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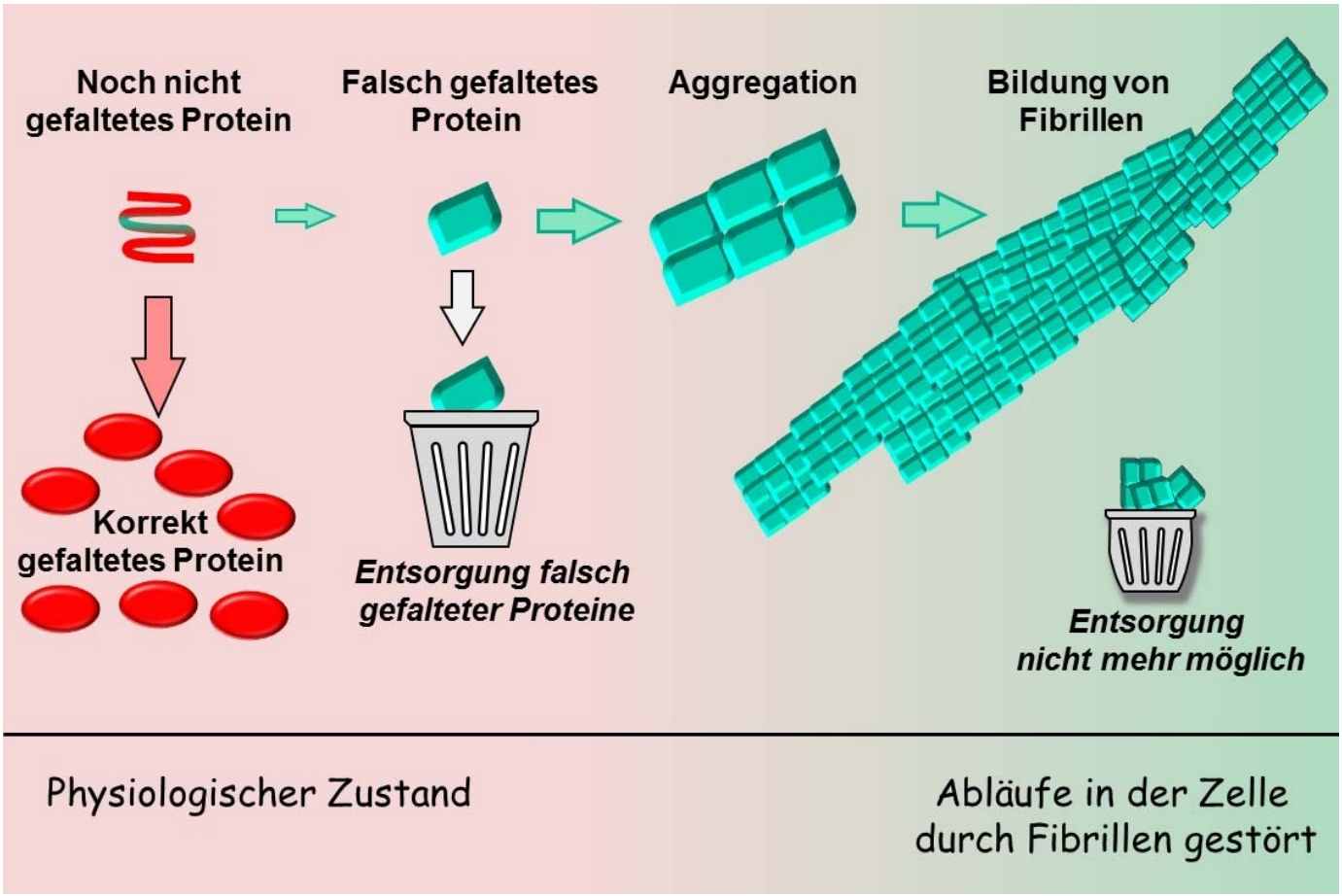
https://www.gesundheitsindustrie-bw.de/en/article/news/protein-depositions-in-the-brain-promote-the-development-of-amyotrophic-lateral-sclerosis-als

Protein depositions in the brain promote the development of amyotrophic lateral sclerosis (ALS)

Being aware of one's own physical degradation as intellect and cognition remain completely intact – this is what the disease amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease) means to sufferers. Physicist Stephen Hawking is probably the best known example of someone with ALS. With a life expectancy after onset between three and five years, Hawking, who has lived with the disease for around 50 years, is a notable exception. ALS is one of the most aggressive diseases of the human nervous system. The disease leads to the gradual degeneration and death of motor neurons, which innervate the muscles. The disease is currently not curable, as far too little is known as yet about its causes. However, basic research is making progress and providing increasing insights into the causes of ALS. Dr. Günter Fritz and his colleagues from the Department of Neuropathology at the Freiburg University Medical Centre have found that it is the properties of certain proteins that accelerate ALS pathogenesis.

The early stages of the disease are highly variable. The first signs can appear anywhere in the body. The gradually reduced innervation of the muscles leads to their degeneration, leading in turn to muscle atrophy and spasticity. ALS patients suffer from rapidly progressive weakness of the arm, leg and abdominal muscles. Over time, patients experience difficulties in walking and moving their arms as well as difficulties in speaking, swallowing and breathing. Inhibition of the respiratory muscles or pneumonia ultimately leads to death three to five years after disease onset. Expert opinion is divided on ALS incidence; while some regard it as a rare disease with fewer than four cases in 100,000 people, others believe that – with an estimated 6,000 to 8,000 people affected by ALS in Germany – the disease is more common than previously thought. In any case, the disease affects slightly more men than women, mostly between the ages of 50 and 70. It is striking that many nervous system diseases such as dementia and ALS exclusively occur in humans. There is a great deal of perplexity as to the potential causes of ALS: is it caused by genetic factors, environmental influences, extremely high physical activity or traumata?

Disease and death caused by erroneous protein folding



Fibrils develop as a result of erroneously folded proteins (green).
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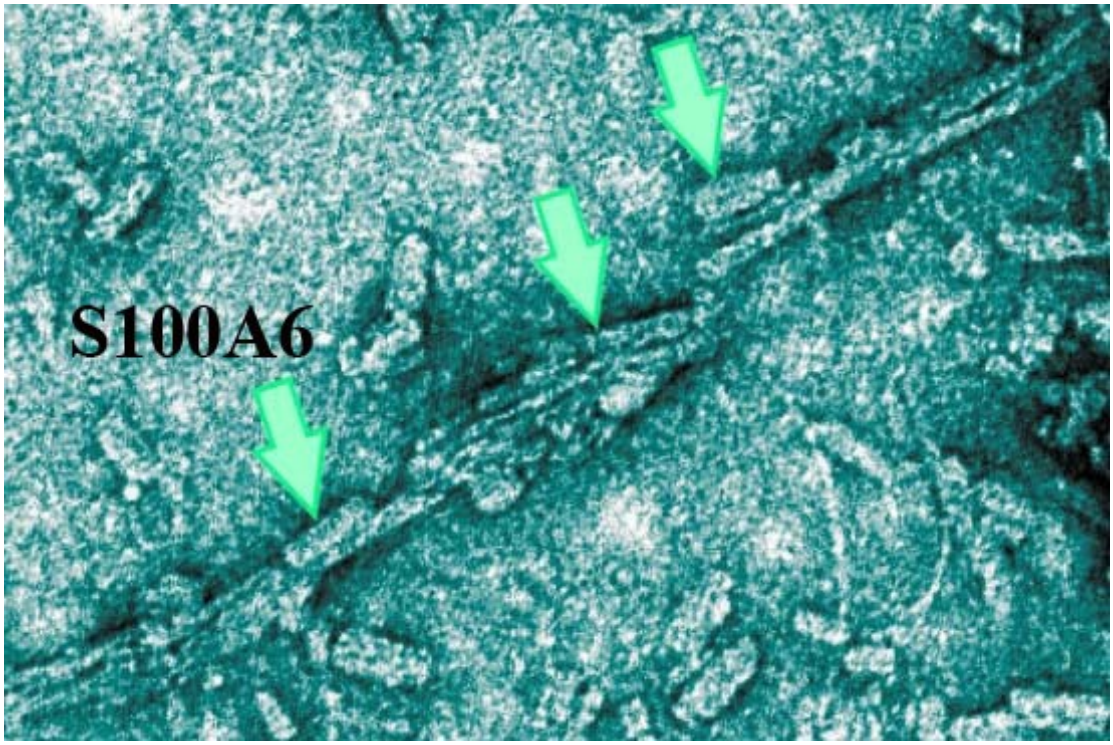
The basic protein construction plans are determined by genes; however, 'native' proteins need to adopt a specific three-dimensional structure in order to exert their respective functions. Researchers have recently identified faulty versions of some protein candidates that are strongly suspected to cause ALS by accumulating inside the cell; these include the protein ubiquitin and the enzyme superoxide dismutase (SOD1) which plays a key role in breaking down reactive oxygen species that result from cellular respiration and accumulate primarily in the neurons. "Protein misfolding plays a far greater role in degenerative diseases than previously thought," said Dr. Günter Fritz from the Department of Neuropathology at the Freiburg University Medical Centre. Fritz believes that the occurrence of misfolded proteins is a relatively normal process that occurs every now and then. However, cells have an effective mechanism for getting rid of such proteins: defective proteins are labelled for destruction in cellular garbage chutes, i.e. proteasomes. If a larger number of misfolded proteins occur as a result of genetic or other factors, cells are unable to keep up with destruction and increasing numbers of defective proteins accumulate and aggregate in the cytoplasm.

S100A6 facilitates aggregation of SOD1

Some time ago, researchers discovered that mutated superoxide dismutase aggregated into fibrils in neurons. However, the cause of fibril formation remained elusive until 2012 when Fritz and his colleague Dr. Claudio Gomes from the Instituto de Tecnologia Quimica y Biologica (ITQB) in Portugal discovered that yet another protein (S100A6, which belongs to the S100 family) was involved in the formation of the deposits. "The aggregates are not formed by just one protein, but by two, three or even more," said biochemist and biophysicist Fritz. "And this facilitates the formation of aggregates."

The process of aggregation can be described as follows: a small cluster of misfolded S100A6, whose



Small S100A6 aggregates form larger fibrils.

native form is normally responsible for the transmission of calcium signals in cells, is a kind of seed crystal for further proteins. This leads to a chain reaction that proceeds faster when there are a greater number of aggregates or when they are bigger. And this not only holds true for one specific protein, but also for others, including SOD1 that preferentially adheres to S100A6 aggregates.

"We have been able to show in vitro that S100A6 aggregates at a specific pH and that this pH also facilitates SOD1 deposition," said Günter Fritz, who currently works at the Freiburg University Medical Centre, supported by a Heisenberg fellowship.

When cells can no longer manage the mountain of garbage

Fritz has been focusing on S100 proteins for around 20 years. Humans have around 24 different S100 proteins with a broad range of different functions. Fritz has chosen the bottom-up approach, in which analyses of subsystems are pieced together to give rise to bigger systems with the goal of understanding the larger abstractions. Fritz and his team produced numerous recombinant S100 proteins in order to allow the proteins to form fibrils in a reaction tube and find an answer to the question: "Is it possible that these aggregates are responsible for certain diseases?" Fritz mixed the fibrils with neuroblastoma cells (ed. note: this is a tumour cell line capable of unlimited proliferation in vitro) and was able to show that the fibrils had a toxic effect on the nerve cells, which died prematurely. However, this came as no surprise to him.

"Cells are like well-organised factories; substances are imported, exported and transformed," said the expert. "A pile of garbage that is getting bigger will at some stage mechanically or biochemically interfere with a sensitive but essential process." Fritz believes that the probability of developing this kind of aggregation problem increases with age. "There are different garbage molecules that can accumulate. As in Alzheimer's disease, the body at some stage is no longer able to get rid of the garbage."

Fritz has major plans for the future: he is now also specifically focused on the development of Alzheimer's and is looking for substances that are able to prevent the aggregation of proteins in neurons in collaboration with a Swedish company. He attaches great importance to networking: "Nobody is able to cover an entire scientific or medical field on his or her own; one has to specialise in a specific field or topic. People who have excellent ideas need to exchange information and work more closely together. This will lead to many new results," said Fritz.

Further information:

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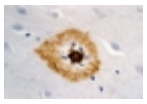

Neurodegenerative diseases