CeBioND

Cellular Bioenergetics in Neurodegenerative Disease; A systems-based pathway and target analysis identifies a glycolytic defect in Alzheimer's disease neurons

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Mitochondrial and bioenergetic dysfunction is implicated in most neurodegenerative diseases, and further research is required to understand whether such dysfunction is a cause or consequence of the underlying pathology. Bringing together significant expertise in neurodegenerative diseases, mitochondrial and bioenergetic function, and systems modelling, the Cellular Bioenergetics in Neurodegenerative Diseases consortium (CeBioND) aimed to elucidate common and distinct disease mechanisms in neurodegenerative diseases, focussing on pathways regulating cellular bioenergetics and mitochondrial function.

We first established experimental protocols across the consortium, resulting in a highly cited consensus guidelines review on experimental methods to assess mitochondrial dysfunction in cellular models of neurodegenerative diseases. We next combined experimental and computational modelling approaches to investigate mitochondrial health and bioenergetic function in neurons from a double transgenic mouse model of AD (PS2APP/B6.152H). Experiments in primary cortical neurons demonstrated that AD neurons had reduced mitochondrial respiratory capacity. Interestingly, the computational model predicted that this mitochondrial bioenergetic phenotype could not be explained by any defect in the mitochondrial respiratory chain (RC), but could be closely resembled by a simulated impairment in the mitochondrial NADH flux.

We validated these computational predictions utilising fluorescence lifetime imaging microscopy (FLIM) and autofluorescence imaging to confirm that transgenic AD neurons had reduced NAD(P)H levels at rest, and impaired power of mitochondrial NAD(P)H production. We also identified an impaired glycolytic flux, and demonstrated that this impaired flux was responsible for the observed mitochondrial hypometabolism, since bypassing glycolysis with pyruvate restored mitochondrial health. This publication highlighted the benefits of a systems biology approach when investigating complex, non-intuitive molecular processes such as mitochondrial bioenergetics, and indicated that primary cortical neurons from a transgenic AD model have reduced glycolytic flux, leading to reduced cytosolic and mitochondrial NAD(P)H and reduced mitochondrial respiratory capacity.

Finally, we performed a cell-based high-throughput screening assay where, out of 1,200 FDA-approved compounds, the flavonoid luteolin was identified as a mitochondrial enhancer. Further analysis revealed that under physiological conditions luteolin improves mitochondrial calcium homeostasis and ATP production, and increases the number of mitochondria-ER contact sites per mitochondria. The approaches established as part of the CeBioND consortium are now being applied to additional neurodegenerative diseases.