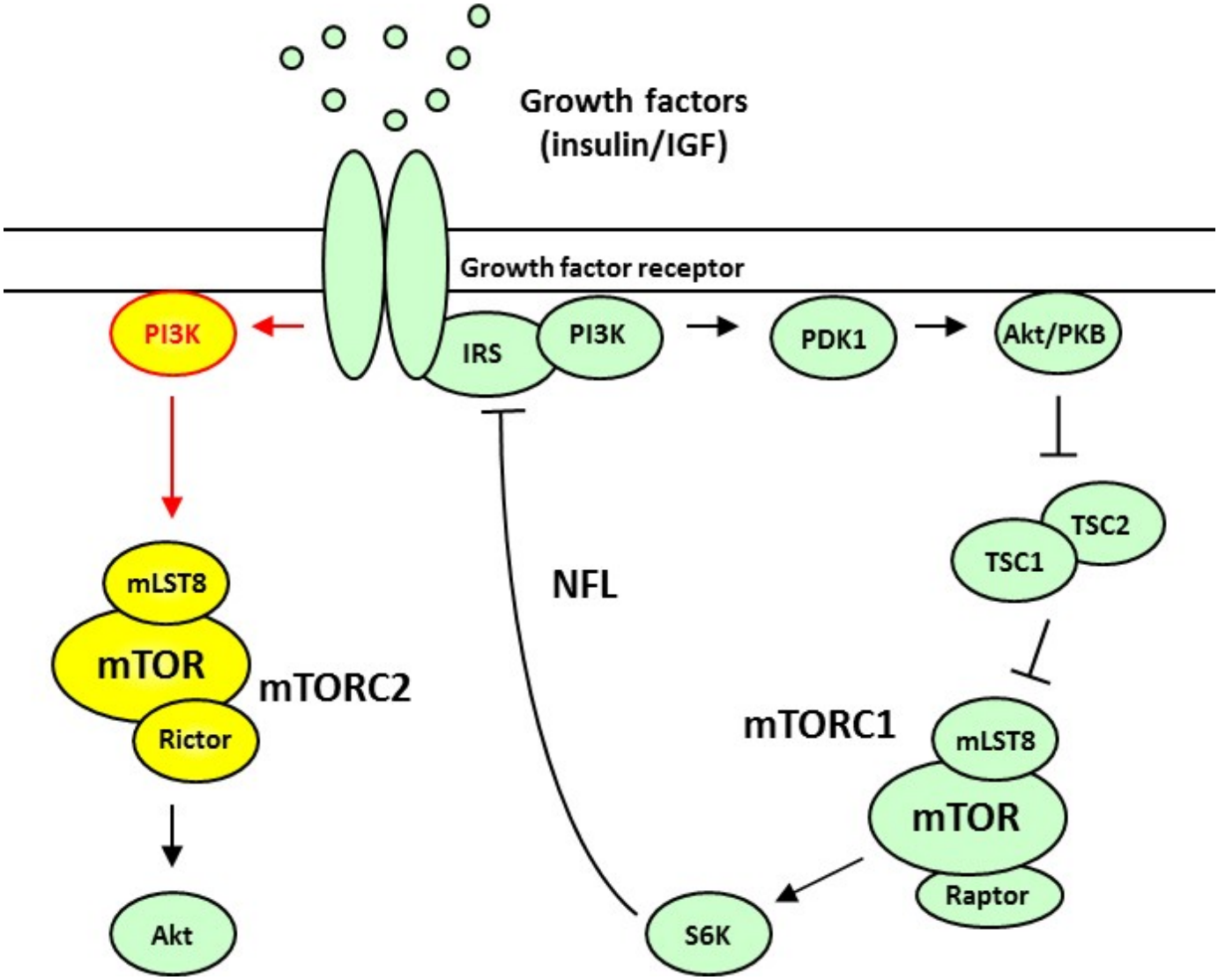
Thedieck and her team from the Institute of Biology III in Freiburg now know that the C. elegans worms reach almost double their normal age (50 instead of 30 days) when the researchers inhibit the insulin receptor and hence TOR (m stands for mammalian; TOR is therefore the term used for the C. elegans homologue). But the whole process would be too easy if mTOR simply acted as a two-stage switch. The protein is part of different multiprotein complexes, for example the mTOR complexes 1 and 2 (mTORC1, mTORC2). These interact in the cells with other molecules and affect a large number of different genetic programmes. Numerous feedback loops in these molecular cascades further increase the complexity of the system and make the interpretation of rather simple experiments in which individual network players are silenced quite difficult. "In addition, the networks are not simply static structures in which molecules are either active or inactive," said Thedieck. "Allowing the interactions to take their temporal course is absolutely essential, as is the gradual change in the concentrations of the players involved."

A dynamic model and excellent future perspectives



A strongly simplified picture of signalling involving mTOR. The mathematical model developed by the team led by Dr. Kathrin Thedieck, which takes into account the 20 or so players involved, provides a fairly accurate picture of the reality of life inside a cell.
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This is why Thedieck and her team chose a systems biology approach. In cooperation with Thedieck's colleague Daryl P. Shanley from the University of Newcastle, the researchers have developed a mathematical model that describes the interaction of around twenty proteins involved in the mTOR network and their temporal dynamics. “Reducing several hundred interaction partners of living cells to around 20 might seem strange – at least at first sight,” said Thedieck. “But the mathematical modelling of a system consisting of 20 variables whose linear courses can also be modulated is highly complex and time-consuming.” However, it is rather astonishing that the reduced model reflects the processes in living cells very well, as biological experiments have shown. The model describes what happens when the cells are exposed to different concentrations of insulin as well as the gradual changes that occur in the signalling processes when combinations of network nodes are inactivated or hyperactivated. The model is thus excellently suited to predicting the effect of potential drugs that inhibit individual proteins or combinations of proteins involved in mTOR signalling. And this is an excellent future perspective for Thedieck’s investigations, for example in the field of tumour and ageing research. But how does a scientist get the idea of choosing a number of potential candidates from the hundreds of proteins that are present in a cell and using them for setting up a theoretical model, whilst excluding others? “This is the creative part, this is where science resembles

the arts," said Thedieck. "On the one hand, you need to be able to visualize the biology behind the mathematical variables and then you need to come up with the right idea at the right time." Some mathematicians even say that an elegant model is somehow aesthetic to the point of being moving – just like a piece of art.

Literature:

P. Dalle Pezze, A. G. Sonntag et al.: A Dynamic Network Model of mTOR Signaling Reveals TSC-Independent mTORC2 Regulation. SCIENCE Signaling (2012) 27 March Vol 5 Issue 217 ra25, DOI: 10.1126/scisignal.2002469

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