Healthcare industry BW

The game needs to be discovered

Prof. Dr. Michael Reth is active in the field of immunology and signalling. He is an experienced scientist with a solid grounding in his field who is well aware of the difficulty and the cumbersome nature of deciphering signals and signalling pathways. But he is also a visionary with the courage to do completely new things. The Freiburg bioss excellence cluster – the Centre of Biological Signalling Studies – is Reth's brainchild. Karin Bundschuh from BioRegio Freiburg spoke with the scientist who works at the Max Planck Institute of Immunobiology and the Institute of Biology III at Freiburg University.

Signalling research is booming. Why?

Prof. Michael Reth, immunobiologist and passionate signalling researcher (Photo: kb)

In my student days, hardly anything was known about the transduction of signals in the plant, animal or human cells. Since then, this has fundamentally changed. Nowadays, many signalling proteins and receptors are known and the players involved have been identified. The only thing we still do not know is the game they are playing with each other, how they interact with each other. However, knowledge of this is extremely important because the signalling pathways control the entire development of all cells in an organism. They determine its growth, cell division, differentiation and cell death.

What has already been discovered?

Genome research, genome sequencing and biochemical investigations have enabled scientists to discover many components that are involved in the signalling pathways. They have found out that many diseases are the result of missing or incorrectly regulated signalling pathways. Our immune system also often fails as a result of missing signalling components.

Can you give me some examples?

One example of such diseases is X-linked agammaglobulinaemia, a genetic disorder caused by a defect in Bruton's tyrosine kinase (Btk). Patients – mostly boys - lacking this signalling molecule do not generate mature B-lymphocytes which normally manufacture antibodies to defend the body against infection. It has only been known for a short time that these and similar signalling molecules are the key to understanding and treating such diseases.

You are, as I see from the example you have just given, not just a signalling researcher but also an immunobiologist. Which discoveries in your field have surprised you the most?

Immune system cells are normally activated through the binding of ligands to specific receptors on the cell surface. A big surprise was the discovery that B-lymphocytes die very rapidly once they lose their antigen receptor. This shows that the antigen receptor sends out signals into the cell's interior a long time before a ligand actually binds to the cell surface. This constitutive signal controls the survival of B-cells. The research done by Sebastian Herzog and Hassan Jumaa, two researchers in my department, was able to show for the first time ever that this signal is processed by way of what is known as the PI3 kinase signalling pathway.

Does this signalling pathway also play a role in other cells or is it only of importance for the immune system?

Let me explain it like this: each cell has ten to twenty major signalling pathways which are controlled by different receptors and then specifically modulated. All body cells have several such signalling pathways. The PI3 kinase signalling pathway also plays an important role in many other cell types, for example in nerve cells. But the way these signalling pathways are controlled and regulated differs from one cell type to another. It seems that the evolution of cells required the use of a limited number of signalling pathways for very different tasks.

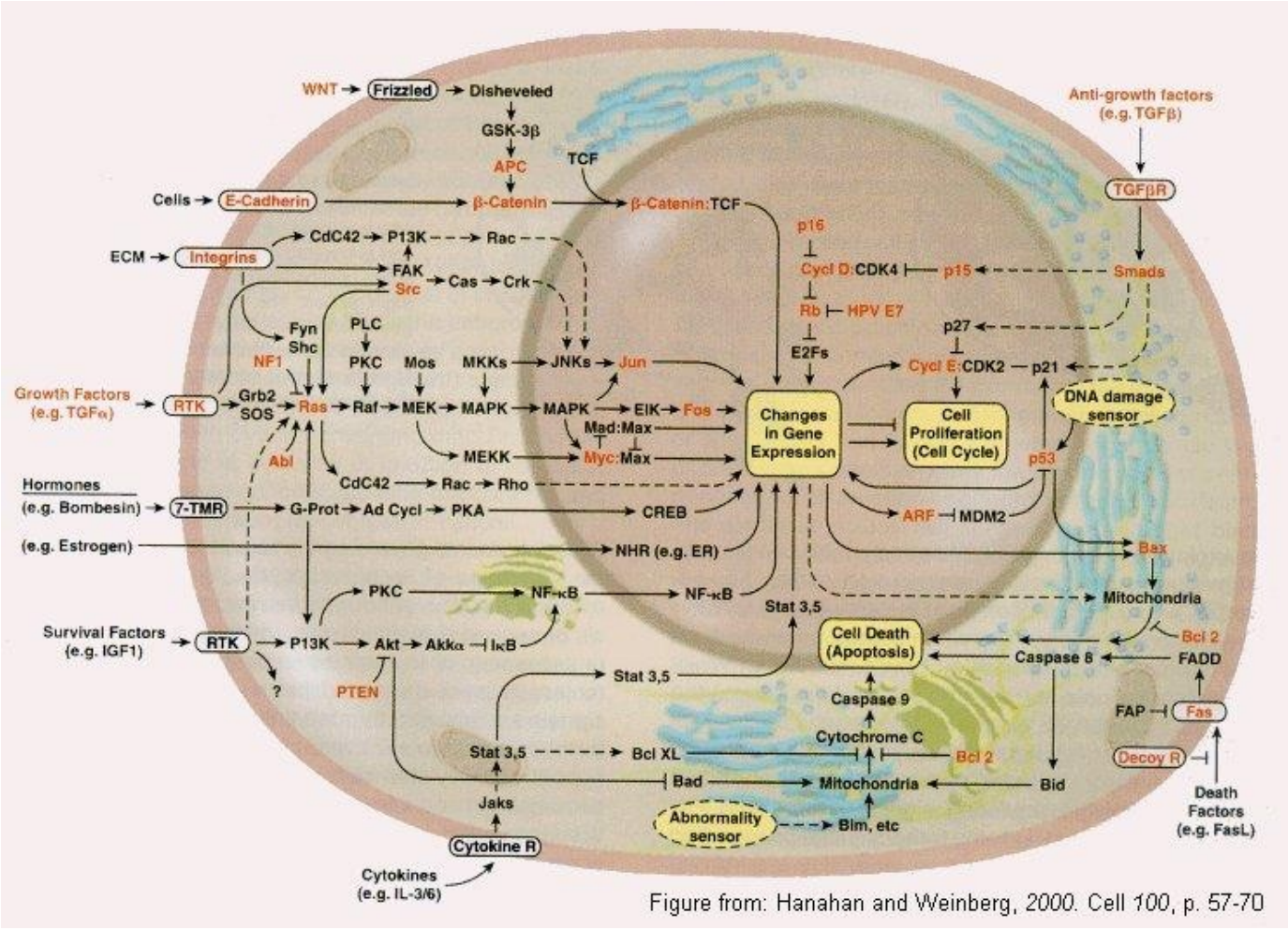
Is it the possibility of soon being able to decipher the secret of cellular fine control that is a huge motivating factor for signalling researchers at the moment?

We are a long way from being able to investigate cellular fine control. At the moment, our major goal is to discover the fundamental principles of signal transduction. Let's get back to the aforementioned example and ask: how does the PI3 kinase signalling pathway control the survival of B-lymphocytes? The two researchers that I mentioned before have found out that this signalling pathway has a permanent effect on phosphorylation and the subsequent degradation of the FoxO transcription factor. The interruption of the signalling pathway, for example through the loss of the B-cell receptor, leads to the stabilisation of FoxO which subsequently activates a differentiation and death programme in the cell nucleus. The B-cells can only survive if they receive signals from other receptors that invoke a survival programme.

What knowledge and possibilities offers signalling research in the future?

In order to gain an in-depth understanding of the intracellular signalling processes, seven questions need to be answered. First question: Who or what is involved in the transduction of signals? Second question: What are the exact functions of the different components involved? Third question: What are the interaction partners of these proteins? Signalling depends on the communication between different proteins, i.e. protein-protein interactions. Fourth question: How exactly is this signalling mechanism controlled? Fifth and sixth question: Where and when does this signal occur in the cell? Each signal is an event that happens at a specific location with specific temporal kinetics. The last, and most difficult, question is: How much signal is there? Of these seven questions, we are mainly interested in the last three. We have already found many of the answers. The next question as to "how" is currently a major aspect of our research. However, little is still known about the localisation, temporal course and the quantitative aspects of the signalling pathways. We need to develop methods that enable us to quantify the signals.

Aren't you dealing with these questions in the bioss excellence cluster? How is this possible if you do not have the tools required?



The transparent cell is a dream. The excellence cluster hopes to make this dream real sometime in the future. (Photo: bioss)

The central idea of bioss is the investigation of biological signal transduction using a dialectic process involving both analytical and synthetic approaches. Analytical methods will be used to find answers to the first three questions. We have plans to use an expensive, but highly modern ion trap mass spectrometer (an Orbitrap) to identify new signalling proteins and their modifications and binding partners. The synthetic work will involve the production of chimeric proteins which function as signal switches or detectors and the imitation of biological signalling pathways.

How are you going to achieve this?

At first, the work will be done on a very simple level. We will use cells that lack a signalling pathway, for example yeast or fly cells that do not have the signalling pathways that are present in mammalian cells. We will then take these simple cells to reconstruct the mammalian signalling pathway. In this synthetic approach we have a great deal of experimental freedom and will be able to mix and alter the components as we wish. This will give us information on the ability of signalling protein mutations to alter the function of a signalling system. The idea behind this is that we will only be able to gain an in-depth understanding of biological processes if they can be recapitulated by way of syntheses. We have learned this from chemistry, a field which identifies chemical substances in order to subsequently analyse and synthesise them. The possibility of synthesising the substances provides chemists with information on the composition of these substances. As biologists, we would like to do the same but we only have a limited range of techniques available. This work is called synthetic biology. Another goal of synthetic biology is the production of molecules and proteins that cannot be found in nature. By bringing together different protein domains we hope to develop switch proteins that are able to create signals at specific locations in the cell. For example, we hope to equip mitochondria – which are regarded as the power stations of the cells – with signal switches, switch them on and off and get an idea as to how the signal spreads in the cells.

Is this type of work still part of basic research or are you already thinking of specific applications?

Initially, this is pure basic research. The synthetic approaches we are using are quite new and synthetic biology is still an emerging field of science. The combination of synthetic biology with signalling research, such as planned here in Freiburg, is totally unique. We are at the very beginning. However, switch proteins where specific signalling pathways can be switched on might also be of importance for clinical research. For example, we have plans to construct models for human cancers. There are many tumours that are caused through deregulated signalling pathways, some of which have no mouse models. Therefore, we are hoping to express certain modified signalling proteins, which we have isolated from actual tumours of patients, in mice. If the mice develop a tumour then the disease can be studied in greater detail. In this way, our results are useful for clinical research and concrete projects.

You've created something very special at bioss – the signalling engineer. Why? What is the job of this new science professional?

We want to stay small at first and have no immediate plans to establish a synthetic biology course. We would like to develop an innovative research programme and develop training and study programmes. Maybe this will result in a full course of study in about five years. We will see. What we would like to do is to work with our cooperation partners in the 11th Faculty of Applied Sciences and establish working contacts between our engineers and biologists and medical experts. We hope that this cooperation will lead to exciting projects. For example, we are keen to generate signalling pathways in vitro, i.e. outside the cell, using small microfluidics systems. We are currently working on establishing a resource centre in Freiburg where we will be able to store the required materials, notably expression plasmids for the construction of signalling molecules, and distribute them efficiently. We hope that we will soon be able to accept the first plasmids and pass them on to interested parties.

Can scientists who are not part of the bioss consortium also contact the new resource centre?

The resource centre is open to all scientists. Any scientist from anywhere in the world can contact the centre and order plasmids. Of course, there are certain rules. I am hoping that many scientists will contact us. When they receive the material they will automatically learn about our research and this will help bioss to achieve a greater international profile.

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