Prion protein as a therapeutic target in Alzheimer’s disease

Soluble oligomeric forms of amyloid-β (Aβ) appear to be the most neurotoxic assemblies in Alzheimer’s disease (AD). The cellular prion protein (PrPC) is a neuronal surface receptor for soluble Aβ oligomers, mediating their neurotoxicity. A cholesterol-rich, lipid raft-based cell surface complex, along with the transmembrane low density lipoprotein receptor-related protein-1 (LRP1), is critical for mediating the neurotoxic effects of Aβ oligomers, including the activation of Fyn kinase. Remodelling of the Aβ oligomers with the polyphenols resveratrol or EGCG prevents their binding to PrPC and the downstream neuronal toxicity. These data indicate that soluble Aβ oligomers bind to PrP C in a conformation-dependent manner and require the integrity of lipid rafts and the transmembrane LRP1 for their cytotoxicity, thus revealing potential targets to alleviate the neurotoxic properties of Aβ oligomers in AD. However, PrPC is also involved in regulating the production of Aβ through its inhibition of the β-secretase BACE1 and enhances the uptake of zinc into neurons through AMPA receptors. A reduction in PrPC results in an increase in Aβ and in synaptic zinc which promotes the formation of Aβ oligomers. In the human brain in AD and aging there is a reduction in PrPC, which inversely correlates with BACE1 activity and Aβ levels, consistent with its role as a neuroprotective agent. This apparent dichotomy in the role of PrPC in AD (neurotoxic versus neuroprotective) will be discussed, along with the potential for, and limitations with, PrPC being a therapeutic target in AD.

Biography

Nigel M Hooper completed his PhD at the University of Leeds in 1987. He was then awarded a Mr and Mrs John Jaffe Donation Research Fellowship from the Royal Society. Between 1989 and 2014, he was on the academic staff, including as Professor of Biochemistry, and Dean of the Faculty of Biological Sciences, at the University of Leeds. He has recently taken up a Chair appointment in the Institute of Brain, Behaviour and Mental Health at the University of Manchester. He is Chair of the Scientific Advisory Board of Alzheimer’s Research UK and has published over 170 research papers.