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The complexities of signal transduction

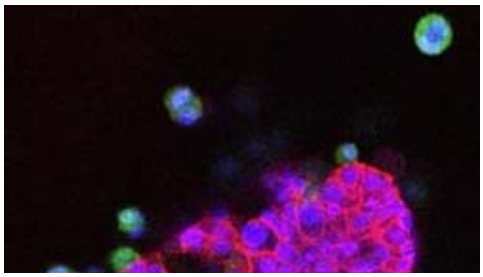
Ten years ago, cellular signalling was a simple and straightforward process. Nowadays, what once seemed so simple is riddled with complexities. Dr. Tilman Brummer and his team at the Centre for Biosystems Analysis (ZBSA) in Freiburg are investigating the complex molecular interactions sparked off by signals inside cells. They are especially interested in the signalling network involving the protein Raf. Faults in the dynamic processes involving the molecule and its numerous interaction partners can lead to cancer. The researchers can only effectively intervene if they know and understand the entire network.

For a long time it was believed that the process worked as follows: a signal from the tissue (for example a growth factor) activates a receptor on the surface of a cell, and the receptor then activates the Ras protein which is attached to the membrane inside the cell. Ras works like a switch. Upon activation, Ras activates Raf which triggers the activity of MAP kinases. MAP kinases are enzymes that transfer phosphate groups to other proteins, a process known as phosphorylation. Phosphorylation can either activate or inhibit substrates, which triggers a broad range of cellular processes. This means that the cell responds to the external signals: genes are transcribed, the cytoskeleton is rearranged and ion channels open or close. For example, growth factors, which act as signalling molecules between cells, are capable of stimulating cell division. This is a simple chain of events. “When we take a closer look at what is happening, it becomes clear that the whole process is far more complex,” said Tilman Brummer, head of a group of junior researchers at the Centre for Biosystems Analysis (ZBSA) and partner in the Freiburg University bioss excellence cluster.

A signal transduction loading station

Brummer and his team are involved in a field of science that enables them to have a detailed look into cells. It has only been possible in the last few years to use modern systems biology, proteomics or genomics methods in combination with automated high-throughput methods in order to carry out a very large number of experiments in a very short time. These methods enable scientists to screen the entire genome for certain alterations or all the proteins produced by cells. The scientists in Brummer’s group are increasingly finding that the simple signalling pathway from Ras to Raf and from Raf to the MAP kinases is in reality far more complex than it initially appears. The following example illustrates the complexity: the transduction of signals from Ras to Raf is associated with a large number of phosphorylations, the majority of which are not yet understood in detail. The researchers found that the Raf protein has several sites to which a phosphate group can be transferred. “It is clear to us that Raf can be influenced by many different proteins,” said Brummer. Therefore, the molecule seems to be a kind of signal transduction loading station where many different signals, not just the signal transduced by Ras, come together. Brummer’s team of researchers is working to find out the ways in which the proteins interact.

Many tasks



One thing has already become clear: cells are highly complex networks of information carriers that react to a plethora of external signals and induce a finely tuned reaction when they are acting together. This is also of biological importance: scientists around the world have known for a long time that the Ras and Raf molecules play an important role in growth and differentiation processes. These proteins are involved

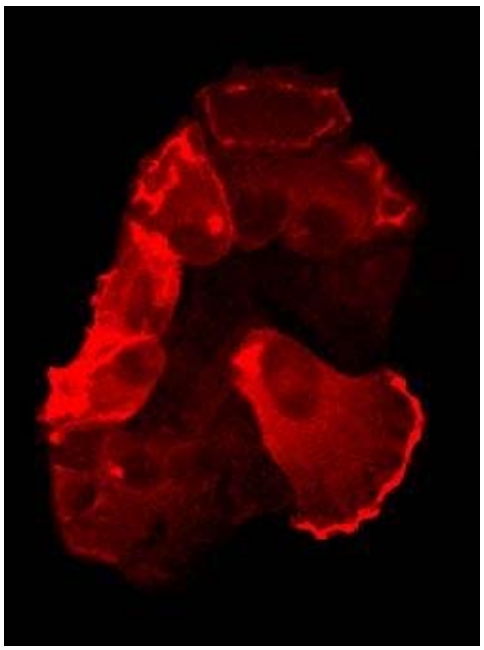
Three-dimensional cultures of human epithelial cells. The cell nuclei and the cell-cell contacts are shown in blue and red. Cells expressing oncogenic B-Raf (green) are unable to form cell contacts and detach from the cell complex. (© Dr. Tilman Brummer)

in processes such as immune defence, memory and many others. How can one and the same signalling pathway lead to such different reactions in the tissues?

In order to answer this question, Brummer's team are trying to identify all the signalling pathways that run up to or away from Raf. In addition, the researchers are also investigating how the activation of Raf occurs on the molecular level. In the meantime, the researchers have found out that this process requires the protein to undergo several conformational changes. The protein is phosphorylated step by step and eventually adapts a conformation which enables it to become active. "The entire process is extremely complex," said Brummer. "Several proteins are already involved in the first phosphorylation step, where Raf unfolds like a pocket knife." Which proteins are involved in this phosphorylation step? Brummer and his team are currently pursuing different approaches in order to find these proteins.

Networks are the solution to effective research

Clinical issues show how important it is to clarify these processes. Dysregulated Raf signalling can lead to oncogenesis and cancer. Mutations in ras genes can permanently activate the protein Raf and cause inappropriate transmission of signals inside the cell, thereby permanently stimulating the division of cells, a process that turns the cells into tumour cells. "Only the knowledge of all the proteins involved in the activation cycle will help us understand the dynamic processes that they trigger. And this will help us to bring the processes that are associated with tumour diseases under control," said Brummer. His team is carrying out a broad range of experiments focusing on Raf. In addition, the Freiburg researchers are also investigating other components of the Ras/Raf/MAP kinase pathway because there is evidence that they may all have something to do with the pathogenesis of cancer. Such components could be proteins that play a role early in the signalling process, for example the proteins located directly at the receptor that translates external signals into the cell and leads to the activation of this signalling pathway. "We also found that a large number of proteins is involved," said Brummer referring to Gab proteins which also have numerous phosphorylation sites and interaction motifs, thereby enabling them to communicate with other signalling pathways.



In growth factor-stimulated human epithelial cells, the Gab2 signalling complex (shown in red) is primarily found in the plasma membrane. (© Dr. Tilman Brummer)

Brummer and his team need to use a broad range of different methods in order to understand the complexity of cells. "Different specialists are working together in the bioss excellence cluster and at the ZBSA," said the researcher. "The collaboration between molecular biologists, bioinformaticians and the core facilities works very well and all researchers involved benefit from this collaboration." Just like cells, which are a network of different molecules, systems biology can also only be effectively pursued as part of a network.

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A contribution from:

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