Speaker Presentations

WEDNESDAY, 14 JUNE 2017

Joint EULAR - APLAR session: novel animal models - where no researcher has gone before...

SP0001 RELEVANCE OF ANIMAL MODELS IN OSTEOARTHRITIS

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Osteoarthritis (OA) is the most frequent joint disease and a leading cause of disability in the Western world. Currently, we do not have a cure for this degenerative disorder and despite a high individual and socioeconomic demand, available therapeutic strategies have not changed substantially within the last 40 to 50 years, largely involving basic symptomatic control using analgesics and NSAIDS, physiotherapy and behavioural changes, and eventual prosthetic replacement in end-stage disease. While prosthetic joint replacement constitutes an effective surgical treatment option for patients whose joints are irreversibly damaged by OA, demographic development together with altered physical activities in our aging society increasingly demonstrate the limitations of joint replacement surgery as the only real treatment modality. There is, therefore, an urgent requirement for disease modifying drugs that aim to halt OA disease progression during the early stages and potentially to kick start cartilage regeneration. This need is contrasted, however, by a sustained "translational roadblock" in OA research with very few conceptually novel therapeutic approaches on the horizon. Amongst others, this "translational roadblock" results from a general lack in our understanding of how articular chondrocytes as the only cells in joint cartilage acquire and maintain their specific and highly specialised phenotype and how this phenotype changes during OA onset and progression. Investigation of this developmental aspect of disease pathology in OA patients and using human samples has many limitations, which is why animal models remain to constitute a key element of cartilage and OA research. This lecture summarizes the relevance of different animal models for understanding fundamental principles of cartilage homeostasis and remodelling in health and osteoarthritic cartilage degeneration. By focusing on the analysis of chrondrocyte phenotypic stability, it provides examples for how the use of such models can contribute to understanding OA and to the development of new therapeutic strategies for the disease.

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SP0002 NOVEL ANIMAL MODELS IN SYSTEMIC SCLEROSIS

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Systemic sclerosis (SSc) is a severe autoimmune disease with a considerable reduction of life expectancy. Autoimmunity, vasculopathy and fibrosis are three hallmarks of SSc, while the pathogenesis of the disease is largely unknown. Animal models of SSc provide an excellent tool to for exploring the disease pathogenesis of the disease. Aiming to provide a concise and curate updates in the field of animal models of SSc, this lecture will concentrate on emerging novel animal models and highlight new development and their impact on understanding pathogenesis of SSc.

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SP0003 NOVEL ANIMAL MODEL IN ARTHRITIS

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We have generated two rheumatoid arthritis (RA) models, human T-cell leukemia virus type I (HTLV-I) transgenic mice and IL-1 receptor antagonist (Ra)-deficient (KO) mice, to elucidate the pathogenic mechanisms of the disease. Both models spontaneously developed arthritis that closely resembles RA in humans. We found that TNF-, but not IL-6-, deficiency suppressed development of arthritis in IL-1Ra KO mice, while IL-6 but not TNF was involved in the development of arthritis in HTLV-I transgenic mouse model. IL-17 plays an important role in both models, suggesting the central role of IL-17 in these RA models.

We found that the expression of C-type lectin receptor (CLR) genes was augmented in the affected joints of these models using DNA microarrays. Dendritic cell immunoreceptor (DCIR) is one of such CLRs with a carbohydrate recognition domain in their extracellular carboxy terminus and an ITIM in its intracellular amino terminus. Because human syntenic locus for the CLR genes is linked to several autoimmune diseases including RA and SNPs in the *Dcir* gene is associated with RA, we have generated *Dcir* KO mice to examine the roles of this gene in the immune system. We found that aged *Dcir* KO mice spontaneously developed autoimmune enthesitis and ankyloses accompanied by fibrocartilage proliferation and ectopic ossification. DCs were excessively expanded in *Dcir* KO mice, causing these mice autoimmunity and also highly susceptible to induced-autoimmune diseases. *Dcir* KO mouse–derived bone marrow cells differentiated into DCs more efficiently than did wild-type BMCs upon treatment with GM-CSF, due to enhanced STAT-5 phosphorylation. Furthermore, we found that IFN-g producing T cells were increased in *Dcir* KO mice and IFN-g enhanced bone and cartilage formation, resulting in the increase of bone volume and aberrant ossification in joints. DCIR is also expressed in osteoclasts and suppresses osteoclastogenesis upon activation. These findings suggest that DCIR plays important roles in both immune system and bone metabolism.

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SP0004 PEPTIDYL ARGININE DEIMINASE 4 AND RHEUMATOID ARTHRITIS: FROM HUMAN GENETICS TO MURINE MODELS

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We have previously reported that functional haplotypes of peptidyl arginine deiminase 4 *(PADI4*) are associated with rheumatoid arthritis (RA). We found that transcripts of the risk haplotype of *PADI4* are more stable than those of the non-risk haplotypes, suggesting that increased expression and function of PAD4 (encoded by *PADI4* gene) increase the risk of RA. The association has been confirmed by several studies with different ethnics. Further, we also reported *PADI4* polymorphisms highly predispose male smokers to RA. Since PAD4 catalyzes an arginine residue in a protein to citrulline and anti-citrullinated protein antibodies (ACPA) are highly specific in RA, it has been reasonable to speculate that increased PAD4 is associated with increased citrullinated proteins, leading to the initiations of tolerance breakdown or inflammatory arthritis.

However, the mechanisms of PAD4 involvement turned out to be more complex than previously thought in animal models. In order to investigate the pathological process in detail, we made *Padi4* knockout mice. Decreased severity of experimental autoimmune arthritis wad observed in these mice. Further, we found PAD4 regulates the pro-apoptotic fate of neutrophils, and promotes the expression of pro-inflammatory cytokines in macrophages. These actions could result in the pro-arthritic roles of *PADI4*. Recently, neutrophil extracellular traps (NETs) were reported as an important immune stimulator in RA and SLE, and PADI4 is required for the generation of NETs. Especially, NET-containing immune complex (IC) stimulated plasmacytoid dendritic cells to accelerate the interferon secretion in SLE. Therefore, *PADI4* could play several different roles in the immune system and also in the pathogenesis of autoimmune diseases.

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Health professional welcome session

SP0005 LOOKING BACK AT 70 YEARS OF EULAR AND 30 YEARS OF HP INVOLVEMENT: A REHABILITATION PERSPECTIVE

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The medical treatment of people with rheumatic and musculoskeletal diseases (RMDs) has improved enormously over the past decades. As medical treatment is not completely successful or available for all rheumatic conditions or individual patients, and the demands society imposes on people to participate fully are increasing, there is a substantial proportion of people with RMDs who have functional disabilities.

Health professionals (HPs) play an essential role in the management of people with RMDs with disabilities by enabling to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. They provide people with the tools they need to attain independence and self-determination. As such, their contribution is in line with the World Health Organisation definition of rehabilitation [http://www.who.int/topics/rehabilitation/en/]. An important feature of rehabilitation is its multidisciplinarity. Over the past decades, it has been more and more acknowledged that HPs' role in the management of people with RMDs concerns a team effort rather than the summation of single interventions by individual HPs or specific professions. This view is reflected in multiple guidelines and standards of care for the clinical management of RMDs, where the need for people with RMDs to have access to a multidisciplinary team of HPs is underlined.