Cell research opens new avenues in combating neurodegenerative diseases

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Scientists at the University of Manchester have uncovered how the internal mechanisms in nerve cells wire the brain. The findings open up new avenues in the investigation of neurodegenerative diseases by analysing the cellular processes underlying these conditions.

Dr Andreas Prokop and his team at the Faculty of Life Sciences have been studying the growth of axons, the thin cable-like extensions of nerve cells that wire the brain. If axons don't develop properly this can lead to birth disorders, mental and physical impairments and the gradual decay of brain capacity during aging.

Axon growth is directed by the hand shaped growth cone which sits in the tip of the axon. It is well documented how growth cones perceive signals from the outside to follow pathways to specific targets, but very little is known about the internal machinery that dictates their behaviour.

Dr Prokop has been studying the key driver of growth cone movements, the cytoskeleton. The cytoskeleton helps to maintain a cell's shape and is made up of the protein filaments, actin and microtubules. Microtubules are the key driving force of axon growth whilst actin helps to regulate the direction the axon grows.

Dr Prokop and his team used fruit flies to analyse how actin and microtubule proteins combine in the cytoskeleton to coordinate axon growth. They focussed on the multifunctional proteins called spectraplakins which are essential for axonal growth and have known

roles in neurodegeneration and wound healing of the skin.

What the team demonstrate in this recent paper is that spectraplakins link microtubules to actin to help them extend in the direction the axon is growing. If this link is missing then microtubule networks show disorganised criss-crossed arrangements instead of parallel bundles and axon growth is hampered.

By understanding the molecular detail of these interactions the team made a second important finding. Spectraplakins collect not only at the tip of microtubules but also along the shaft, which helps to stabilise them and ensure they act as a stable structure within the axon.

This additional function of spectraplakins relates them to a class of microtubule-binding proteins including Tau. Tau is an important player in neurodegenerative diseases, such as Alzheimer's, which is still little understood. In support of the author's findings, another publication has just shown that the human spectraplakin, Dystonin, causes neurodegeneration when affected in its linkage to microtubules.

Talking about his research Dr Prokop said: "Understanding cytoskeletal machinery at the cell level is a holy grail of current cell research that will have powerful clinical applications. Thus, cytoskeleton is crucially involved in virtually all aspects of a cell's life, including cell shape changes, cell division, cell movement, contacts and signalling between cells, and dynamic transport events within cells. Accordingly, the cytoskeleton lies at the root of many brain disorders. Therefore, deciphering the principles of cytoskeletal machinery during the fundamental process of axon growth will essentially help research into the causes of a broad spectrum of diseases. Spectraplakins like at the heart of this machinery and our research opens up new avenues for its investigation"

What Dr Prokop's paper in the *Journal of Neuroscience* also demonstrates is the successful research technique using the fruit fly Drosophila. The team was able to replicate its findings regarding axon growth in mice which in turn means the findings can be translated to humans.

Dr Prokop points out fruit flies provide ideal means to make sense of these findings and essentially help to unravel the many mysteries of neurodegeneration.

Dr Prokop continues: "Understanding how spectraplakins perform their cellular functions has important implications for basic as well as biomedical research. Thus, besides their roles during axon growth, spectraplakins of mice and humans are clinically important for a number of conditions and processes including skin blistering, neuro-degeneration, wound healing, synapse formation and neuron migration during brain development. Understanding spectraplakins in one biological process will instruct research on the other clinically relevant roles of these proteins."

The recently published paper represents six years of work by Dr Prokop and his dedicated team.

More information: The paper is entitled "Spectraplakins Promote Microtubule-Mediated Axonal Growth by Functioning As Structural Microtubule - Associated Proteins and EB1-Dependent +TIPs (Tip Interacting Proteins). It was published on July 4 2012 in *The Journal of Neuroscience*.

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