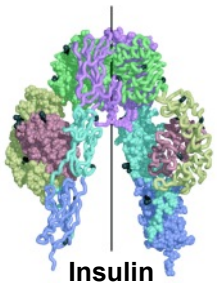
Potential Research Projects Investigating Insulin and Insulin-like Growth Factors in normal growth and disease

The Insulin and IGF structure/function group
Dr Briony Forbes
Room 2.42 (lab), 3.37 (lab), Tel: 8303 5581 (lab), 8303 5980 (office)
Briony.forbes@adelaide.edu.au
(http://www.adelaide.edu.au/directory/briony.forbes).

Insulin-like growth factor-I (IGF-I) is produced under the control of growth hormone (GH) and acts *via* the insulin-like growth factor type 1 receptor (IGF-1R) to stimulate cell proliferation, differentiation, survival and migration. IGF-I plays a significant role in growth and development of many tissues including bone, brain, muscle and fat, and is therefore required for normal control of body weight and size. Marked IGF-I deficiency in humans leads to severe growth and developmental defects and mild deficiency accounts for a significant number of children diagnosed with idiopathic short stature (ISS). Conversely over expression is associated with an increased risk of many cancers. IGF-I and IGF-II act via the IGF-1R to promote survival and proliferation of cancer cells even in the presence of chemotherapies and promote cancer cell migration. Inhibitors of IGF action via the IGF-1R are now in clinical trials. In contrast, insulin is involved in metabolic control, maintaining the correct blood glucose concentration.

The lab is aiming to understand the molecular mechanisms which control insulin and IGF action. One major focus is on understanding how insulin and the IGFs act to induce their respective biological activities despite the high degree of similarity between the ligands and their receptors. We are also investigating the control of IGF action by an IGF binding protein (IGFBP-2). Such information will be useful in the future design of receptor antagonists as inhibitors of IGF action in cancer and also novel insulin mimetics for the treatment of diabetes.

1. Development of IGF receptor antagonists: understanding the mechanism of interactions between insulin and insulin-like growth factors and their receptors.

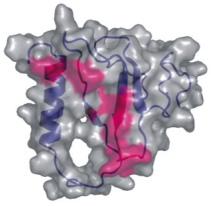


Insulin receptor

We are generating a series of novel IGF molecules with unique cross-linking amino acids and fluorescent molecules incorporated into specific sites within the IGF structure. These molecules will be used to define the specific sites of contact between the ligand and receptors as there is currently no structure of an IGF:IGF receptor or insulin:insulin receptor complex. This information will ultimately be important in the design and development of highly specific IGF receptor inhibitors for the treatment of cancer.

In addition, we are collaborating with chemists who are developing novel insulin and IGF analogues with unique receptor binding and activation properties. We aim to produce improved insulin mimetics for the treatment of diabetes and specific IGF receptor inhibitors for the treatment of cancer.

Techniques: protein expression, chemical synthesis, protein purification, biophysical analysis of protein:protein interactions, surface Plasmon resonance (BIAcore).



C-BP-2

2. Control of IGF action by IGFBPs

No structure of an intact IGFBP in complex with its ligand has been generated to date. We are using NMR and crystallography to generate structures of IGFBP-2 and IGF:IGFBP-2 complexes. This will allow us to

better understand how IGFBP-2 controls IGF action. We are also defining the mechanisms by which IGFBP-2 is proteolysed and how IGFBP-2 binds to extracellular matrix. Both of these functions are important for the release of IGFs from the IGFBP:IGF complex in normal situations as well as in cancer.

Techniques: protein expression, protein purification, biophysical analysis of protein:protein interactions, surface Plasmon resonance (BIAcore), tissue culture, cell biology.

3. Metabolic control in the platypus: structure/function analysis of platypus insulin and incretins.

Following the sequencing of the platypus genome it has become evident that metabolic control in the platypus is quite different to mammals. Monotremes have very small stomachs and they lack fundamental mammalian genes important for food breakdown eg gastrin. While the platypus appears to express metabolic control proteins such as insulin and the incretins (including glucagon-like peptide 1) these proteins and their receptors differ in their amino acid sequences in regions of the molecules important for function. The aim of this project is to understand the way in which these molecules interact with their receptors to generate a biological function. This comparative approach will shed new light on mechanisms of metabolic control.

Aspects of this project involve collaboration with Assoc. Prof. Frank Grutzner in Genetics and Prof. Andrew Abell and Dr Denis Scanlon in Chemistry.

Techniques: protein expression, protein purification, biophysical analysis of protein:protein interactions, surface Plasmon resonance (BIAcore), tissue culture, cell biology, receptor binding assays, in vitro assays of biological activities.