

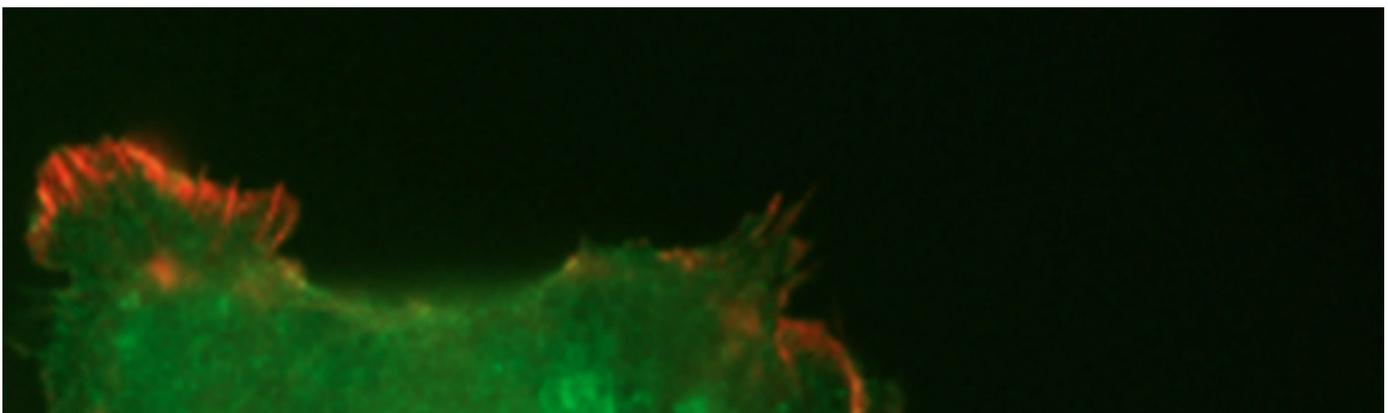
Healthcare industry BW

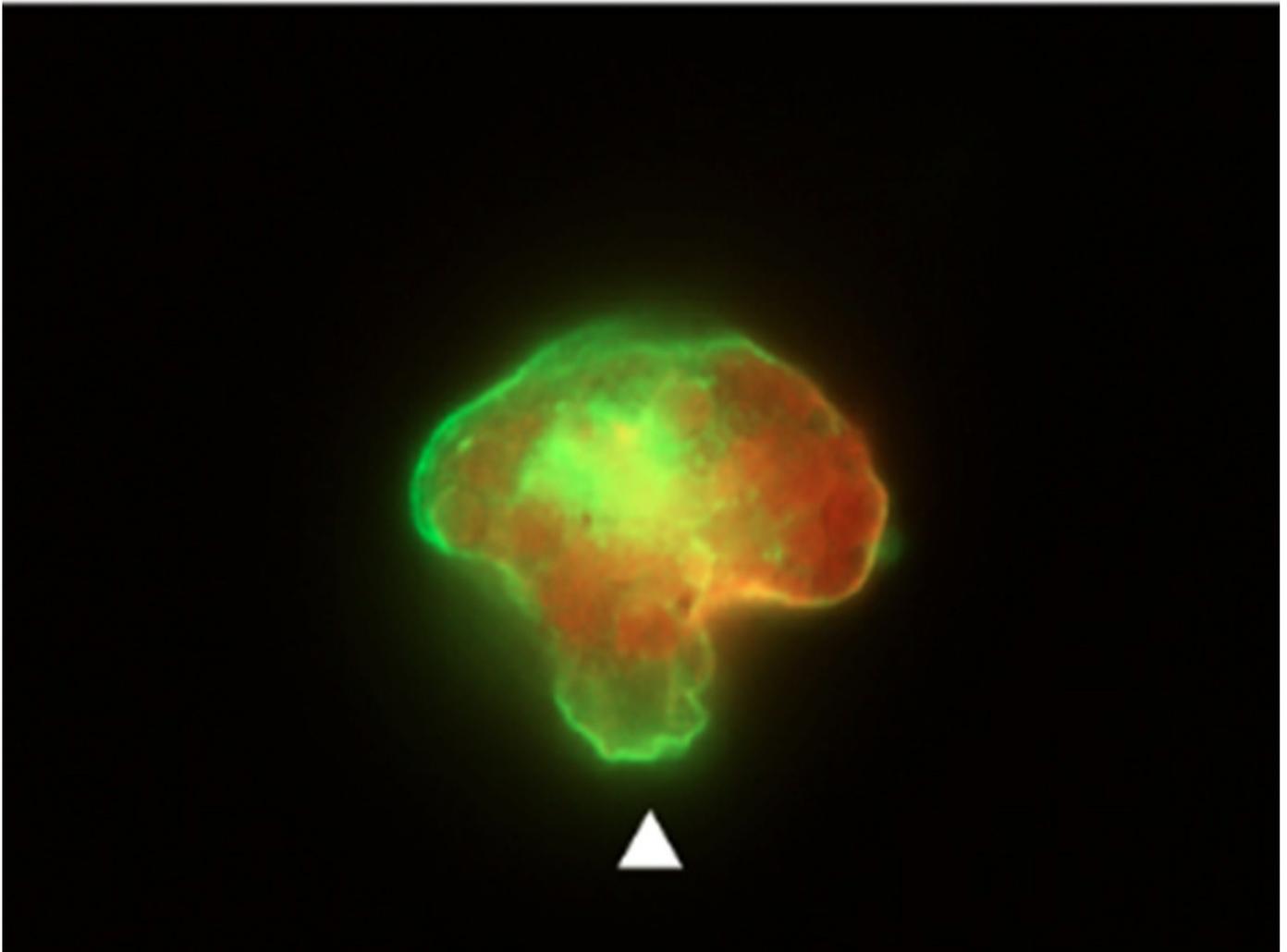
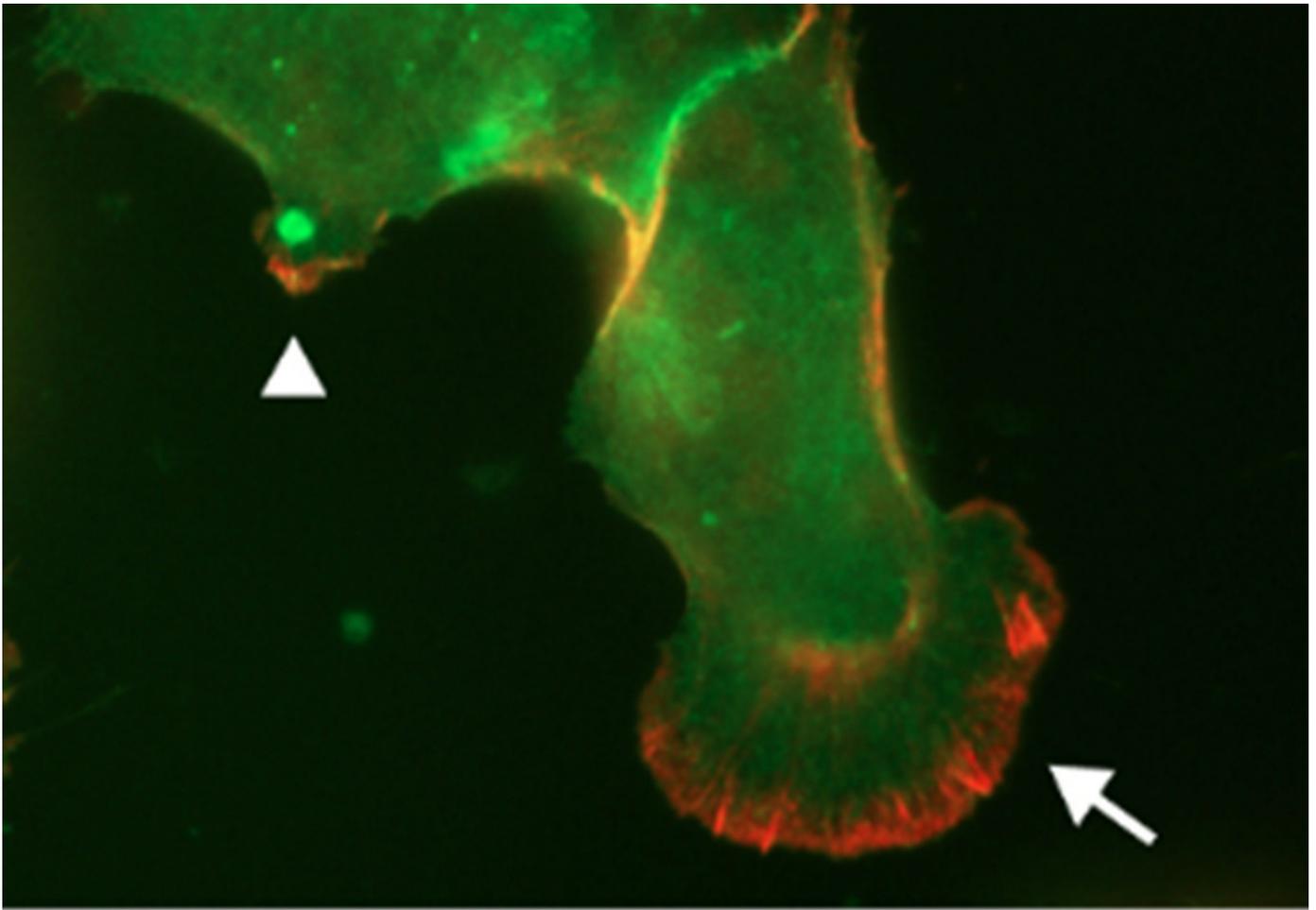
Cadherins and Wnt signals – cell adhesion or growth and dispersion?

Researchers have long had a clear idea about the function of cadherin proteins: the proteins of the cadherin family form a kind of molecular zip that binds cells closely together, thereby preventing cancer cells from migrating, for example. However, research carried out since has shown that the behaviour of cadherin protein family members varies considerably and depends on the proteins' interaction partners. Prof. Dr. Doris Wedlich and her team from the Karlsruhe Institute of Technology (KIT) were involved in the discovery that cadherins are not only involved in cell adhesion, but also have other functions. In addition, cadherins are also part of the Wnt signalling pathway, which plays a key role in the development and life of organisms.

Cadherins are transmembrane proteins that play important roles in cell adhesion. They are anchored in the cell membrane and extend into the extracellular matrix where they can connect up with cadherin molecules of neighbouring cells in a zip-like fashion. In epithelial tissue of the intestinal wall, lung wall or the skin, long chains of cadherins bind cells together, thereby forming an impermeable barrier to ions, water and other substances. When a cell loses the molecules that exert this function (e.g. by gene mutation), it detaches from other cells and starts to migrate. "This happens in cancer cells. And it is the reason why the lack of specific cadherin types can lead to cancer metastases," said Prof. Dr. Doris Wedlich from the Department of Cell and Developmental Biology at the Institute of Zoology at the Karlsruhe Institute of Technology (KIT). "Cadherins that bind cells together are only one type of known cadherins; recent research has produced evidence that there are many cadherins that have exactly the opposite function. Such cadherins promote the detachment of cells from the tissue and their migration."

Individual cadherin types and their interaction partners







Cell protrusions are characteristic of migrating cells. Top: cells with cadherin-11 have clearly visible cellular protrusions with actin filaments (red); bottom: cells without cadherin-11 do not develop cellular protrusions and actin filaments (red). Green: green fluorescent protein (GFP) used for the labelling of the cells.

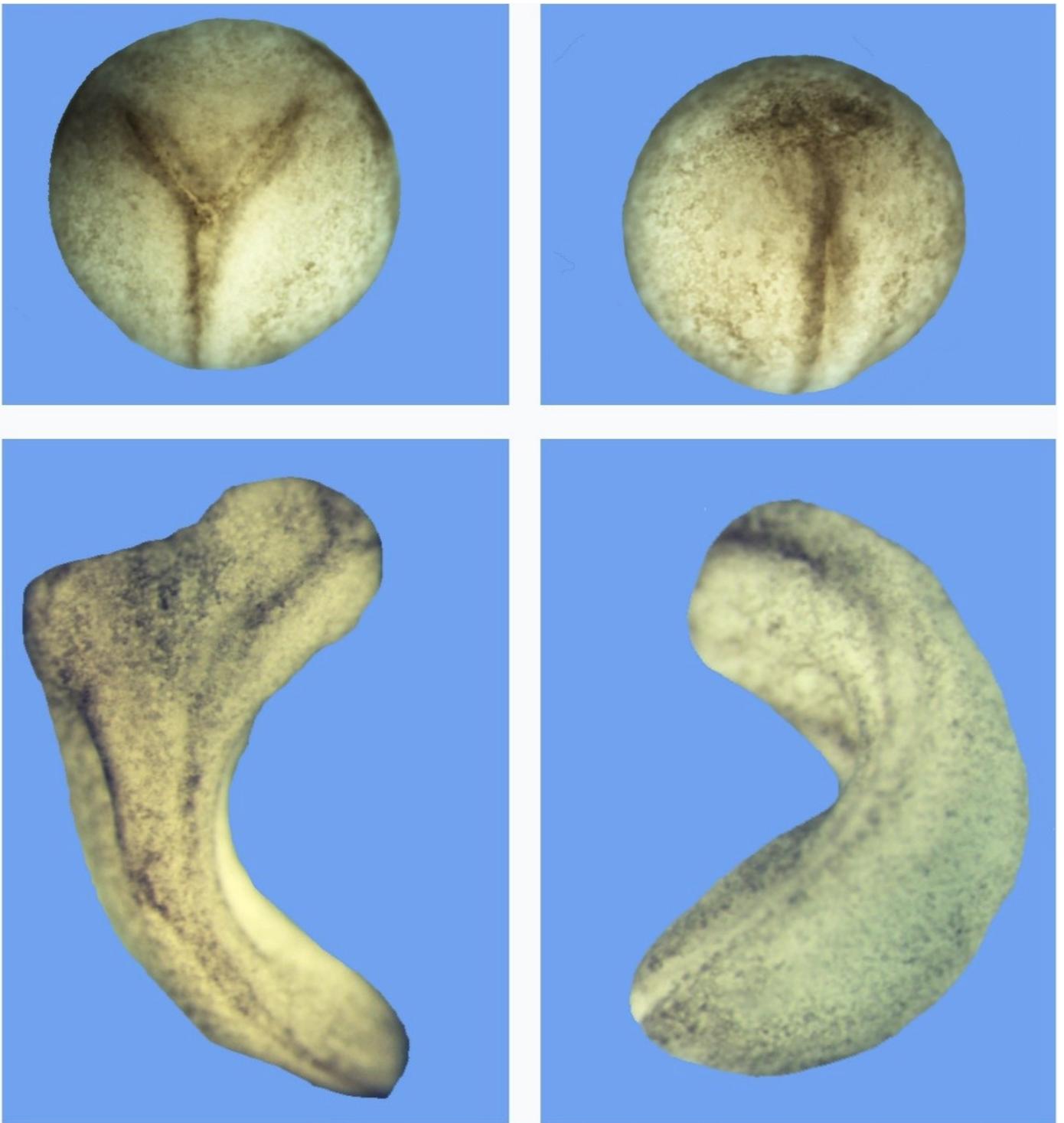
© Prof. Dr. Doris Wedlich

According to the current state of knowledge, the family of cadherins is composed of more than one hundred members. Wedlich's team and other research groups have shown in the last few years that the individual proteins display rather different types of behaviour patterns despite having highly conserved structural properties. It appears that the behaviour of cadherins depends on the proteins with which they interact. An example that illustrates this finding involves cadherin-11, which stimulates the migration of synovial cells into the bone tissue when it interacts with the Trio molecule. Synovial cells are part of a more or less liquid layer that lines the cavities of synovial joints. Their migration has been found to be associated with the development of arthritis. "In arthritis, there is a specific cadherin molecule which, rather than binding cells together, does exactly the opposite," said Wedlich. "There is increasing evidence that we need to look closely at the individual cadherin types and their respective interaction partners." There is also evidence that the loss of function of a specific cadherin type in tumours is not the only reason for the migration of the cells. Researchers and doctors have found out that a specific cadherin type becomes a different one shortly before cancer cells lose their sedentariness and start to migrate. One of the questions Wedlich and her team are trying to resolve relates to what the new cadherin actually does.

Cadherins can also be cleaved into smaller fragments that are then able to enter the cell nucleus and interfere with the regulation of gene activation. This means that they are also involved in cellular signalling. Wedlich and her team are therefore working to find out why different cadherins have different properties. In addition to their work on cadherins, Wedlich's team are also working on another closely related research topic, namely the signalling network involving the molecule Wnt. The Wnt signalling network is found in all multicellular animals. Even organisms as simple as water polyps have the same number of Wnt molecules as humans. Wedlich and her team have recently shown that the molecules also have similar functions in all organisms. The canonical Wnt signalling pathway, which was the first Wnt signalling pathway to be discovered, is crucial for correct embryonic development. Dozens of signalling proteins interact in order to silence or activate the genes at specific points during embryonic development and thus guarantee the correct formation of tissues such as the nervous system or the intestines. It is now known that the canonical Wnt pathway consists of several branches. Three branches in addition to the original one have now been discovered. These branches play a role in wound healing, the development of stem cells and in tumorigenesis, which is why researchers prefer to speak of a Wnt signalling network. Cadherins interact with Wnt signalling by competing for binding partners. The canonical Wnt signalling pathway involves the protein β -catenin, which can also bind to cadherins. In addition, the Wnt signalling network regulates the cadherin genes. It would appear that all the processes are somehow interrelated.

Which developmental processes are defective?

"When a specific cadherin type is no longer formed in a tumour, this leads to changes in the balance of the Wnt signalling network. This is because β -catenin can no longer bind to this specific cadherin and thus becomes freely available," said Wedlich. "This leads to the enhanced activation of the Wnt signalling effect with the result that more molecules that promote the division and migration of cells are generated. All this can promote the growth of tumours and the formation of metastases." Wedlich's team uses *Xenopus laevis* (South-African clawed frog) for their research, a popular model



Xenopus laevis embryos and the influence of Wnt-8. Left: The presence of Wnt-8 leads to the formation of a double axis in early embryos. Right: the formation of the double axis is impeded following the addition of JW74, a compound that switches off the effect of Wnt-8. The upper row shows embryos up to 36 hours after fertilisation, the lower row embryos up to 72 hours after fertilisation.

© Prof. Dr. Doris Wedlich

organism in many laboratories around the world. The researchers manipulate the expression of different cadherins or key proteins of the Wnt signalling pathway during the embryonic development of the frog. Subsequent analyses provide them with information about the development processes affected by these manipulations. The higher expression of β -catenin and Wnt-8 leads to embryos with two heads and two spinal columns, i.e. a double body axis. "We use this unique test system to test the effect of drugs that have the potential to interfere with Wnt signalling and hence prevent the growth and spread of metastases in the body," said Wedlich.

In addition to experiments involving *Xenopus laevis*, Wedlich and her team have also increasingly started using mouse stem cells in their effort to identify the key cadherins and Wnt signalling pathways involved in the development of stem cells. Working in cooperation with chemists and physicists from the KIT, the researchers vary the composition of the surfaces of their cell culture dishes and add different gradients of signalling molecules or cadherins. The group consists of around 20 people who work with other KIT research groups and also with national and international partners, collaborative activities which are crucially important for the success of the projects. "Embryonic research requires us to use a broad range of different methods," said Wedlich pointing out that one research group alone is unable to deal with such complex research issues and the plethora of methods available. Interdisciplinary cooperation has become pivotal in this type of research; this creates interest in each other's projects and contributes to the development of new problem-solving approaches.

Further information:

Prof. Dr. Doris Wedlich
KIT (Karlsruhe Institute of Technology)
Institute of Zoology
Cell and Developmental Biology
Kaiserstr.12
76131 Karlsruhe
Tel.: +49(0)721-608-4 3990
Fax: +49(0)721-608-4 3992
E-mail: doris.wedlich(at)kit.edu

Article

24-Oct-2011

mn

BioRegion Freiburg

© BIOPRO Baden-Württemberg GmbH