Twenty-five years ago Professor Thomas Jentsch opened up a new field of research

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Professor Thomas Jentsch Credit: David Ausserhofer/ Copyright: MDC

A quarter of a century ago, the physicist, physician and cell biologist Professor Thomas Jentsch and his research team opened up an entirely new field of research in the field of ion transport. Now the British

journal *The Journal of Physiology* has devoted a special section in its latest issue to his discovery.

In this issue, Professor Jentsch, who leads a research group at the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) and at the neighboring Leibniz-Institut für Molekulare Pharmakologie (FMP), and several authors, report on this field, which has acquired great importance not only for basic research but also for clinical research.

Professor Jentsch's main research interests are ion transport processes. These are of crucial significance for the functioning of the cell and for the whole organism. Disruption of these processes can lead to the development of serious diseases.

The electric ray and the Torpedo chloride channel

In 1990, after more than four years of work, Thomas Jentsch and his research team identified and isolated the gene for a voltage-gated chloride channel in the electric organ of the electric ray (Torpedo marmorata). A protein encoded by this gene - the Torpedo chloride channel - transports the negatively charged chloride ions through the cell membrane, depending on the electric voltage. With this discovery, the researchers had molecularly identified the first voltage-gated chloride channel and had launched a new field of research.

A decade earlier, Professor Christopher Miller had accidentally discovered the electric activity of this chloride channel in the electric organ of the electric ray Torpedo, which he then characterized biophysically. Until Thomas Jentsch cloned the corresponding gene, however, the underlying protein remained unknown. The cloning of the channel from the exotic electric ray was the breakthrough that later enabled Jentsch and his research team within a few years to identify and

characterize related chloride channels of humans. The scientists discovered that several inherited diseases in humans are due to mutations in these channels, which Jentsch named "CLC". (Cl is the chemical abbreviation for chloride and C stands for channel).

"Meanwhile," Professor Jentsch said, "more than 2000 scientific publications have been published on the properties and multifaceted physiological functions of this chloride channel family in the organism and in the pathogenesis of disease." In the journal Dr. Jentsch described the situation in the eighties: "Twenty-five years ago only a few physiological studies were concerned with chloride channels." The reason: "Almost all electrophysiologists investigated channels for sodium and potassium and suppressed currents of chloride channels, which only interfered with their studies."

However, at that time it was already known that the dysfunction of chloride channels - that is, their failure to mediate an electric currents and transport salt - was probably the cause of two genetic diseases: cystic fibrosis, a serious disorder in which the glands form thick mucus and among other things lead to a decline in lung function and to muscle stiffness (myotonia congenita). "This unexplored field of research seemed to promise many new biological insights and surprises," said Jentsch. "Today we know that humans have nine different CLC chloride channels and transporters, which perform functions in the outer cell membrane and in intracellular vesicles."

Jentsch and his staff also identified two other smaller proteins that bind to specific CLC channels and are essential for their functions. The loss of these proteins causes the same diseases as the loss of the actual channel: renal salt loss and a form of deafness, and/or osteopetrosis (severely calcified bones) and neurodegeneration.

Less than two years after cloning the Torpedo channel, in collaboration

with human geneticists, Thomas Jentsch showed that a mutation in such a chloride channel causes several inherited forms of muscle stiffness. Furthermore, his research group showed that mutations in another chloride channel lead to blindness and destruction of white brain matter (leukodystrophy). His research group also deciphered the functions of three chloride channels in the kidney. If defective, they lead to different renal diseases, such as massive salt depletion, renal stones and renal calcification, and additionally to deafness if two of these channels are completely lost.

He also discovered that mutations in another chloride transporter lead to severe bone disease and neurodegeneration. On mouse models, his team showed that these diseases result from a disturbance in the lysosomes, cellular, membrane-enclosed "waste bins" of the cell. Together with Dr. Stefanie Weinert and Dr. Gaia Novarino in his research group, he showed that, contrary to scientific consensus, the protein degradation in the tiny cell organelles is not solely dependent on the pH value, but also on chloride ion accumulation in their interior.

In addition to his work on CLC chloride transporters, Thomas Jentsch and staff are concerned with specific potassium channels. Again, they were able to elucidate the cause of several hereditary diseases. They showed for instance that mutations in the potassium channel KCNQ2 lead to a form of inherited epilepsy in humans. Drugs that open these channels are already being used in clinical practice. The Jentsch research group also discovered that mutations in the KCNQ4 cause a form of deafness in humans. A few years ago Professor Jentsch, together with Professor Gary Lewin from the MDC and clinicians in Spain and the Netherlands, also showed that people with this specific form of inherited deafness have a heightened sensitivity in their fingers for the perception of vibrations.

Last year his research team achieved a breakthrough which may be of

similar significance. Thomas Jentsch, Felizia Voss and Tobias Stauber succeeded in identifying another chloride channel, which had been biophysically known for over 20 years, but whose molecular identity had remained elusive despite the efforts of many groups. This anion channel VRAC is a kind of "pressure relief valve" in the cell membrane, which is activated by the swelling of the cell. Cells thus regulate their volume in order to prevent them from bursting. Unlike the CLCs, this channel is also permeable to small organic molecules that among other functions serve as messenger substances. "This finding will also lead to an important new field of research," Professor Jentsch said.

Study of physics and medicine

Thomas Jentsch was born in Berlin on April 24, 1953 and studied physics and medicine there at the Free University (FU). In 1982, he earned his PhD degree in physics at the FU Berlin and at the Fritz Haber Institute of the Max Planck Society, and completed his MD degree in 1984. He then worked as a staff scientist at the Institute for Clinical Physiology at the FU and from 1986 - 1988 he was a postdoctoral fellow at the renowned Whitehead Institute of the Massachusetts Institute of Technology (MIT) in Cambridge, MA, USA.

In 1988 he became a research group leader at the Centre for Molecular Neurobiology Hamburg (ZMNH) where, from 1993 to 2006, he was director of the Institute for Molecular Neuropathobiology. In 1998, he was offered a professorship at the ETH Zurich, Switzerland, and in 2000 he was offered a position as director of the Max Planck Institute for Experimental Medicine in Göttingen. In 2006 the Leibniz-Institut für Molekulare Pharmakologie (FMP) and the Max Delbrück Center jointly offered him a position in Berlin-Buch.

Professor Jentsch has received numerous awards for his research, both in Germany and abroad, among them the most highly endowed German

research award, the Leibniz Prize of the German Research Foundation (1995), the Franz Volhard Prize for Nephrology (1998), the Zülch Prize for Neurology of the Gertrud Reemtsa Foundation (1999), the Prix Louis-Jeantet de Médecine (2000), the Ernst Jung Prize for Medicine (2001) as well as the Adolf Fick Prize for Physiology and the Homer W. Smith Award for Nephrology (both 2004).

Professor Jentsch is an elected member of the Berlin-Brandenburg Academy of Sciences, the German Academy of Natural Scientists Leopoldina, the Academia Europaea, and the Hamburg Academy of Sciences. He is one of the German scientists whose research is most frequently cited internationally.

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