SP0007 OSTEOARTHRITIS: NEW CONCEPTS OF PATHOGENESIS AND MANAGEMENT GUIDELINES

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Osteoarthritis (OA), the most common form of arthritis, is increasing in prevalence as the population ages. Osteoarthritic pathology occurs as a result of an imbalance between synthesis and repair (catabolic) processes. Synthesis, increased early in the osteoarthritic process, cannot keep pace with catabolic processes in which proteolytic and collagenolytic enzymes destroy cartilage matrix. Inflammation, the result of an interplay between cartilage breakdown and synovial reaction, increases in severity as the disease progresses.

Current concepts suggest a specific role for the ageing process wherein formation of Advanced Glycation End-products (AGEs) increase with age, resulting in increased cross-linking of cartilage matrix components. AGEs also activate cytokines, adding to the inflammatory reaction.

Genetic defects in type II collagen have been described. The most common mutation demonstrated is an error in one base leading to a substitution of cysteine for arginine in the collagen matrix, resulting in generalised precocious familial OA. Additional mutations have been described in other sites in type II collagen.

Pain in OA results from multifactorial interplays, including inflammatory and non-inflammatory factors. Management is targeted to treating pain, improving function and disease modification. Symptomatic therapy includes simple analgesics, Cox-2 selective non-steroidal anti-inflammatory agents, traditional non-steroidal anti-inflammatory agents (with or without gastro-pathy-protective agents), and, at times, opiates. Cox-2 non-steroidal anti-inflammatory agents represent a significant advance in therapy, based on decreased peptic-ulcer-related gastropathy including haemorrhage, perforation or obstruction. Intra-articular steroids are helpful for acute flares. Intra-articular hyaluronans, an additional new modality, leads to relief of pain in OA of the knee in a significant number of patients; pain is relieved for prolonged periods of time, and therapy with repeated cycles is safe and effective. Hyaluronans are of particular benefit in patients in whom non-steroidal anti-inflammatory agents are not effective or well-tolerated.

Nutraceuticals such as glucosamine and chondroitin sulfate have been shown to relieve pain in a number of studies, and, in some recent investigations, to modify the basic disease process.

Agents which inhibit enzymatic or cytokine-induced breakdown and/or which stimulate matrix synthesis may lead to structure modification. Demonstration of such modification is difficult, and studies require several years duration. A number of agents appear to be disease-modifying in animal models, and successful disease-modification in humans is now considered tenable. Replacement of cartilage with autologous chondrocytes, or mesenchymal bone marrow stem cells shows promise for direct cartilage repair.

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Activity related diseases – Friday 15 June, 16.00-17.30/Congress Hall

SP0077 INNATE VERSUS ADAPTIVE IMMUNITY IN THE PATHOGENESIS OF ARTHRITIS

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Despite large efforts, the genetic and environmental factors that cause rheumatoid arthritis (RA) have not been found. The only significant genetic clue today is an association with the major histocompatibility complex (MHC) region coding for class II peptide receptors, which are known to be crucial for immune responses. However, the MHC region only partially reflects the genetic influence as this is a polygenically controlled disease. In addition environmental factors are likely to strongly influence the disease. One such important environmental factors are adjuvants, derived from pathogenic organism or from other exogenous and endogenous sources.

These complex issues are better clarified in animal models. In fact there are mainly two ways to induce arthritis in rodents.

Firstly, injection of various adjuvants trigger arthritis in certain rat strains.^{1,2,3} The properties of these adjuvants are that they are difficult to degrade *in vivo* and are soluble in cellular membranes. In contrast to antigens they do not bind to MHC molecules and can therefore not elicit an antigen specific response. Nevertheless, adjuvants trigger an arthritic disease which in certain cases closely mimics RA(3). One of the best models is pristine induced arthritis (PIA) which is a MHC class II dependent, ab T cell dependent chronic relapsing disease.^{3,4,5} It can be prophylactically and therapeutically vaccinated against with the help of joint specific antigens.⁶

Secondly, immunisation with joint-specific proteins may induce arthritis. In this case fragments of the protein bind to MHC molecules and elicit an immune response cross-reactive with joint antigens.^{7,8,9} Subsequently the joints are attacked and may develop into a chronic relapsing disease depending on the specificity of the immune response and the genetics of the strain. Examples of joint antigen specific models are type II collagen induced arthritis (CIA) and cartilage oligomeric matrix protein-induced arthritis (COMPIA).^{10,11,12}

Genetic analyses of adjuvant and joint specific models show that most, but not all, genetic regions are shared indicating that they share pathogenic mechanisms. These models will be further discussed mainly based on genetic dissection of MHC and non-MHC genetic regions.

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Tissue engineering and stem cell biology – Friday 15 June, 16.00-17.30/Forum Hall

SP0083 EFFORT-INDUCED HYPERTHERMIA: SIMILARITIES WITH MALIGNANT HYPERTHERMIA

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Effort-induced hyperthermia, also called exertional heat stroke (EHS) is due to an imbalance between internal heat production and heat loss, generally exacerbated by several factors such as inadequate fluid, caloric, and/or electrolyte intake, and is associated with a classical symptomatology, i.e. increased body temperature (higher than 40°C), neurological impairment that could lead to coma with the addition of rhabdomyolysis-induced myoglobinuria and acute renal failure. EHS generally occurs during strenuous activity under hot and humid environmental conditions. Subjects are often healthy young adults with no apparent clinical or biological deficits. The pathogenesis of a EHS episode differs from a malignant hyperthermia (MH) crisis. However, both conditions share some similarities in symptoms, such as the abnormal increase in core temperature. The triggering agent is different. MH is a disorder of skeletal muscle in which volatile anaesthetics and depolarizing muscle relaxants trigger a sustained increase in myoplasmic calcium concentration, thereby producing hyper-metabolic and contractile activities. MH crisis occurs in predisposed subjects and leads to a dramatic increase in core temperature. In addition, neurological signs are rarely recorded during a MH crisis, and dantrolene is used to prevent a fatal issue, whereas cooling is largely used as therapy during EHS. DNA mutations involved in the susceptibility to MH have been reported for only 50% of subjects susceptible to MH and for the remaining 50% this information is still not available. With respect to EHS subjects, no information regarding MH mutations has been reported so far.

Due to some similarities between MH and EHS, it could be hypothesised that EHS, in the same way as MH, is associated

with the existence of an infraclinical myopathy. In this respect, electromyographic, histological and metabolic studies have provided conflicting and scanty results. In the present study, we analysed the physiological (using *in vitro* contracture tests) and metabolic (using 31-phosphorus magnetic resonance spectroscopy, 31P MRS) bases of EHS. We addressed the issue of possible etiological similarity between the group of EHS subjects and MH susceptible (MHS) subjects for whom a noninvasive diagnostic strategy has been recently reported.

Using 31P magnetic resonance spectroscopy, we have analysed the muscle energetics of 26 EHS subjects for whom *in vitro* halothane-cafeine contracture tests were abnormal and investigated possible similarities with subjects susceptible to malignant hyperthermia. An early decrease of pH was noted during the first minute of exercise in EHS subjects as compared to controls. EHS subjects were divided into two subgroups according to the diagnostic score previously developed for MHS subjects. The 19 subjects (73%) with a score higher than 2 displayed a significantly larger caffeine-induced and earlier ryanodine-induced contractures on muscle biopsies as compared to the rest of the group (7 subjects). The results demonstrate that muscle energetics is abnormal in subjects who have suffered from EHS and suggest a possible link between MH and EH, although all EHS patients cannot be considered as MHS. Metabolic abnormalities in EHS subjects detected by 31P MRS may indicate a defect affecting the calcium release channel of the sarcoplasmic reticulum which translates as a very abnormal ryanodine contracture test by IVCT. We conclude that, similarly to MH crisis, EHS is related to a failure of muscle energetics that may be associated with a latent myopathy which is readily identified by non invasive 31P MR spectroscopy.

SP0084 DYSBARIC OSTEONECROSIS

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Dysbaric osteonecrosis is a serious complication for those exposed to a hyperbaric environment, occurring in 17% amongst compressed air workers and 4.2% amongst divers. The prevalence of bone lesions increases with age, the number of bends, the number of hours worked in the present contact, obesity, experience greater pressures of air or at greater depths. Dysbaric osteonecrosis appears to be independant of decompression sickness.

Bones lesions are mainly symmetrical and multiple, occurring in (1) the shafts of the femora or tibiae and the heads and necks of the humeri or femora, (2) next to the joint surface, the so-called "juxta-articular lesions". The juxta-articular lesions almost never occur near the articular surfaces of the knee or elbow joints. The sites in the skeleton at which the lesions occur are those at which fatty marrow is found in the mature adult.

The pathogenesis of osteonecrosis may involve several factors: circulatory impairment by extravascular or intravascular bubbles, lipid aggregation, fibrin-platelet thrombi, release of vasoactive substances, bas-induced osmosis. It has been suggested that injured marrow adipocytes can release vaso-active substances that can play a systemic procoagulant role in triggering disseminated intra-vascular coagulation.

The basic radiologic abnormality is usually an increase in the density, less often it may be a decrease. There may be a long