Grant A. Challen

In Search of Kidney Stem Cells

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In Australia, there are over 60,000 cases of advanced chronic renal disease (CRD) with about 7000 patients receiving dialysis at a cost of AUS$360 million per annum. The current treatment options are dialysis, which is expensive and has considerable morbidity, and transplantation which is limited by the number of donor organs available for transplant. An alternative treatment strategy currently being explored is the potential for stem cell therapy in renal failure patients. The main goal of this study is to identify and isolate potential stem cell populations from embryonic and adult mouse kidneys. Two approaches have been undertaken to facilitate this; (1) determining the molecular phenotype of the renal progenitor population via microarray gene expression profiling and (2) the characterisation of purified potential stem cell populations from embryonic and adult mouse kidneys.

(1) By analysing the genetic profile of the earliest cells in development that become committed to forming the kidney by microarray, it is anticipated that genes strongly expressed by these cells might be used to identify any resident stem cells in the adult kidney. Cell surface markers of renal progenitor cells are now being used to isolate cells with similar characteristics from adult kidneys by fluorescence-activated cell sorting (FACS).

(2) I have isolated potential stem cells from adult mouse kidneys based on properties that identify stem cells in other organs. I have purified these cells and analysed their stem cell capacity in numerous ways such as microinjection into embryonic kidneys and injection into mice with a chemically induced model of kidney disease. These models are now being employed to test the ability of various kidney cell populations to act as renal stem cells.

This work forms part of the renal regeneration consortium (RRC), a collaboration of Australian researchers with the long-term goal of developing cellular therapies for the treatment of kidney disease.

Becky L. Conway-Campbell

Nuclear Localization of the Growth Hormone Receptor is Associated with Dysregulated Cell Cycle Progression and Tumorigenesis *In Vivo*

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Growth hormone (GH) is the major regulator of post-natal growth. Disease conditions include GH excess (acromegaly or gigantism) and GH deficiency (dwarfism). In addition to GH's most obvious effect on long bone growth, GH is known to have a number of beneficial metabolic effects including decreased fat deposition, increased lean muscle mass, anti-aging properties, immune and reproductive function. However the subject of debate recently has the disturbing occurrence of side effects associated with GH excess and GH treatment. One particular concern is that GH excess patients are predisposed to a variety of cancers, with colorectal, breast, and haematological malignancies being reported most frequently. Furthermore, a significant risk of metaplasia with long term GH treatment has been reported, and epidemiologic studies have indicated an increased risk from colon cancer with elevated plasma GH. Therefore our research is focussing on determining which signalling pathways are involved in this uncontrolled proliferative effect of GH, versus its beneficial metabolic effects. We have found that in normal proliferating cells, the GH receptor (GHR) is transiently nuclear localized at the beginning of the growth phase of the cell. However in cases of proliferative disorders, we find that there is an aberrant increase in nuclear GHR present. We have reconstituted this finding in a cell model, by targeting the GHR to the nucleus of a pre-leukemia cell line. We find that the increased nuclear localization is sufficient to render the cells factor independent, and to upregulate a number of genes associated with high proliferative status and tumorigenicity. When the nuclear-targeted GHR expressing cells were injected into immunocompromised mice, large aggressive metastatic tumours formed at every site of injection. In contrast, no tumours arose from cells expressing normal wild type GHR. Our research indicates that it is the deregulated nuclear localization of the GHR, rather than normal GH signalling per se that is associated with its cancer progressing properties. Therefore, strategies aimed at blocking GHR nuclear localization may provide potentially useful cancer therapeutics.

Daniel F Wallace

The Liver in the Regulation of the Iron Homeostasis: Role of Hepcidin and Transferrin Receptor 2

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Iron is essential for life. However, too much or too little can be harmful. According to the World Health Organisation up to 80% of the world's population may have iron deficiency, with 30% having anaemia (low haemoglobin). The iron overload disorder hereditary haemochromatosis is one of the most common genetic conditions, affecting 1 in 200 Australians. Excess iron in haemochromatosis can lead to liver damage, diabetes and arthritis. Most haemochromatosis is caused by mutations in the HFE gene. Other rare forms are caused by mutations in other genes such as transferrin receptor 2 (TfR2). Recent research suggests that the liver produced hormone hepcidin holds the key to most forms of haemochromatosis and anaemia. Hepcidin regulates body iron levels by reducing iron absorption in the intestine. In patients with HFE haemochromatosis hepcidin levels remain low, making the body think it is iron deficient and hence absorb too much iron. The converse is the case in the anaemia of chronic disease. Inflammation in patients with chronic diseases such as cancer, autoimmune disease and infections can cause hepcidin levels to rise and shut off iron absorption, leading to iron deficiency and eventually anaemia.

Hepcidin has proved to be a difficult molecule to study. We have produced a specific antibody to help us study the cell biology and regulation of this important molecule. Using this antibody we have shown where hepcidin goes to in liver cells and how it is regulated in mouse models of haemochromatosis and anaemia. In mice with haemochromatosis due to lack of TfR2, hepcidin levels remain low, suggesting that TfR2 as well as HFE are important for the regulation of hepcidin and the maintenance of body iron levels. Future studies are aimed at further defining the roles of hepcidin and TfR2 with the intention of identifying new therapeutic targets for the diagnosis and treatment of a wide range of iron-associated disorders, both overload and deficiency.