RESEARCH HIGHLIGHTS

The Sackler Institute of Pulmonary Pharmacology

Role of Platelets in Airway inflammation

Bronchial asthma has been recognized as a chronic inflammatory disease associated with leukocyte infiltration and airway epithelial damage. It is now clear that eosinophil, neutrophil, mast cell, and T-lymphocyte activation occurs in allergic asthma, whereas platelets appear to be important in murine models of chronic allergic inflammation. The presence of intravascular platelet aggregates within bronchial biopsy specimens in patients with asthma has also been reported. Substantial clinical evidence demonstrates intravascular platelet activation accompanying allergen-induced bronchoconstriction in patients with asthma; suggestive of participation of these blood elements in the pathophysiology of asthma.

In their study, published in the journal Am J Respir Crit Care Med, research within the Sackler Institute of Pulmonary Pharmacology headed by Professor Clive Page showed that platelets migrated out of vessels and localized to peribronchial regions of the lung in a murine model of allergic inflammation. Interestingly, this migration was not observed in mice deficient in the expression of the high affinity IgE receptor, thereby implicating a role for IgE complex formation in stimulating the migration of platelets to sites of airway inflammation. In vitro chemotaxis assays revealed that platelets obtained from asthmatic subjects, or from wild type sensitised and allergic mice migrated in response to allergen or anti-IgE. In contrast, platelets obtained from mice deficient in the expression of the high affinity IgE receptor did not migrate in response to these stimuli. Together these studies suggest that platelets may directly participate in the pathogenesis of asthma following antigen-antibody complex formation in these cells.

Neurodegenerative Group

Understanding the mechanisms neurodegeneration in Parkinson’s Disease

Cell death in Parkinson’s disease (PD) is linked to alteration in proteasomal function resulting in the mishandling of damages and unwanted proteins. This results in the build up of proteins within the cell body which are then aggregated. It is likely that the build up of these aggregated proteins ultimately results in the death of the neuron. Present models of PD do not reflect this process, and so we have developed and characterised the proteasome inhibition model of PD which reflects the pattern of cell loss seen, and also more closely reflects the progressive nature of the disease. We have used this model to study the mechanisms involved in the cell death process. There is clear evidence for a long term inflammatory reaction in response to proteasomal inhibition, and for apoptotic cell death in affected brain areas. We predict that this model will be advantageous in the search for agents that slow down or stop the progression of the disease.
There are a number of endogenous neuroprotective factors present in brain, one of which is a protein called osteopontin (OPN). This is normally found in the substantia nigra, and is reduced in Parkinson’s disease. We are investigating the mechanism by which OPN exerts its protective action on neuronal cells and are looking at links with integrins which are known binding sites for OPN. Replacement of OPN, or mimetics of its function may reduce cell death in PD.

Retrograde fluorogold labelling of dopaminergic cell bodies in the substantia nigra showing loss of neurones in proteasome inhibitor (PSI)-treated rats

OPN + DAPI staining in N1E-115 mouse neuroblastoma cell line

Key references

