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Review

Alkaptonuria: An example of a "fundamental disease"—A rare disease with important lessons for more common disorders

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ABSTRACT

"Fundamental diseases" is a term introduced by the charity Findacure to describe rare genetic disorders that are gateways to understanding common conditions and human physiology. The concept that rare diseases have important lessons for biomedical science has been recognised by some of the great figures in the history of medical research, including Harvey, Bateson and Garrod. Here we describe some of the recently discovered lessons from the study of the iconic genetic disease alkaptonuria (AKU), which have shed new light on understanding the pathogenesis of osteoarthritis. In AKU, ochronotic pigment is deposited in cartilage when collagen fibrils become susceptible to attack by homogentisic acid (HGA). When HGA binds to collagen, cartilage matrix becomes stiffened, resulting in the aberrant transmission of loading to underlying subchondral bone. Aberrant loading leads to the formation of pathophysiological structures including trabecular excrescences and high density mineralised protrusions (HDMPs). These structures initially identified in AKU have subsequently been found in more common osteoarthritis and appear to play a role in joint destruction in both diseases.

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1. Introduction: What are fundamental diseases?

"Fundamental diseases" is a term introduced by the charity Findacure, which promotes research into development of new treatments for rare diseases [1]. They coined the term "fundamental diseases" to capture the concept that rare diseases, especially those that have a genetic cause, are gateways to understanding common conditions and human physiology. Findacure regards the usual terminologies "rare", "orphan" and "neglected" as contributing to why

Abbreviations: AGE, advanced glycation end products; AKU, alkaptonuria; ECM, extracellular matrix; HDMPs, high density mineralised protrusions; HGD, homogentisate 1,2 dioxygenase; HGA, homogentisic acid; OMIM, online Mendelian inheritance in man; OA, osteoarthritis; PG, proteoglycan; TEM, transmission electron microscopy; ssNMR, solid state nuclear magnetic resonance.

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this group of diseases has been relatively overlooked. However, the concept that rare diseases have important lessons for biomedical science is not new. William Harvey the great English physician of the 17th century wrote in a frequently quoted letter that "careful investigation of cases of rarer forms of disease" was the best way "to advance the proper practice of medicine" [2]. Nearly two and a half centuries later, William Bateson, who was a major advocate of the work of Mendel and first coined the term genetics, repeated Harvey's advice in his inaugural lecture at the University of Cambridge when he urged young scientists to "Treasure your exceptions" [3]. Bateson had a major influence on his colleague Archibald Garrod, the father of metabolic disease who introduced the term inborn errors of metabolism. Through discussions with Bateson, Garrod came to recognise that the ultra-rare disease alkaptonuria (AKU) was a recessive disorder and thus became the first human disease shown to follow Mendelian inheritance [4]. Garrod also was aware of the wider benefit of the study of rare diseases. In his article "The Lessons of Rare Maladies," Garrod paraphrased Harvey, "The study of nature's experiments is of special value; and many lessons which rare maladies can teach could hardly be learned in other ways" [4].

In this chapter, we describe some of the recently discovered lessons from the study of AKU (OMIM 203500) which have shed new light on understanding the pathogenesis of osteoarthritis (OA). AKU is one of around 8000 Mendelian diseases and for every patient in the UK with AKU there are around 100,000 with OA. However by studying rare diseases like AKU which are characterized by severe phenotypes with rapidly developing pathologies, it is easier to identify earlier molecular and microanatomical changes that are also fundamental to the pathogenesis of more common disorders like OA. Pathological changes in OA are less conspicuous because they are not as abundant and progress more slowly. An additional benefit of investigating Mendelian diseases is that it is possible to trace the succession of pathological changes back to the altered function of a single gene.

2. Genetics and pathophysiology of alkaptonuria

Half a century after Garrod's recognition that AKU was a genetic disease with recessive inheritance, La Du and colleagues discovered that the disorder was caused by a deficiency of homogentisate 1,2 dioxygenase (HGD) [E.C.1.13.11.5], an enzyme in the metabolism of tyrosine and phenylalanine [5]. The single-copy human HGD gene maps to chromosome 3q21–q23, encompassing 14 exons and encoding a protein of 445 amino acids [6]. AKU arises from homozygous or compound heterozygous mutations in the HGD gene, with more than 130 different human mutations now identified [7,8]. The prevalence of AKU is calculated to be 1:100,000–250,000 in most ethnic groups. However, in several hotspots including the Dominican Republic and the north western region of Slovakia, the incidence is greater than 1:20,000. Whereas the high incidence in the Dominican Republic appears to be a classical founder effect, the high regional incidence in Slovakia is a baffling result of more than 12 distinct mutations [6]. Increased international interest in AKU research over the past few years through the FindAKUre and DevelopAKUre (www.developakure.eu/) [9] consortia has led to the identification of a high incidence of the disease in some regions of Jordan [10] and in specific ethnic groups in India [11]. It is likely that there is a vast reservoir of undiagnosed AKU worldwide, particularly in developing countries.

Loss of HGD enzyme activity increases the circulating concentration and urinary excretion of homogentisic acid (HGA), causing urine to darken on exposure to air. Raised HGA levels eventually lead to ochronosis, the deposition of polymers of HGA as pigment in connective tissues including cartilage, heart valves and sclera [12] (see Fig. 1). Patients present with disease in early adult life and they are markedly affected in the fourth and fifth decades of life. Over time, patients develop the characteristic external features of ochronosis, blue-black pigmentation of the ear cartilage and sclera of the eyes. Ear ochronosis can lead to pain in the external ear whilst scleral ochronosis may affect vision. Aortic and mitral valve disease is also common and may require valve replacement [13].

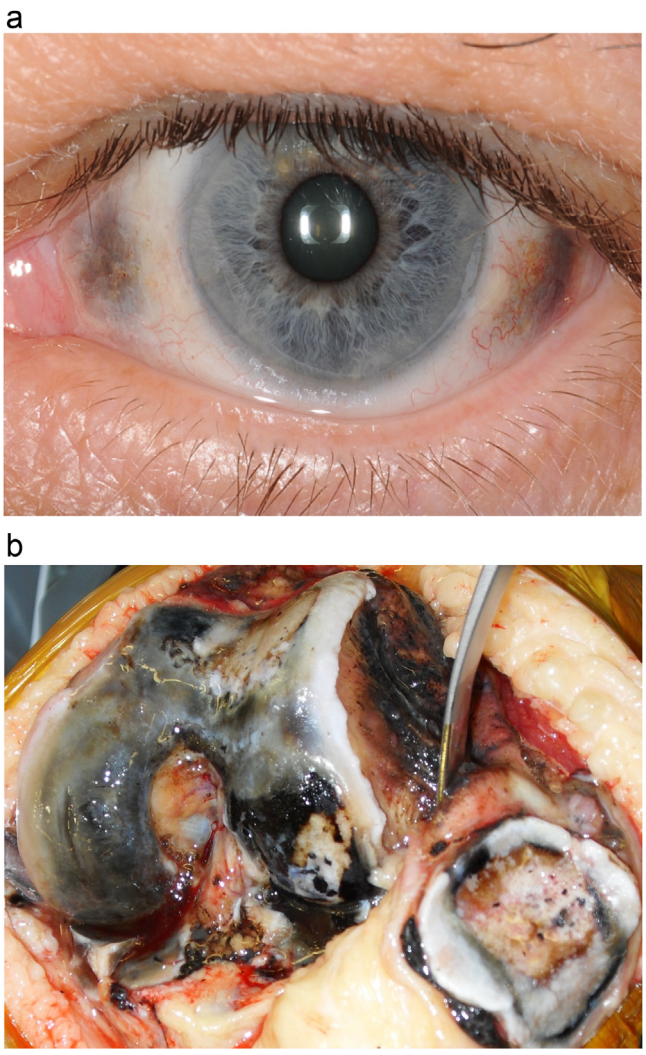

Fig. 1. Ochronosis in tissues of a patient with AKU (a). Sclera of the eye and (b). Knee joint. HGA is deposited in collagenous tissues forming pigmented polymers. The pigment cause the extracellular matrix to become stiff leading to severe pathophysiological changes.

3. Osteoarthropathy in AKU

Joint ochronosis and the subsequent osteoarthritis appear to be an inevitable consequence of AKU causing considerable disability and pain in the peak of adulthood due to premature joint and spine disease. Ochronotic disease of the intervertebral disc develops in the third decade of life causing severe pain, and progressive kyphoscoliosis. Disc degeneration impacts on spinal and thoracic mobility with consequent respiratory problems. Pain due to joint disease is progressive, eventually affecting most synovial joints in the body. Multiple joint replacements are almost inevitable. Other musculoskeletal manifestations of AKU include tendon and ligament ruptures, osteopenia and fractures [13].

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