Newly identified pathways could advance understanding of neurodegenerative diseases and define novel therapeutic strategies

Dr Benoit Schneider is a researcher for the National Centre for Scientific Research of France (CNRS), based at Paris Descartes University. He is head of a team that uses stem cells to tackle a variety of clinical challenges, such as neurodegeneration. His current research looks at whether deregulation of the PrPα/ROCK-PDK1/TACE signalling axis contributes to neurodegeneration in several amyloid protein-based neurodegenerative diseases.

Neurodegenerative diseases affect the neurons in the brain, causing their function to be progressively impaired. The reasons for this remain largely unknown, and have been the focus of much research throughout the years. Millions of people worldwide currently live with some form of neurodegenerative disease, and this number is increasing exponentially as the population continues to age.

Neurodegenerative diseases like prion, Alzheimer’s and Parkinson’s diseases are all characterised by the accumulation of abnormal proteins that are toxic for neurons in the brain (‘neurotoxic’). Despite their different aetiologies and clinical manifestations, these neurodegenerative diseases may share common biological causal pathways, known as ‘pathogenic (disease-inducing) cascades’. This means that there may be a shared explanation, and therefore a shared solution, to these related neurodegenerative diseases.

Starting from studies on prion diseases, Dr Schneider’s work focuses on identifying common pathways and examining the shared biological mechanisms that cause neurodegenerative diseases. The team notably uses an inducible neuronal stem cell to investigate the mechanisms sustaining degeneration of neurons in prion and Alzheimer’s diseases. The team’s work paves the way to help the development of effective therapies against these pathologies.

PRION DISEASES
Transmissible Spongiform Encephalopathies, commonly known as prion diseases, are caused by tiny infectious particles called pathogenic prions (PrPα). These are misfolded proteins that transmit disease by causing, in healthy tissue (notably in brain), the conversion of the non-pathological cellular prion protein PrPα into PrPαα, that is, the replication of the PrPαα-associated misfolded structure. This causes infected brain tissue to become spongy and riddled with holes. By provoking PrPαα conversion into a diseased form, PrPαα corrupt the physiological function(s) of PrPαα in neurons, which is at the heart of prion diseases.

DEMystifying PrPαα functions to unravel pathogenic cascades in prion diseases
It is thus essential to find the function(s) of PrPαα in neurons, so that the mechanisms by which pathogenic prions exert toxic effects can be elucidated. However, PrPαα normal function(s) largely remain(s) a mystery. To challenge PrPαα role(s), Schneider’s team has explored a neuronal stem cell line (1C11) that expresses PrPαα. Key to their approach is the identification that PrPαα is a critical actor for the differentiation of the stem cell (the process whereby ‘blank slate’ stem cells specialise and develop into specific cells) into neurons and the regulation of neuronal functions through the control of diverse signalling effectors, including the enzymes TACE alpha-secretase and the Rho kinases (ROCK). When pathogenic prions PrPαα alter the regulatory action of PrPαα, prion diseases could then form.

Dr Schneider follows this approach: exposure of 1C11 neuronal cells to pathogenic prions PrPαα. Neuronal cells infected by prions, that is, chronically replicating PrPαα, were instrumental in the team’s search for the nature and sequence of molecular events leading to neurodegeneration that take place in prion diseases.

From this method, they found that over-activation of the kinase enzyme PDK1 (Phosphoinositide-dependent kinase-1) is important in prion-induced neurodegeneration because it stops TACE alpha-secretase acting. TACE, another enzyme, has neuroprotective qualities, which means it guards against some of the neurodegenerative properties of pathogenic agents like PrPαα. The suppression of TACE alpha-secretase activity preferentially allows the production and accumulation of pathogenic prions, and makes infected neurons sensitive to inflammatory stress. This is because the suppression of TACE alpha-secretase leads to a build-up of TNF (a critical mediator of inflammation and cell death) receptors, and makes cells vulnerable to TNF-induced inflammation. This finding has been validated in vivo in mice infected by pathogenic prions.

APPLICATION TO OTHER NEURODEGENERATIVE DISEASES
Following the discovery that deregulation of the PKD1-TACE cascade in prion diseases leads to increased sensitivity to inflammatory stress and amplifies the production of toxic PrPαα protein, the team next investigated whether this same mechanism was present in other neurodegenerative diseases. Sure enough, they found that deregulation of the PKD1-TACE pathway also occurs in Alzheimer’s disease. The team was the first to show that the PKD1-TACE pathway is...
Evidence shows an increase in PDK1 activity in the post-mortem brains of Alzheimer’s patients. This suggests that PDK1 could be a useful therapeutic target, not only for prion diseases but also Alzheimer’s disease.