Prohibitin-mediated Mitochondrial Signalling in the regulation of ageing

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Ageing is characterised by a decline in physiological function. Altered mitochondrial function is particularly relevant due to the central role of mitochondria in metabolism, a vital process affecting general cellular function. As such, manipulations of mitochondrial activity profoundly affect the lifespan of diverse organisms and mitochondria play a prominent role in age-associated human disorders. However, the cellular mechanisms regulating mitochondrial activity and the molecular basis of mitochondrial dysfunction in ageing are poorly understood.

We have recently uncovered a novel, key role of the mitochondrial prohibitin (PHB) complex in coordinating fat mobilization and mitochondrial metabolism, in response to insulin signalling and energy demands, during ageing. Prohibitin depletion shows striking, opposing effects on ageing: it reduces lifespan in wild type animals, while by contrast, under stress or low insulin signalling it dramatically extends lifespan. The striking opposite effect of prohibitin on longevity under different conditions offers a unique opportunity to understand how mitochondrial function relates with the cellular signalling status to regulate longevity. We are generating new genetic tools to identify the molecular signalling pathways involved in the cellular response to PHB depletion under normal and reduced insulin signalling conditions.