Can you outline the characteristics of oxidative stress, and describe how can it be detected?

Oxidative stress is defined as an imbalance between the formation of damaging oxidant species and the host’s antioxidant defence system. Different antioxidants act selectively against different types of oxidant species and so a change in the natural defence system can lead to an overabundance of damaging oxidants.

The imbalance is often detected using biomarkers of oxidative damage, which can manifest at different biological targets. Information on the type of oxidants being produced can be implied by an increase in a given biomarker of oxidative damage. This method of assigning oxidant identity is termed the biomarker footprint.

What are the aims of your current investigations?

My research focus is to understand the relationship between oxidative processes and tissue damage. If a causal link can be established then interventions designed to inhibit oxidative damage (using natural and synthetic antioxidants) may provide therapeutic benefit in clinical settings such as for stroke, heart attack and acute kidney failure.

What is currently known about the relationship between oxidative stress and tissue damage in the acute setting of stroke, heart attack and renal dysfunction?

Functional protein units are central to efficient cellular metabolism. Oxidant damage to proteins can lead to protein dysfunction. This may play a role in promoting a pathological process, as cells can no longer respond adequately to changing microenvironments. Unregulated oxidant production can cause widespread damage to biological tissues.

Cellular mitochondria are a major source of energy production in cells and tissue. Under normal conditions, mitochondria produce energy in the form of adenosine triphosphate (ATP – the energy molecule that drives all cellular processes). A characteristic of heart attack and stroke (and possibly acute renal injury) is the rapid loss of cellular ATP followed by the production of oxidants by the affected mitochondria (termed mitochondrial dysfunction).

This unregulated oxidant production coupled with altered host antioxidant defence mechanisms can lead to permanent tissue damage. Understanding pathways that promote this tissue damage offers a route to the development of therapeutic drugs to inhibit this form of damage.

How has your background led you to the study of hydrogen peroxide in the context of physiological cellular processes and disease?

My PhD in Chemistry has provided me with a strong grounding in the understanding of redox reactions leading to the production of free radicals (termed one-electron oxidants) – that is, the study of oxidation and reduction processes central to the formation of free radical species.

Hydrogen peroxide is one type of oxidant species that is implicated in the oxidative modification of proteins and other biological targets. At low levels, hydrogen peroxide can be a cell-signalling molecule that is important in maintaining cellular function. However, at higher concentrations, this oxidant can promote unregulated cellular and tissue damage.

Subsequent to heart attack and stroke, mitochondrial dysfunction leads to the accumulation of hydrogen peroxide in the brain...
Antioxidant answers

Based within the Charles Perkins Centre at The University of Sydney, the Redox Biology Group is conducting cutting-edge experiments focused on improving treatment and recovery options for individuals affected by age-related vascular diseases including stroke, kidney failure and Alzheimer’s disease.

OXIDATIVE STRESS PLAYS a central role in ageing and the pathogenesis of numerous age-related diseases. To date, research has found evidence of oxidant-induced tissue damage in a wide range of illnesses, from neurodegenerative conditions to cancer. Elucidating the specific pathways and mechanisms involved in such damage may therefore pave the way for the development of novel targeted therapeutics.

Age-related disease in Australia is expected to increase significantly in the coming years, as a result of Australia’s ageing population. According to Australian Government estimates, the proportion of Australians aged 75 or older will reach 14.4 per cent by 2060, as compared with just 6.4 per cent in 2012.

In response to this impending public health challenge, research is increasingly focused on the role of oxidative stress in ill health as a means of driving forward new drug development. If successful, significant improvements in terms of mortality, morbidity and quality of life can be expected, both in Australia and internationally.

INVESTIGATING VASCULAR EVENTS

At The University of Sydney, Associate Professor Paul Witting is leading the Redox Biology Group in its efforts to untangle the complex relationship between oxidative processes and tissue damage in disease. The Group’s overarching goal is to produce findings that facilitate the development of interventions that will provide effective clinical benefits for a range of health conditions, with a particular focus on acute vascular events such as strokes, heart attacks and acute kidney failure.

To achieve these aims, the Redox Biology Group utilises experimental models together with advanced imaging techniques to delineate the exact mechanisms at play during the evolution of tissue injury, and to test natural and synthetic inhibitors of oxidative damage.

For the past year, the Redox Biology Group has been based within the Charles Perkins Centre – a new AUS $385 million research and education hub at The University of Sydney geared towards tackling obesity, diabetes and cardiovascular disease. The Centre was launched in 2014 with the aim of promoting innovative, interdisciplinary research by providing researchers with access to cutting-edge facilities and frequent opportunities to connect and collaborate due to its shared research infrastructure and busy calendar of cross-disciplinary events.

SELENIUM’S POTENTIAL

Much of Witting’s recent research has been devoted to exploring the capacity of the micronutrient selenium to inhibit oxidative damage resulting from the toxic accumulation of hydrogen peroxide – a process caused by mitochondrial dysfunction that has been linked to stroke and heart attack events. Witting and his colleague Hugh Harris, from Adelaide University, hypothesised that dietary selenium supplementation may have a protective effect against oxidative damage and resulting injuries.

To test this theory, the researchers conducted animal experiments in which they initiated acute kidney injury (AKI) in rat models that had been fed selenium. The results were mixed: while supplementation did appear to reduce oxidative damage and inhibit biomarkers of inflammation in renal tissues, renal function was nonetheless impaired. This has led the Sydney researchers to conclude that oxidative damage and inflammation do not cause AKI but are merely secondary effects – a finding that will inform future drug development strategies in this area.

A PRETREATMENT FOR STROKE

In addition to analysing the effects of selenium in acute vascular events such as stroke, Witting and his co-workers have been exploring potential stroke therapies. Strokes can frequently lead to neuronal cell death and vascular complications as a result of tissue injuries sustained during impaired blood flow to the brain. In an effort to prevent this, the Redox Biology researchers supplemented the diets of animal models of stroke with di-tert-butyl-bisphenol (BP) – a synthetic polyphenolic antioxidant – prior to injury.

Their findings were positive, with supplementation leading to a significant reduction in injuries, ameliorating oxidative damage while preserving cerebral tissue. The data therefore indicate that oxidative stress likely plays a causative role in tissue injuries sustained following strokes, and also point towards BP as a potent inhibitor of this process. Given that few other effective neuroprotective...
**OBJECTIVE**
To understand the relationship between oxidative processes and tissue damage in conditions such as stroke, heart attack and acute kidney failure, and use this understanding to design interventions that inhibit such processes.

**KEY COLLABORATORS**
- Dr Greg Sutherland, The University of Sydney, Australia
- Professor Ron Grunstein, Woolcock Institute of Medical Research, Sydney Medical School, The University of Sydney, Australia
- Professor Saul Benedict Freedman, Concord Repatriation General Hospital, Sydney Medical School, The University of Sydney, Australia
- Professor Michael Davies, Panum Institute, Copenhagen University, Denmark
- Professor A Grant Mauk, The University of British Columbia, Canada
- Associate Professor Hugh Harris, School of Physics and Chemistry, The University of Adelaide, Australia
- Associate Professor Ravinay Bhindi, Kolling Research Institute, Sydney Medical School, The University of Sydney, Australia
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**PAUL WITTING** is Associate Professor in the discipline of pathology at The University of Sydney and a career biomedical researcher. In addition, he is the current President for the Society for Free Radical Research Australasia and Group Leader of the Redox Biology Group. Previously, Witting held postdoctoral positions at the ANZAC Research Institute (Sydney, ARC Research Fellowship) and University of British Columbia (Vancouver, Heart Foundation Travelling Fellowship).

**BEYOND ACUTE VASCULAR EVENTS**

**Lung cancer**
Witting and the Redox Biology Group have extended their studies to the potential anticancer properties of selenium. The investigators have found that selenite (an inorganic form of selenium) can induce the formation of reactive oxidants within lung cancer cells and so inhibit their growth, via a mechanism likely involving the accumulation of hydrogen peroxide.

**Obstructive sleep apnoea**
Alongside respiratory clinicians from the Woolcock Institute at the University of Sydney, the Group recently contributed to a research project on obstructive sleep apnoea (OSA). The purpose of the partnership was to determine whether oxidative damage was elevated in individuals with OSA and, by examining plasma biomarkers of lipid oxidation, Witting and his collaborators were able to conclude that this does not in fact appear to be the case – another important finding that will shape further developments in this area.

**INSIDE ALZHEIMER’S DISEASE**
Oxidative stress also has a role to play in the pathogenesis of Alzheimer’s disease – a condition that is approaching epidemic proportions in Australia. At present, considerable research efforts are underway aimed at identifying pathways or molecules that can be targeted to halt neuronal loss, and the Redox Biology Group has been no exception.

Witting, together with his collaborator Dr Greg Sutherland from The University of Sydney, conducted preliminary studies aimed at evaluating the role of endogenous antioxidant proteins and biomarkers of oxidative tissue damage in the superior temporal gyrus (a moderately affected region of the Alzheimer’s brain). “Our results suggest that the Alzheimer’s brain is exposed to accumulating hydrogen peroxide early in the disease process, with the resulting oxidative stress possibly causing neuronal cell death through a process called apoptosis,” the researchers reveal.

**CLOSE AND CONTINUED COLLABORATION**
With so many important insights already made, Witting is confident that the Redox Biology Group – enriched by cross-disciplinary collaborations within the Charles Perkins Centre – will continue to elucidate the role of oxidative stress in diverse disease states, and in the future identify novel strategies for neuroprotection, cardioprotection and renal protection.