What does the arthropathy of alkaptonuria teach us about disease mechanisms in osteoarthritis and ageing of joints?
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2015. The authors

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Strap line: Lessons from a rare disease

Rare diseases are a neglected area of study in OA. Our hypothesis is that greater focus on rare cartilage syndromes would lead to more rapid advancement in understanding OA and age-related joint degeneration. OA is one of the major causes of disability, yet despite major research efforts, there are no therapies and a limited number of biomarkers. In extreme phenotypes of Mendelian disorders, disease progression is often rapid and predictable, so it is easier to identify the initiation and advance of pathological changes. Careful observation of extreme phenotypes could help elucidate the pathogenesis of OA and lead to new biomarkers and therapeutic targets. Here we describe how investigating arthropathy in the rare genetic disease alkaptonuria (AKU) has provided important lessons for OA and ageing of joints.

The idea that we can learn from rare diseases is not new. In the Annual Oration to the Medical Society of London in 1928, Sir Archibald Garrod, whose research on AKU led to the concept of inborn errors of metabolism, delivered a presentation entitled ‘The Lessons of Rare Maladies’ [1]. Garrod recalled the teaching of William Harvey, who, in a letter to John Vlackveld in 1657, observed ‘nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease’ [2].

The words of Garrod and Harvey proved to be prophetic, as research on monogenic diseases has helped elucidate the pathogenesis of common disorders. Several therapies for common diseases, including the blockbusters statins and bisphosphonates, were discovered in part through the study of rare syndromes. The investigation of high bone mass phenotypes in sclerostosis and Van Buchem’s disease has revealed the role of Wnt signalling and sclerostin in bone, leading to new drug targets.

Despite many examples from other fields on the wider benefits of rare disease research, the potential impact of studying less common cartilage syndromes in OA has been neglected. Research has been focused on prevailing trends, including cell signalling, stem cells and genomics, all important areas of research, but none of which has been particularly productive in elucidating the pathogenic mechanism or identifying new therapies and biomarkers.

Tissue homeostasis is regulated by many interacting signalling pathways. Once joint degeneration has been initiated and there are ultrastructural, anatomical and mechanical changes, all pathways will be disrupted. Research on the secondary downstream consequences will not reveal the primary pathological mechanism of OA.

The potential for cell therapy with stem cells or chondrocytes to repair damaged joints is limited, probably to conditions of focal trauma rather than degeneration. OA is a disease of the whole joint and anatomical changes in the underlying bone accompany or even precede cartilage loss. Resurfacing a joint in which the subchondral bone plate and trabeculae are disrupted is analogous to the futile renewal of tiles on an uneven roof in which the underlying timbers are warped.

Despite the resources pumped into untargeted genomics, the candidate gene with the most impressive OA association is GDF5, which is a chondrodysplasia gene, already known through rare disease research [3]. Similarly, mutations of ANKH in chondrocacrinosis [4] have highlighted the role of pathological mineralization in more common OA. More than 40% of patients with OA have detectable mineral deposits in cartilage [5]. These are separate examples of how research on rare diseases other than AKU can contribute to understanding the pathophysiology of OA.

Our research has focused on AKU, a monogenic defect in tyrosine metabolism that leads to early onset, aggressive joint degeneration. Although joint destruction in AKU is associated with the deposition of pigmented polymers in cartilage, termed ochronosis, there are parallels with the pathophysiology of OA. Studies on tissue samples from AKU patients and from an AKU mouse model have revealed previously unidentified microanatomical, cellular and biochemical changes in joints that have been subsequently recognized in human OA.

The sequence of pathological changes in AKU and the parallels in OA are as follows. Age-related changes occur in the composition and organization of the extracellular matrix, including loss of proteoglycans and disruption of collagen fibrils. These are exacerbated by trauma. Collagen fibres lacking protective proteoglycans are attacked by reactive molecules. In AKU, homogentisic acid is the culprit leading to ochronosis [6], whereas in non-AKU joints, reaction with sugar molecules lead to
formation of advanced glycation end-products. Chemically modified collagen fibres become stiffened and less resistant to mechanical loading, leading to a downward spiral of structural damage. In AKU and possibly in OA, this cascade is initiated in calcified cartilage and spreads throughout the hyaline cartilage to the articular surface [7]. Increased stiffness of collagen leads to aberrant transmission of mechanical loading through cartilage to underlying bone [7]. The subchondral plate is subjected to direct damage through aberrant loading and load-induced remodelling. There is focal loss and focal sclerosis of the subchondral plate [7] and aberrant remodelling of the underlying bone, including formation of trabecular excrescences [8]. Of major significance is that microscopic cracks appear in the subchondral plate, leading to formation of high-density mineralized protrusions [9]. These abrasive structures contribute to the destruction of cartilage. Although we initially discovered high-density mineralized protrusions in the cartilage of a femoral head from a patient with osteoarthropathy of AKU, we have subsequently found these novel microanatomical structures in OA hip and knee joints, indicating that they are widespread in OA. Their formation constitutes a newly recognizable mechanism of joint destruction in AKU and in OA and provides a new imaging biomarker and a potential target for drug therapy.

These features are easily recognizable in the severe phenotype of AKU. The analogous changes in OA are more difficult to detect because they occur at a lower frequency, but they are no less important. In conclusion, we provide evidence that studying rare cartilage syndromes can help elucidate the pathophysiological mechanisms involved in joint destruction. Further support for rare disease research could make a significant contribution to the development of effective therapies and new biomarkers for OA.

Acknowledgements

This article is dedicated to the memory of Robert Gregory (1949–2014), founder of the AKU Society. Our research would not have been possible without generous support from the AKU Society, the Rosetrees Foundation, the Childwick Trust, the Big Lottery and EUFP7. We are grateful to the AKU patients who have donated tissues for our research. We thank Jane Dillon for advice on the manuscript.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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Revised version accepted 3 November 2015
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Author Query Form

Journal: Rheumatology
Article Doi: 10.1093/rheumatology/kev401
Article Title: What does the arthropathy of alkaptonuria teach us about disease mechanisms in osteoarthritis and ageing of joints?
First Author: James A. Gallagher
Corr. Author: James A. Gallagher

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