ASMR QLD Premier's Awards 2008 - Postgraduate Student Award Semi-finalists

Matthew W A Dixon. Queensland Institute of Medical Research.

MALARIA PARASITES RENOVATE!

Malaria the disease is caused by the protozoan parasite from the genus Plasmodium. Over a third of the worlds population lives within malaria endemic regions and around 2-3 million people die each year from this disease. The malaria parasite is transmitted from person to person through the bite of a female Anopheles mosquito. Of the 4 species of malaria effecting humans P.falciparum is medically the most important with the majority of morbidity and mortality associated with this species. A characteristic of P.falciparum infection is the parasites ability to adhere to the lining of blood vessels throughout the body, this phenomenon is called cytoadherence. A parasite derived protein called the P.falciparum erythrocyte membrane protein 1 (PfEMP1) is responsible for this cytoadherence.

The malaria parasite lives within the red blood cell, a cell which doesn't contain a nucleus, and thus is missing many of the cellular components essential for growth and development. In order for the parasite to survive within this inert cell it exports a large number of proteins into the red blood cell establishing the missing cellular components and remodeling the cell to allow the parasite to grow and develop. One important structure formed by the parasite which is essential for the export of PfEMP1 is the Maurer's clefts. These structures form within the RBC and contain several proteins that are essential for the transport of PfEMP1 to the surface. The ring exported protein 1 (REX1) is a resident Maurer's cleft protein, and our studies have shown that it is essential for maintaining the shape of the clefts. In addition to this the mechanisms used by this protein to target to the Maurer's clefts and to be exported to the RBC were studied in depth. Using green fluorescent protein (GFP) tagged REX1 we were able to narrow down the regions responsible for firstly the export of REX1 and secondly attachment to the Maurer's clefts.

These studies will allow mechanisms employed by the parasite during its "renovation" of the RBC to be better understood. Without this remodeling the parasite is unable to survive and replicate. A greater understanding of these processes may lead to novel anti malaria treatments, which are essential due to the recent resurgence of resistance to the more commonly used drugs for malaria.

Brett G Hollier, Queensland University of Technology.

MECHANISMS UNDERLYING ENHANCED BREAST CELL MIGRATION STIMULATED BY IGF-I:IGFBP:VN COMPLEXES

Breast cancer is the most common form of cancer in women, with one in nine women developing breast cancer in their lifetime. Significantly, one in four women diagnosed will die from their disease. The primary tumour is rarely the cause for the high mortality associated with breast cancer, which rather, arises from the metastatic spread of malignant cells and the establishment of secondary tumours in critical sites in the body. Understanding the processes that lead to the establishment of secondary tumours and strategies to halt the spread of cancer beyond the primary site are therefore highly valuable. Two factors thought to be pivotal in breast cancer metastasis are exposure to elevated levels of hormones and growth factors, and altered cellular interactions with proteins in the matrix surrounding cancer cells. Insulin-like growth factor-I (IGF-I) is one such growth factor which has been shown to play critical roles in both normal mammary gland development and breast cancer. Recent observations from our laboratory demonstrate that IGF-I can associate with the extracellular matrix protein vitronectin (VN), a protein which also has well documented roles in tumour biology. In view of this, we hypothesized that the IGF:VN interaction would be important for the spread of breast cancer cells. Hence, studies were undertaken to determine the effect of IGF:VN complexes on breast cell functions and to uncover the mechanisms which govern these responses. The results from these studies have uncovered novel mechanisms by which IGF:VN complexes stimulate not only the motility of breast cells, but also function to modulate the expression of genes associated with promoting the spread of cancer cells. These studies have uncovered new insights into the mechanisms which govern the spread of cancer cells. This holds promise for not only the discovery of novel drug targets for the treatment of breast cancer, but also for improved prognostic bio-markers for aggressive breast disease.

Nirmala Pandeya, Queensland Institute of Medical Research

SMOKING AND ALCOHOL INTAKE AND THE RISK OF OESOPHAGEAL ADENOCARCINOMAS AND SQUAMOUS CELL CARCINOMAS

Of the two most common histologic types of oesophageal cancer, incidence of adenocarcinoma is rising in the Western world whereas incidence of squamous cell carcinoma has been stable or declining and the reason is unknown. Smoking and alcohol have different associations with different types of cancers. Both have been identified as a risk factor for oesophageal cancer however it is likely that their association differ according to different histologic types. The aims of this study were to measure and compare the effect of smoking and alcohol on risks of oesophageal squamous cell carcinomas (OSCC) and adenocarcinomas of the oesophagus (OAC) and gastro-oesophageal junction (GOJAC). The authors used data from a population based case-control study in Australia with 367 OAC, 426 GOJAC and 309 OSCC cases and 1580 controls. Statistical models such as multivariate logistic regression and generalized additive logistic regression were used to obtain the effect of smoking and alcohol on this cancer. We found those ever smoked (more than 100 cigarettes in their lifetime) had a significant 70%, 140% and 180% increase in the risk of OAC, GOJAC and OSCC respectively. The duration smoked had a significant effect on all three types however the average quantity smoked was associated only with GOJAC and OSCC. Irrespective of the duration and the quantity of cigarettes smoked, quitting smoking decreased the risk of all types by 18-20% per decade of quitting. No association was observed between lifetime alcohol consumption and OAC or GOJAC, however heavy drinkers (lifetime average of more than 3 drinks per day) were significantly associated with 133% increased in risk of OSCC.

Rebecca Pelekanos, Institute for Molecular Bioscience, University of Queensland

DETERMINING A NOVEL MECHANISM FOR GROWTH HORMONE RECEPTOR DIMERIZATION AND ACTIVATION

Growth hormone is one of the most important hormones in the body and is responsible for overall body growth, fertility, muscle and fat metabolism. Mutations in Growth Hormone or its receptor cause diseases including dwarfism, giantism, and cancers including lymphoma, colorectal and breast cancer. The Growth Hormone and its receptor can also be exploited for many novel therapies including to assist skin repair after burns, to assist the body to self renew and slow the aging process, increase muscle mass in wasting disorders, decrease fat deposition in the obese and diabetic related complications. Unfortunately, as GH is a large protein, it can only be administered via injection so currently, a major focus in drug discovery is to make a Growth Hormone-like drug that could be taken as a pill. Because of the myriad of potential uses for Growth Hormone in treating many disorders listed above, it is extremely important to uncover the exact mechanism GH activates the Growth Hormone Receptor, to open the door for Growth Hormone to be more widely used in clinical practice. This current study used a variety of conventional and novel techniques to discover a novel mechanism for Growth Hormone Receptor activation that will revolutionise the future design of Growth Hormone like drugs, as well as the understanding of related hormone receptors.

Erin Rayment, Queensland University of Technology.

INVESTIGATION INTO THE PROTEOLYTIC ACTIVTY IN CHRONIC WOUND FLUID: DEVELOPMENT OF A REMEDIATION STRATEGY

The issue of chronic non-healing ulcers is a major medical challenge. They are not only a significant cause of pain and anxiety for the over sixties, but also largely contribute to their lessening mobility, decreased social interactions and overall diminished quality of life. Through the research outlined in this project, we have shown that it is important to inhibit the proteases present in chronic wound fluid, while not affecting those that show decreased activity in the wound bed. This new data has underpinned a novel strategy to treat these otherwise compromised wounds. In particular, a novel protease inhibitor has been identified for the majority of proteases found in chronic wound fluid. Subsequently, this novel inhibitor has been incorporated into a hydrogel-based wound dressing and tested using a number of techniques. Most importantly, it has been shown to be both biocompatible in a human skin equivalent, as well as still being able to inhibit the excessive levels of proteases present in chronic wound fluid from this tethered state. In conclusion, this novel wound dressing should lead to shorter healing times and improved healing outcomes for patients.

Nadia Whitelaw, Queensland Institute of Medical Research

AN ENU MUTAGENESIS SCREEN FOR EPIGENETIC MODIFERS IN THE MOUSE REVEALS A ROLE FOR THE TRIM28 GENE IN MENTAL HEALTH, OBESITY AND INFERTILITY

Many human diseases such as cancer and psychosis are the result of mutation in the genes of the affected individual. Sometimes the genes themselves are normal but they are inappropriately switched on, or off, and in these cases an essential extra layer of information carried by the DNA, called the epigenetic state, is perturbed. Normal epigenetic modifications to the DNA are established and maintained by a subset of genes called epigenetic modifiers. Mutations in known human epigenetic modifiers cause a variety of human disorders, and commonly show neurodevelopmental symptoms.

In an effort to discover novel epigenetic modifiers we have used the classic genetic approach of random mutagenesis. In this way we have created a dozen colonies of mice that carry mutations in epigenetic modifier genes. One such colony was found to have a mutation in a gene called Trim28. By studying mice which harbour a mutated copy of this gene, we have found that a deficiency of Trim28 can result in several abnormalities. Most mutant mice become obese by five months of age and all female mice develop premature infertility. Behavioural problems also occur in some mutant mice. This study has demonstrated roles for Trim28 in the aetiology of a number of complex diseases and may change our thinking of how epigenetic modifier genes contribute to the human disease burden. The Trim28 mouse provides an invaluable resource for understanding the development of these illnesses in humans and may provide novel avenues for therapeutic intervention in the future.