Strategic Promotion of Ageing Research Capacity

Calorie Restriction (CR)

Calorie restriction | Histone deacetylation | Sirt1 | DNA methylation

Molecular Basis of the Effects of CR on Ageing

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The Investigation

Calorie restriction (CR) delays the ageing process but the underlying mechanisms are poorly understood. The protein Sirt1 may play a pivotal role in mediating the beneficial effects of CR on ageing and is increased in the tissues of calorie-restricted rats. This project will investigate if increased Sirt1 levels lead to changes in chemical modification, known as methylation, of the DNA in cultured cells. It is already established that changes in DNA methylation may be involved in ageing, so demonstrating a link between increased Sirt1 levels and DNA methylation will be an important step towards understanding fully how CR affects the ageing process.

Objectives

The main objective is to establish proof of principle that increased expression of Sirt1 in cells can alter DNA methylation and also a related chemical modification, acetylation, of the core of proteins called histones around which the DNA is wound (Fig. 1).

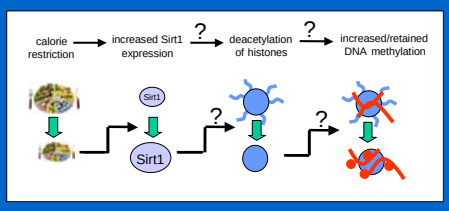

Figure 1. Summary of the hypothesis. Calorie restriction increases Sirt1 expression. We propose that increased Sirt1 expression leads to deacetylation of histone proteins and that this, in turn, increases or retains DNA methylation.

Methodology

A highly-expressed Sirt1 gene will be introduced into cultured human cells, to mimic the effect of CR, and molecular techniques will be used to measure the effect of this gene (i.e. the effect of increased Sirt1 expression) on the methylation of DNA and on the acetylation of histone proteins in the cells.

Collaborator

Professor John Mathers, Newcastle University

Potential Benefits

For older people and society

Diet is an attractive target for healthcare strategies aimed at delaying the ageing process. It is important that we gain a better understanding of the impact of nutrition on the ageing process to underpin advice on maximising health through diet. At present, CR appears the most effective dietary strategy for delaying the ageing process in model organisms, but it is currently unknown to what extent this is an effective measure in humans, nor if is effective if introduced later in life.

The findings of the project will contribute to improved understanding of the molecular basis of the beneficial effect of CR on ageing to inform dietary advice and potentially guide the discovery of therapeutic or alternative dietary interventions to delay the ageing process. The findings will also indicate if DNA methylation might be an informative biomarker of a positive effect of CR and thus provide a measure of efficacy in older people to guide research in this group. The project will indicate if resources should be directed, in the future, towards exploring the importance of changes in DNA methylation in the beneficial effects of CR on ageing.

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