

## EDITORIAL

### *Nuclear Receptors: Guardians of Homeostasis*

The family of nuclear receptors is an important group of transcriptional regulators that have diverse roles in the regulation of important biological processes involved in growth, development and homeostasis. The human nuclear receptor superfamily of proteins comprises 48 receptors of which 28 are ligand-activated; the remaining 20 are currently designated as orphan receptors. The biology and importance of these receptors as drug targets have come a long way in the twenty or so years since the first nuclear receptor, the glucocorticoid receptor, was cloned by Ron Evans and co-workers at the Salk Institute. The signalling pathways and biological processes that these receptors regulate are now important targets for the development of novel drugs to treat many common diseases such as osteoporosis, obesity, hypertension, diabetes and cancer. These range from the triglitazone drugs for the treatment of diabetes to reloxifene for the treatment of osteoporosis.

The review articles of this Showcase are from four internationally recognised Australian groups in the nuclear receptor field and provide examples of the great detail that we now have on the biology of nuclear receptor signalling pathways and their utility in developing treatments for disease. The first article by Peter Fuller and Morag Young from the Prince Henry's Institute in Melbourne describes the biology and pathophysiology of the cardiovascular steroid hormone aldosterone that signals via the mineralocorticoid receptor (MR). This nuclear receptor is in fact regulated by two important endogenous steroids, aldosterone and cortisol, but with very different outcomes in different target tissues. Antagonism of the mineralocorticoid receptor by the drug spironolactone has been the stalwart for the clinical treatment of high blood pressure for decades and new research is aimed at developing novel MR ligands to treat cardiac fibrosis and hypertrophy.

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The second article by Myers *et al.* from George Muscat's laboratory in Brisbane describes the emerging role of orphan nuclear receptors in skeletal muscle metabolism and their role in controlling insulin resistance, a key abnormality in metabolic syndrome. Understanding how these orphan receptors regulate metabolic activity and energy expenditure in muscle cells may provide clues for the development of new pharmaceutical treatments for metabolic disorders. The third article by Centenera *et al.* from Wayne Tilley's group in Adelaide describes the pivotal role the androgen receptor plays in the regulation of cell proliferation in the prostate gland and the authors demonstrate that this nuclear receptor plays a critical role in prostate cancer development and progression. Agents that block androgen signalling, used in androgen ablation therapy, are initially very effective in the treatment of prostate cancer. Acquisition of an androgen-resistant state can sometimes occur where therapy is ineffective and means further treatment strategies need to be developed that perhaps target other parts of the androgen receptor signalling pathway.

The final article by Shane Colley and Peter Leedman from WAIMR in Perth describes some key nuclear molecules involved in mediating the signalling pathway of nuclear receptors. These so-called co-regulatory factors are recruited by ligand-bound nuclear receptor complexes and facilitate transcriptional activation or repression of gene targets in the nucleus. Two co-regulators, SRA, an RNA co-activator, and SLIRP, a novel SRA-binding protein corepressor, are described and are shown to interact with many of the steroid hormone receptors and be important in a number of disease processes, including some cancers. In summary, these four articles demonstrate the complex nature of nuclear receptor signalling pathways and their importance in the maintenance and regulation of a wide range of physiological processes.

#### Cover Illustration

##### Mineralocorticoid receptor crystal structure.

The mineralocorticoid receptor ligand-binding domain crystal structure (PDB 2AA2) contains 11  $\beta$ -helices in three anti-parallel layers with the binding pocket in the lower third shown here containing aldosterone. The region 820-844 which confers aldosterone binding specificity is shown.

*Image courtesy of Peter Fuller and Morag Young (Prince Henry's Institute), in collaboration with Brian Smith (Walter and Eliza Hall Institute) and Fraser Rogerson (Murdoch Childrens Research Institute).*

#### Nuclear Receptor Signalling: Biology and Disease

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In August, the Showcase on Research will be on **Chemotherapeutic Resistance Mechanisms of Cancer** – Guest Editor: Ross Davey

*Australian Biochemist* – Editor Rebecca Lew, Editorial Officer Liana Friedman

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