

RESEARCH PROFILE

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Current position: NHMRC CJ Martin Research Fellow. Currently establishing a research group and laboratory space that will initially consist of two research assistants and myself.

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RESEARCH INTERESTS

1. Role of redox reactions in endothelial cell signaling and function

The endothelium is critical for maintenance of vascular homeostasis. Central to this is endothelial-derived nitric oxide (EDNO), synthesized by the endothelial isoform of nitric oxide synthase (eNOS). Vascular diseases including atherosclerosis are characterized by endothelial dysfunction that is manifested as impaired EDNO bioactivity that may contribute to clinical events [1]. Considerable evidence indicates that endothelial dysfunction is due, in part, to vascular oxidative stress and there is great interest in defining the oxidative processes involved [1]. Diseased blood vessels produce increased amounts of reactive oxygen species, derived primarily from endothelial and smooth muscle cells and detected principally as superoxide anion radical ($O_2^{\cdot-}$) and its dismutation product hydrogen peroxide (H_2O_2) [2]. It is established that $O_2^{\cdot-}$ rapidly reacts with nitric oxide (NO) to limit EDNO bioactivity. Increasing evidence indicate that H_2O_2 also represent an important signaling molecule governing vascular cell phenotype and vascular tone [1, 2]. Our research focuses on defining to what extent and how H_2O_2 impacts on endothelial function and phenotype and EDNO bioactivity during vascular disease. In collaboration with John Keaney and Kai Chen (Whitaker Cardiovascular Institute, Boston University, USA) to date we have discovered that H_2O_2 activates eNOS by altering the enzyme's phosphorylation status [3]. We have also identified mitochondria as a novel target that mediates the proximal cell signaling events induced by H_2O_2 in endothelial cells [4]. Currently we are investigating the effects of H_2O_2 on EDNO bioactivity. Our recent data indicates that despite activating eNOS the oxidant can limit EDNO bioactivity by promoting oxidative inactivation of NO. We are in the process of characterizing the nature of the oxidative reactions limiting NO and the extent to which these processes are important for endothelial dysfunction during vascular disease states. Our research also focuses on determining the role of myeloperoxidase for endothelial dysfunction and redox control of cell signaling in endothelial cells stimulated with physiological agonists, in particular vascular endothelial growth factor.

2. Roles and regulation of indoleamine 2,3-dioxygenase

Indoleamine 2,3-dioxygenase (IDO) is an intracellular heme protein that catalyses the oxidative metabolism of L-Trp via the kynurenine pathway [5]. IDO is induced at sites of inflammation by interferon- γ (IFN γ) and is traditionally thought to function as an anti-microbial and anti-tumour effector of the cytokine. Recent groundbreaking studies have established that IDO also represents an important immune regulatory enzyme that inhibits T lymphocyte activation by reducing the local concentrations of L-Trp, the least abundant of all essential amino acids. Considerable evidence supports an IDO-based mechanism for immune suppression. For example, induction of IDO and inhibition of T cell activation protects against inflammatory disorders including colitis and collagen-induced arthritis in mice. We have discovered increased IDO expression in atherosclerotic lesions and have initiated a NHMRC funded project examining the role of IDO in this disease in which inflammation of the vascular wall represents an important pathogenic event. In light of the important immune regulatory role of IDO our research also focuses on determining the molecular mechanisms by which the enzyme is controlled. Together with Roland Stocker, we have previously described that IDO is inhibited by nitric oxide (NO) [6]. Currently we are investigating how NO inhibits IDO by characterizing the nature of the inactive NO-IDO heme adduct using Resonance Raman Spectroscopy with Andrew Terentis (Florida Atlantic University, USA) [7]. We have also identified that IDO is subject to post-translational control and that this form of control may be subject to redox control [8]. We are in the process of extending these studies to determine the mechanisms by which IDO is subject to post-translational control and if these processes are important in the regulation of the enzyme's immune regulatory actions in innate immune cells.

Selected publications

1. Thomas SR, Chen K, and Keaney JF, Jr. 2003. *Antioxid Redox Signal* 5: 181-194.
2. Chen K, Thomas SR, and Keaney, JF, Jr. 2003. *Free Radic Biol Med* 35: 117-132.
3. Thomas SR, Chen, K, and Keaney, JF, Jr. 2002. *J Biol Chem* 277: 6017-6024.
4. Chen K*, Thomas SR*, Albano A, Murphy MP, and Keaney JF Jr. 2004. *J Biol Chem*. 279: 35079-35086. *Co-First Authors
5. Thomas SR, and Stocker R 1999. *Redox Rep* 4: 199-220.
6. Thomas SR, Mohr D, and Stocker, R. 1994. *J Biol Chem* 269: 14457-14464.
7. Terentis AC, Thomas SR, Takikawa O, Littlejohn TK, Truscott RJ, Armstrong RS, Yeh SR, and Stocker R. 2002. *J Biol Chem* 277: 15788-15794.
8. Thomas SR, Salahifar H, Mashima R, Hunt NH, Richardson DR, and Stocker R. 2001. *J Immunol* 166: 6332-6340.