EDITORIAL

Osteoarthritis—Slow but Steady Steps Forward

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Osteoarthritis (OA) is a major cause of pain and disability that affects millions of people worldwide. It mainly occurs in older people but can affect younger individuals with monogenic disorders and inborn errors of metabolism. Clinically it is characterised by focal loss of articular cartilage, subchondral osteosclerosis, osteophyte formation at the joint margin and remodelling of joint contour with enlargement of affected joints. This special issue of Calcified Tissue International focusses on recent advances in knowledge concerning the pathogenesis and treatment of OA. The slow progress in developing therapies for OA contrasts sharply with that seen in other common disorders such as cardiovascular disease, osteoporosis and also in less common disorders such rheumatoid arthritis, which have all seen transformative advances in clinical management over the last 3 decades, underlying the complexity of disease in OA. The search for disease modifying drugs in OA is dependent on relevant preclinical models and on the availability of validated biomarkers for preclinical research and clinical trials.

Samvelyan et al. [1] have reviewed the established and emerging experimental models, which are used to study the pathogenesis of OA, to identify new therapeutic targets and to screen potential pharmacological agents. They include in vitro and in vivo models of primary and secondary OA. They describe how 2D cell culture models can be used to investigate cellular regulation and are useful for high throughput screening. However, the applicability of 2D models is limited because they are non-physiological, particularly in regard to not capturing the interactions of different cell types. The authors report on the promising development of 3D culture models but conclude that at present animal models are an imperative stepping stone for pre-clinical discovery and translational research. Much preclinical research in OA has focussed on mouse models of induced OA, but the authors highlight the value of studying spontaneous models of OA which have been reported in several species.

The pathogenesis of OA is complex in which genetic, mechanical and metabolic factors interact. Disorders which lead to aberrant joint formation or aberrant joint maintenance can result in mechanical overloading which inevitably leads to osteoarthritis (OA). The role of genetics in OA is reviewed by Wilkinson and Zeggini [2] with a specific focus on the genetics of bone shape. The heritable component of OA accounts for around 50% of susceptible risk, yet despite an intensive international research effort that has identified nearly 100 risk loci, these only explain a small part of the disease susceptibility. Wilkinson and Zeggini describe what is currently known about the genetic regulation of synovial joint development and review the genetic epidemiology of joint shape variation. They point to the advances that have been made in understanding the contribution of hip shape to OA risk, whereas at other sites including the knee, shape phenotypes are more difficult to define and there is a pressing need for more research.

Loss of articular cartilage is a hallmark of OA and metalloproteinases have long been recognised as the key enzymes in cartilage matrix degradation. At one time, blocking the activity of these proteases was seen as a potential route to cartilage and joint preservation but the complex roles of metalloproteinases in homeostasis of many tissues made it inevitable that simple inhibition of these enzymes would not be a successful strategy. Yamamoto and colleagues have reviewed recent discoveries on functions of the metalloproteinase family in OA pathogenesis [3]. They highlight studies which have identified the involvement of these enzymes in synovial hypertrophy, osteophyte formation and subchondral bone remodelling in addition to cartilage matrix degradation. Advances in understanding the regulation and function of metalloproteinase may again lead to selection of these enzymes as targets for therapeutic interventions in OA and other connective tissue disorders.

Shepherd et al. highlight lessons that can be learnt from study of less common cartilage syndromes [4]. They describe how studying rare bone disease has contributed

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significantly to understanding the physiology and pathology of bone turnover and influenced the development of effective pharmacological interventions to inhibit bone resorption and promote bone formation. In contrast, the study of rarer forms of osteoarthritis has been comparatively neglected by researchers and the mainstream OA funders in favour of other approaches, including cell signalling and stem cells. The authors describe some recent examples of knowledge gained from rare osteoarthopathies, particularly chondrodysplasias and alkaptonuria (AKU), a metabolic disease which leads to a severe early onset form of OA. Interestingly, AKU recently became the first of any causes of OA that has an efficacious therapy approved.

Alan Boyde revisits the theme of aberrant mechanical loading, complex tissue interactions, rare diseases, biomarkers and animal models of osteoarthritis in a paper that considers what role the bone–cartilage interface plays in OA [5]. The article and the accompanying and extensive supplementary material are filled with images that should enthral and inform readers. An array of imaging techniques, some of them recently developed by the author, has been used to illustrate the anatomical and microanatomical structure of the bone–cartilage interface. The tissues under investigation are human and equine, the latter an underlooked model of large animal OA. These are not just beautiful images; they reveal new osteoarticular knowledge with the discovery of novel pathoanatomical structures including HDMPs, new culprits in joint destruction and pain. The role and distribution of classical structures is also revisited, including Sharpey fibres, which are identified at the marrow–trabecular bone interface for the first time, implying that these interfaces are subjected to significant mechanical stress and re-emphasising the importance of loading in the normal physiology and the aberrant pathology of the joint. The images in this article ought to be a source of inspiration and discussion for OA researchers.

The current state of the art in OA biomarkers is presented by Kraus and Kardsdal [6], who have constructed their review by considering the case for and against biomarkers in OA. Their article forms a comprehensive review of the current reality and the future potential for OA biomarkers. Importantly, they conclude that a single biomarker cannot be sufficiently efficacious and that a panel of markers will be required for early detection, prediction of progression and monitoring response to therapy.

In the final article, Ghouri and Conaghan describe the current limited treatment options available for OA [7]. They have reviewed the use of pharmacological therapies which are currently available and also discussed results from the recent clinical trials, both positive and negative. They have categorised agents according to the tissues they target: bone and cartilage, nerves and synovium. They have also reviewed some preclinical studies, which offer hope for the future.

In conclusion, this volume describes the small but steady steps forward that are being made in OA research. The current situation is nowhere near satisfactory but there are prospects of improved movement at every level of the journey from basic laboratory research to clinical practice. In basic research, there have been some impressive jumps forward in genetics, biochemistry and anatomy which are changing our understanding of this complex disease and which should eventually translate into patient benefit. In the clinic, the potential availability of new disease modifying drugs coupled with validated biomarkers provides hope for better treatment.

Declarations

Conflict of interest J. A. Gallagher declares that they have no conflict of interest.

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