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Amyloid-β precursor protein presence on the neuron surface is required for the iron pore ferroportin to efflux iron

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Iron is an integral cofactor in many metabolic processes involved in transcriptional signaling, synapse formation and neuroplasticity, in all of which a function for amyloid-β precursor protein (APP) has also been heavily implicated but remained unclear. Imbalances in intraneuronal iron are a predominant catalyst for the production of reactive oxygen species, particularly within iron accumulating neurodegenerative diseases such as Alzheimer's disease. While APP has historically been associated with AD due to the prevalence of the APP derived amyloid-β (Aβ) peptide within insoluble extracellular 'plaques' deposited within the AD brain, we recently discovered that APP has a role in neuronal iron homeostasis by, in part, promoting iron efflux through cell surface stabilization of the iron pore ferroportin. Detailed cell surface characterization confirms that the location of ferroportin on the neuron surface is increased upon iron incubation and is dependent upon APP. By altering the trafficking of APP to the cell surface via tau or the proteolytic processing of APP, consequential changes in neuronal iron homeostasis arise. Deletion of tau decreased cell surface APP expression, resulting in an age-dependent neuronal iron accumulation that parallels studies with APP depletion. Comparably, enhancing the amyloidogenic pathway of APP processing, leads to intracellular iron accumulation. With increased amyloidogenic processing of APP and post-translational modification of tau being major contributors to sporadic AD, these studies increase our understanding as to why iron accumulation and increased susceptibility to reactive oxygen species neurotoxicity are prevalent with this disease.

Biography

James A Duce completed his PhD in 2002 from University of Wales College of Medicine, Cardiff before leaving the UK to study in the US and Australia. At present he concurrently runs research teams at the University of Leeds, UK and The Florey Institute of Neuroscience and Mental Health in Melbourne Australia. In recognition of his strong involvement in identifying the iron regulatory role of β-Amyloid precursor protein (APP) through tau's assistance in its transport to the neuron surface he was recently awarded the JBC/Herb Tabor Young International Investigator award. Continued support is provided through an Alzheimer's Research UK Senior Research Fellowship and projects funded by the European Research Council and Australian National Health and Medical Research Council.

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