

The Genetics of Ageing

Genetics

Oxidative stress

Biomarkers

Loss of function

Gene Variations and their Influence on Protein and Lipid Oxidation in the Ageing Process

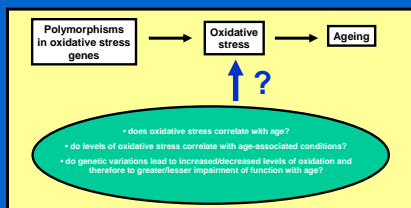
Paul Winyard, Emma Taylor, Jennifer Littlechild, Tim Frayling & David Melzer

Peninsula Medical School

The Investigation

Objectives

- To validate a panel of *in vitro* assays of oxidative stress that can be used to measure the modification of proteins and lipids during ageing.
- To optimise and modify these assays for simultaneous high throughput screening of large numbers of samples.
- To use these assays to investigate the hypothesised link between age and oxidative stress-mediated events, plus the effect of single nucleotide polymorphisms in oxidant/antioxidant-related genes on such parameters.



Plan

We will set up and validate 3 separate commercially-available assays, which measure the established biomarkers of oxidative stress; 3-nitrotyrosine (NT) and advanced oxidation protein products (AOPP) in plasma, and 15-isoprostane F2t in urine. These will then be applied to previously-collected samples from a number of ageing studies to which we have access, in subjects spanning a wide range of ages and with differences in key oxidant/antioxidant genes which we hypothesise to influence the decline in function associated with ageing. From these studies, we aim to delineate any trends between particular genetic variations and oxidative modifications in proteins or lipids, and thence the severity of particular conditions of ageing via a shift in the oxidant/antioxidant balance.

Examples of Candidate Genes

OXIDANT

- myeloperoxidase
- xanthine oxidase
- nitric oxide synthases
- NADPH oxidases

ANTIOXIDANT

- catalase
- superoxide dismutases
- thioredoxins, peroxiredoxins, sulfiredoxin
- glutathione peroxidase/reductase

Potential Benefits

For older people and society

Increased understanding of the mechanisms of both healthy ageing and disease states associated with age will allow the development of improved therapeutics and care for the older people, leading to improved quality of life and greater independence.

The Free Radical Theory of Ageing

Organisms age because protein, lipid and nucleic acids (DNA, RNA) accumulate free radical damage over time, leading to a reduction in their respective function, thereby decreasing cell function, then organ function, and finally, function of the whole organism.

Resources and Collaborators

Plasma and urine samples are available for this investigation via banks of samples and biochemical data from a number of national and international ageing studies (Frayling and Melzer). New material is also being collected from the EPIC (Norfolk) and InChianti studies.

References

- Finkel T & Holbrook NJ. Oxidants, oxidative stress and the biology of ageing (2000) *Nature*, 408; 239-247.
- Stadtman ER. Protein oxidation and aging (2006) *Free Radical Res.*, 40; 1250-1258.
- Musiek ES, Yin H, Milne GL & Morrow JD. Recent advances in the biochemistry and clinical relevance of the isoprostane pathway (2005) *Lipids*, 40; 987-994.

Contact Details

Principal Investigator

Prof Paul Winyard

paul.winyard@pms.ac.uk

Institute of Biomedical and Clinical Science

PMS Building

University of Exeter, EX1 2LU



Researcher

Dr Emma Taylor

emma.taylor@pms.ac.uk

+44 (0) 1392 262937

