In vivo models of inflammation and matrix remodelling: classical to modern approaches

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In vivo models of inflammation and matrix remodelling: classical to modern approaches was a joint symposium between the British Inflammation Research Association and the British Society for Matrix Biology. It was held at Saint Bartholomew’s Hospital, London on 25 February 1999.

This meeting was put together in a period of just over 2 months. The speakers were confirmed with less than a month to go and there were very real fears that the short notice would result in poor attendance. Those fears proved groundless, underlying the importance of in vivo modelling to the study of inflammation and matrix remodelling. The meeting was deliberately wide in scope stressing the need for refined inflammatory models such as experimental pleurisy in rats (models which lend themselves to all manner of morphological, biochemical and molecular biological techniques) and newer models allowing, for example, the effects of specific gene transfer to be assessed.

Working for more than four decades in inflammation research, Professor Derek Willoughby (Experimental Pathology, St. Bartholomew’s & Royal London Schools of Medicine & Dentistry) was asked to take a retrospective look at his career and share in some of its achievements. He started by describing pleural models of inflammation and how these had been used to define a role for mediators released early in the inflammatory response. It was shown that a sequential release of mediators occurred (vasoactive amines, kinins and prostanoids) irrespective of the initiating stimulus. These studies were followed by the demonstration of a role for complement in models such as carrageenan pleurisy and thermal injury. This challenged the prevailing view that complement activation occurred solely as a result of antigen/antibody complexes. A crude extract of lymph nodes, termed lymph node permeability factor (LNPF) was shown capable of duplicating the pathology of delayed type hypersensitivity (DTH) reactions and antibodies to LNPF suppressed models of DTH. We would now recognise many of the attributes of LNPF to be due to the presence of Th1 cytokines. The immunology theme continued with scanning electron microscopy showing for the first time antigen presentation by macrophages to lymphocytes. The bridges formed between these cells and the molecular interactions involved remain an important area of research today. Time and again we were reminded as to how much progress has been made in the last 40 years. For example, the origin of macrophages in inflammatory lesions was thought to be the fibroblast! Simple labelling of blood monocytes indicated the true origin of the macrophage and led to the realisation that granulomatous inflammation could be maintained by continued cell migration or local proliferation- important when deciding which model to use in assessing, for example, agents that inhibit cell accumulation. The effects of granulomatous inflammation on cartilage degradation was described with the importance of assessing inflammatory changes separately from matrix integrity. The animal models predicted that certain non-steroidal antiinflammatory drugs might be detrimental to cartilage. The work was then brought up-to-date with summaries of work currently being undertaken in the areas of angiogenesis, inducible enzymes and apoptosis. Finally, Professor Willoughby was generous in acknowledging his collaborators over the years, the list reading rather like a Who’s Who in inflammation research.

Dr. Dean Willis (Experimental Pathology, St. Bartholomew’s & Royal London Schools of Medicine & Dentistry) introduced the stress response as an adaptation to an inflammatory insult. In acute pleural models of inflammation in the rat he developed the hypothesis that the adaptation to stress was an important aspect in bringing about resolution of the inflammatory response. As an example, he showed how hsp32, an inducible form of the enzyme heme oxygenase (HO), was maximally expressed in terms of protein expression and enzymic activity in cell pellets harvested from carrageenan inflammatory exudates at 48 hours, a time when the inflammatory response was waning. Inducing increased hsp32 activity 24 h into the inflammatory response was markedly antiinflammatory whereas inhibition was proinflammatory. Using tissue homogenates containing both nitric oxide synthase (NOS) and HO, treatments that inhibit NOS
were shown to increase HO activity. These treatments were without effect in homogenates containing HO but low levels of NOS. However, nitric oxide donors decreased HO activity in both homogenates. The suggestion that NOS and HO may have reciprocal modulatory effects in inflammation has been given further support from studies of the expression of these enzymes in an in vivo model of septic shock. Briefly, Dr. Wil- lis touched on other studies showing induction of hsp70 in inflammation. Curiously, aspirin treatment increased expression of hsp70, perhaps contributing to its antiinflammatory effects.

Professor Yuti Chernajovsky (formerly of the Kennedy Institute for Rheumatology and recently appointed head of the Bone & Joint Research Unit, St. Bartholomew’s & Royal London Schools of Medicine & Dentistry) discussed some of the progress being made to treat inflammatory arthritis using gene therapy. First he stressed some of the advantages of this approach. Switching on a gene in diseased tissue to produce an antiinflammatory factor should lead to a high local concentration of the gene product and low systemic levels, the reverse of administering the gene product intravenously. In addition, it is a long term strategy which should not require patients having to attend clinics for multiple treatments. In terms of potential problems, Professor Chernajovsky considered that the use of viral vectors for gene transfer would be a major safety issue to be overcome before the work could progress to man. Exerting control over the administered gene, for example through a tetracycline response element, would effectively allow treatments to be reversible. A number of possible gene vectors were discussed, including genes encoding the soluble TNF receptor, TGFβ and soluble CR1. Adoptive transfer of splenocytes from DBA/1 mice with collagen II arthritis to immunodeficient (SCID) mice results in arthritis development. Arthritis development could be blocked if the splenocytes were infected with a retrovirus expressing the soluble p75 TNF receptor or TGFβ. Because these transferred cells recognise collagen II (the major cartilage collagen), this is a means of targeting the gene therapy to the joint structures. Isolation of collagen II reactive T cell clones from arthritic patients is however very difficult, but in man targeting of the joint structures may be acheived using T bodies, T cells expressing chimeric receptors composed of a fragment of antibody recognising type II collagen and lymphocyte triggering molecules.

The molecular theme of the meeting was continued by Dr. Patricia Sime (Royal Infirmary of Edinburgh). She used an elegant model to study the effects of TNF over expression in lung tissue. TNF expression is up regulated in a number of inflammatory lung conditions where it is associated with fibrogenesis. The possible mechanisms underlying this fibrogenesis were investigated using an adenovirus to transfer cDNA of TNF into rat lung. The vector was chosen because of its ability to target lung epithelial cells and indeed this was where protein was expressed, peaking three days after infection and then waning. This was associated with an accumulation of inflammatory cells, mainly neutrophils and mononuclear cells peaking at about day 7 and thereafter declining. Fibrogenesis (collagen and elastin deposition) became apparent from about day 14. The transient expression of TNF and the temporal disassociation with fibrogenesis suggested that fibrogenesis was through a secondary media-