IMP Press Release

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Novel mechanism to steer cell identities gives clue on how organisms develop

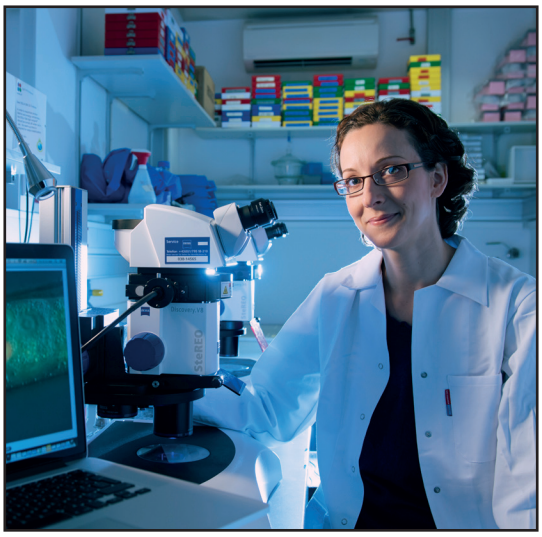
Scientists discovered a new way in which microRNAs can determine the fate of cells in the course of their development. This could be a key to understanding how complex organisms are built, say researchers from the Institute of Molecular Pathology (IMP) in Vienna.

A class of genes called microRNAs are known to prevent gene expression. In a recent study, scientists could show that down-regulating genes through microRNAs can determine unique properties of specific cells in an unexpected way. This finding was now reported in the journal "Genes & Development".

"We set out from a curious observation in the nematode worm C. elegans", explains Luisa Cochella. "We noticed that the gene mir-791 was expressed specifically in neurons we knew were responsible for the detection of carbon dioxide." The tiny worm is a common model organism because its anatomy and cell functions are very well-understood and can be observed easily under a microscope. When the worms detect carbon dioxide, they start moving in a characteristic way, giving the scientists an easy tool to indirectly "watch" molecular processes by observing the worms' behaviour.

When the scientists removed mir-791 from the worms, the animals had trouble responding to carbon dioxide. Normally, mir-791 prevents the expression of two genes exclusively in the neurons that detect carbon dioxide, while these same two genes are expressed in pretty much all other cells of the worm. When this repression mechanism fails, the carbon dioxide sensing neurons do not work properly and animals cannot respond adequately to an environmental cue that, in its natural environment, could determine whether the worm lives or dies. The question how the identity of cells is determined in the course of their development, however, goes far beyond nematodes – it is a fundamental question in biology.

The cells that form our bodies belong to hundreds of different cell types that are shaped by the combinations of genes they express. For example, hemoglobin is produced in red blood cells where it is necessary for oxygen transport, while neurotransmitter receptors are made in neurons where they allow these cells to communicate with each other. On the other hand, a number of genes that are required for more common functions of cells are expressed by most, if not all cells. These are called ubiquitous genes.



"Luisa Cochella studies the ways in which genes specify different cell identities, using a tiny worm as a model organism. The microscope image here reveals the cells that allow the worm to smell carbon dioxide." © IMP/Beck

In rare cases, ubiquitous genes are not expressed in a specific cell type, where reduced levels of these genes are necessary for the correct function of this particular cell type. The unique properties of a cell can therefore not only be specified by the genes it expresses, but also by the genes it prevents from being expressed. However, the mechanisms that underlie the highly specific repression of genes in some cells have remained puzzling, which is why this study is important.

What was characterised as a developmental mechanism could also be relevant for evolution. The responses of different animals to carbon dioxide vary a lot – some are attracted to it because it is linked to food sources, others flee from it because carbon dioxide is often high in environments with little oxygen. "Given this, our work has the

additional implication that microRNAs may be good candidates to give species new tools to adapt to different environments", says Cochella, who points at the known fact that microRNAs evolve faster than the bigger protein-coding genes.

The IMP, with 15 groups focusing on a diversity of fundamental research questions, provided the perfect place for Cochella and her team to carry out this study. The collaboration with co-author Manuel Zimmer, who has long established ways to quantitatively measure behavioural responses in C. elegans, was instrumental to this project.

In addition, this study provides insight into understanding microRNA functions. "In C. elegans there are between 150 and 200 miRNAs but we only know the functions of 25 or so of them", says Cochella. This is not only true for the worm, a similarly low fraction of miRNAs has been characterized out of the hundreds found in humans, even though as a whole, miRNAs are essential for animal development and function. This study hints at why miRNA functions have been difficult to uncover: many miRNAs may be only expressed in restricted cell types and finding their functions may require methods as precise as those used in the worm to know exactly which and how cells are affected.

Original Publication

Tanja Drexel, Katharina Mahofsky, Richard Latham, Manuel Zimmer and Luisa Cochella: Neuron-type specific miRNA represses two broadly expressed genes to modulate an avoidance behavior in C. elegans. Genes & Dev., Published in Advance September 29, 2016, doi: 10.1101/gad.287904.116

About Luisa Cochella

Luisa Cochella studies the ways in which gene expression must be regulated during development in order to specify the properties of the hundreds of different cell types that give rise to a complex multicellular animal. She studies this in the tiny nematode worm C. elegans. This worm is an extremely useful model organism to address this question because it is made of relatively few cells that can easily be followed during development. Luisa Cochella did her undergraduate studies at Universidad de Buenos Aires in her home country Argentina, followed by PhD studies at Johns Hopkins School of Medicine in Baltimore (USA). After her post-doctoral work at Columbia University in New York (USA), Dr. Cochella took the next step in her outstanding academic career and became a group leader at the Research Institute of Molecular Pathology (IMP) in Vienna (Austria), in January 2013.

About the IMP

The renowned Research Institute of Molecular Pathology (IMP) in Vienna is a basic biomedical research institute largely sponsored by Boehringer Ingelheim. With over 200 scientists from 37 nations, the IMP is committed to scientific discovery of fundamental molecular and cellular mechanisms underlying complex biological phenomena. Research areas include cell and molecular biology, neurobiology, disease mechanisms and computational biology.