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Background information on the award of the 2019 Paul Ehrlich and Ludwig Darmstaedter Prize for Young Researchers to Dr Dorothee Dormann

Locked out – how the expulsion of two proteins from the cell nucleus promotes the development of neurodegenerative diseases

In diseases of the nervous system, proteins often end up in the wrong place and clump together. Dr Dorothee Dormann has studied these fatal events in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) and hopes to find target molecules for treatment purposes.

In some diseases, medicine is powerless. In such situations, it can offer those affected just alleviation of the symptoms – nothing more. ALS and FTD belong to this category. Both diseases affect the brain. In ALS, motor neurons die off, which leads to progressive paralysis. The disease is complex. FTD, a rare type of dementia that often occurs before the age of 65, causes changes in the individual's personality, social behaviour and faculty of speech. As a rule, patients with ALS or FTD die within a few years after the diagnosis. The most famous ALS patient was astrophysicist Stephen Hawking, who, however, suffered from a very slowly progressing juvenile form. ALS was present in the media thanks to an unusual fundraising campaign, the "Ice Bucket Challenge". Anyone willing to support ALS research was invited to tip a bucket of cold water over their heads and nominate at least three other people to do the same. Many famous people took part, in Germany too.

Although the two diseases present with quite different symptoms, they exhibit similar types of protein deposits in affected brain cells. They also have some other things in common. About ten per cent of ALS patients also develop frontotemporal dementia. The winner of this year's Prize for Young Researchers, Dr Dorothee Dormann from the Biomedical Center Munich (BMC) of LMU Munich, has explored the question of how these typical deposits form. She

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discovered that in both diseases – apart from many other pathological lesions – two proteins are locked out of the cell nucleus and accumulate in the cytoplasm. If the cell finds itself in a stressful situation, for instance through lack of oxygen or the presence of harmful substances, both proteins end up in what are known as stress granules, where they form distinct droplets which progress to become solid protein deposits.

Disease triggered by defective address

The two locked-out proteins are called FUS and TDP-43. They are both normally active in the cell nucleus, where they help to transcribe the genetic information and participate in the trimming of messenger RNAs. In addition, they both commute between the cell nucleus and the cytoplasm, though the exact reason for this traffic back and forth is currently unknown. Dormann has mainly examined the FUS protein. Her findings can, however, also be applied to the related TDP-43 protein. In 2009, it became known that the FUS gene is mutated in some ALS patients. Dormann demonstrated just a few months later that the mutation affects the area that channels the protein into the cell nucleus. These changes cause the transporter, which is supposed to chauffeur FUS into the cell nucleus, to no longer recognise the protein. Some cases of ALS thus begin with a defective molecular address.

But how is the FUS protein locked out of the cell nucleus in patients without a mutated address? This year's prizewinner discovered that the transport can also be disrupted through faulty postprocessing of the FUS protein. The transporter evidently requires not only a correct molecular address but also methyl groups on the FUS protein, otherwise it no longer lets go of the protein. This methylation is absent in some FTD patients without a mutated address. In 2014, Dormann won the Heinz Maier-Leibnitz Prize of the German Research Foundation in recognition of this work. The prize is regarded as one of the most prestigious awards for young scientists in Germany.

What happens with the misplaced proteins in the cytoplasm? Initially, nothing at all. Only in stressful situations does this mislocalisation become critical. Dorothee Dormann was able to show that FUS and TDP-43 are then drawn into what are known as stress granules. Stress granules are dynamic structures composed of various molecules that do not make an immediate contribution to overcoming a critical state of the cell. Above all, these assemblages include messenger RNAs, whose use is temporarily suspended because overcoming stress takes priority. Once the crisis has been resolved, the granules disintegrate again, and their contents are put to further use. In this way, the cell makes sure that it survives the stress as unharmed as possible.

Critical phase separation

For the FUS protein, Dormann has examined in greater detail how the typical deposits form in the stress granules. Its properties evidently cause it to separate from the rest of the contents in the stress granules. Dormann refers to this as phase separation. Just as water and oil separate and form two separate phases, FUS also forms a separate phase in the granules. The FUS droplets remain soluble by binding to the nuclear transporter. However, this binding is impaired in ALS patients with a defective molecular address. In FTD patients, the distinct droplets form due to the absence of methylation.

Today, Dorothee Dormann is concentrating on three questions. Firstly, she is examining whether the increased concentration of FUS and TDP-43 in the cytoplasm is caused solely

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and exclusively by their missing import into the cell nucleus. Since the two proteins shuttle back and forth continuously between cell nucleus and cytoplasm, enrichment in the wrong place could also be due to increased export out of the cell nucleus. That is why Dormann is interested in possible export factors, although her experiments so far suggest that the two proteins leave the cell nucleus passively and without the help of a dedicated transporter.

Possible targets for therapy

Dormann is also interested in further modifications. Apart from the methyl groups already mentioned, phosphate or other chemical groups can also be attached to the FUS or TDP-43 proteins. Dormann would like to know whether such modifications change the proteins' properties. It might be the case, for example, that certain modifications lead to the proteins being drawn into the stress granules more rapidly and also developing there more quickly into insoluble deposits. Such modifications would then be potential targets for therapeutic purposes.

The third question on which Dormann is working has to do with the generalisation of her results. At first sight, ALS and FTD seem to be two completely different diseases, yet they nonetheless both feature similar molecular malfunctions. Dormann would therefore like to know whether an impaired transport between the cell nucleus and the cytoplasm or the droplet formation in the stress granules associated with phase separation also play a role in other neurodegenerative diseases distinguished by pathological protein deposition. She is therefore seeking to identify a pathophysiological communality of neurodegenerative diseases.

ALS and FTD are complex diseases. In the case of ALS, over 20 relevant gene defects have been identified so far, including mutations in a gene that eliminates oxidative stress, the SOD1 gene. By demonstrating that FUS and TDP-43 clump together in stress granules due to their propensity for phase separation and the absence of protective factors, this year's prizewinner has made an important contribution to this very diverse and highly competitive field of work.

Further information

All press documents and photographs of Dr Dorothee Dormann are available from www.paul-ehrlich-stiftung.de. Publication is free of charge. A detailed vita, selected publications and a list of publications can be obtained from Dr Hildegard Kaulen, Tel.: +49 (0) 6122/52718, Email: h.k@kaulen.wi.shuttle.de