Osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common form of joint disease, and its impact is set to grow as the prevalence of obesity rises and our elderly population increases. Many clinicians regard OA as being simply a disease of 'wear and tear', and by implication one in which disease modification is not possible. Such prejudices have led to significant academic apathy in this disease that is reflected not only in our poor understanding of disease pathogenesis, but also in the failure to classify the disease with greater precision, and to develop sensitive tools for diagnosis and prognostic assessment. The recent identification of key degradative enzymes in cartilage and the use of mouse models to study disease pathogenesis have greatly changed our outlook. The next decade is likely to see significant advances in our understanding of, and treatment for, this condition.

Keywords Aggrecanase; articular cartilage; mechanical injury; osteoarthritis

Pathology

Osteoarthritis (OA) is the most common form of joint disease, estimated to cost a sum equivalent to 1—1.5% of the gross domestic product of developing countries.[1] It is characterized by loss of the articular cartilage, an avascular and aneural tissue that overlies the ends of bone at synovial joints, and this likely leads to changes in the other tissues of the joint that contribute to disease expression.[2] Cartilage is uniquely adapted to perceive and respond to mechanical stress because of the presence of an elaborate, organized extracellular matrix made up of the proteoglycan, aggrecan, and type II collagen. Chondrocytes, which are the only cells in cartilage, are responsible for maintaining the matrix during life. Ultimately, these same cells are probably responsible for making the degradative enzymes that destroy the tissue in disease.

Loss of articular cartilage occurs initially at the articulating surface and then spreads through the matrix down to the subchondral bone (Figure 1). Other changes that occur in the tissue include patchy loss of aggrecan, and clustering and clonal expansion of chondrocytes. Within the joint there is also sclerosis of the subchondral bone, bony expansion with osteophyte formation, and episodic synovitis. Cartilage loss often precedes the development of pain, which explains why patients often present with advanced joint degeneration. The source of pain is unclear, but it may arise from bone or inflamed synovium, or from other peri-articular structures such as entheses, bursae or tendons. Chronic pain, resulting from local sensitization of nerve fibres and central nervous system changes, is common over time.[3]

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Aetiology

Traditionally, OA has been designated as either primary or secondary, based on the presence or absence of a known predisposing factor or factors. In practice, it is usually possible to identify such factors in all patients with disease even though these may be multiple low-impact factors such as family history, obesity and age. We prefer to divide OA into 'age-related OA', where disease is associated with advanced age, and 'premature OA' where there is usually a single strong independent risk factor that leads to early onset of disease.

Mechanics

Irrespective of how the disease is classified, the unifying aetiological factor in OA development is mechanical load — either abnormal load on a normal joint, or normal load on a joint that has lost its mechanoprotective mechanisms (Table 1)(reviewed in[4]). This is perhaps most clearly illustrated in young individuals who have sustained destabilizing injuries to the joint (e.g. meniscal and cruciate ligament injuries). They exhibit an OA risk of approximately 50% within 10 years of injury. It is also the case that repetitive low-impact injuries, often occupational, are strongly associated with disease. Likewise, malaligned and misshapen joints are at increased risk of disease. Conversely, off-loading a diseased joint can halt disease progression, as seen in those who have sustained a cerebrovascular accident or polio. Therapeutic approaches to off-load the diseased joint, for example, by high tibial osteotomy or joint distraction (where a sprung external fixator is placed across the joint for a period of 3 months), show good symptomatic responses and may be disease modifying.[5] Other important aetiological factors then contribute to the expression of disease and presumably explain why disease is highly heterogeneous and the course unpredictable. Some of these are discussed further below.

Age

Age is likely to contribute to disease risk by a number of mechanisms. Aged joints often exhibit mechanical failure; meniscal failure is evident in 40% of 'age-related' OA in the absence of a history of acute knee trauma.[6] Moreover, loss of muscle strength and reflexes with age suppresses normal mechanoprotective gait responses. It is generally accepted that aged cartilage is more susceptible to degradation, due in part to a reduction in new matrix synthesis, as well as an increase in activation of degradative pathways. Ageing also leads to a failure to clear damaged cells that accumulate in tissues, causing release of reactive oxygen species and tissue damage. Such mechanisms have been observed in joint cells (reviewed in[7]).

Obesity

Increased mechanical load on the joint is one obvious consequence of obesity as is poor muscle tone leading to loss of joint protection. In addition, adipocytes probably secrete inflammatory cytokines (adipokines) that drive matrix degradation directly.[8] Individuals with obesity have higher concentrations of circulating

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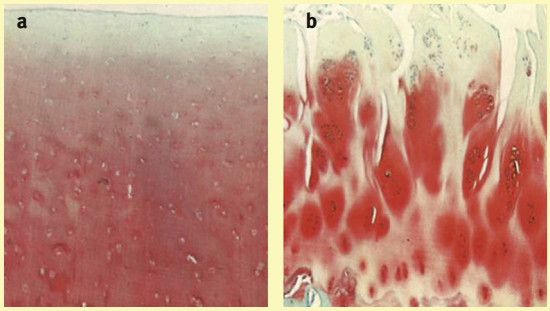

(**a**) Normal and (**b**) osteoarthritic human cartilage stained for proteoglycan (red). Note patchy loss of proteoglycan, tissue fibrillation and clustering of chondrocytes.

Figure 1

inflammatory response proteins and are at increased risk of metabolic syndromes, which are also associated with OA (see below).

Genetics

From twin studies, heritability in OA is calculated to be in the region of 60%.[9] Recent studies have determined that OA is highly polygenic — in other words, disease is increased by polymorphisms in a number of different genes, although the relative risk of each gene is small. Whole genome-wide analyses have confirmed this polygenic association and have identified a small number of weak novel gene candidates.[10] Epigenetics, the complex ways in which gene expression is controlled in a given individual, may be more important and this line of research is currently being pursued.

Metabolic syndromes

A number of metabolic syndromes have been associated with the development of OA. These are listed in Table 2. Chondrocalcinosis (cartilage calcification) can be present (e.g. in haemochromatosis and hyperparathyroidism) and may indicate a predisposition to inflammatory episodes precipitated by calcium pyrophosphate crystal deposition.

Theories of pathogenesis

A number of theories of pathogenesis have been proposed over the decades, but the discovery in the 1980s of a family of matrix-degrading enzymes, known as matrix metalloproteinases (MMPs), substantially changed the face of OA research. A new hypothesis was presented: that osteoarthritis was due to an imbalance of tissue homeostasis, pushing the scales in favour of matrix degradation rather than synthesis. This theory was supported by the identification of fragments of aggrecan in the joint fluid of patients with OA. However, on close examination, they did not appear to have been generated by the action of known MMPs, and it was concluded that another, as yet undiscovered, class of enzymes was responsible for degradation; these were termed 'aggrecanases'.[11] The first aggrecanase was purified and cloned in 1999,[12] and in 2000 a second homologous enzyme (aggrecanase 2) was discovered.[13] Despite much industrial interest, strategies for inhibiting aggrecanases in patients with arthritis have not been forthcoming, possibly due to off-target effects of inhibitors and partly to a lack of good biomarkers to monitor disease in clinical trials.

Aggrecanase expression can be driven in vitro by inflammatory cytokines such as interleukin 1, although the role of such cytokines in driving expression in vivo is controversial. These enzymes can also be induced by mechanical injury in vivo and in vitro, suggesting that the cellular pathways that drive mechanical responses could be highly relevant future therapeutic targets.

Clinical features and diagnosis

Osteoarthritis can be considered as a common clinicopathological syndrome that is a consequence of diverse

Metabolic causes of osteoarthritis

Acromegaly
Hyperparathyroidism
Hypothyroidism
Diabetes mellitus (may relate to obesity)
Haemochromatosis
Wilson's disease
Gaucher's disease
Ochronosis (alkaptonuria)
Kashin—Beck disease
Haemoglobinopathies/avascular necrosis

Table 2

Evidence for mechanical factors in OA aetiology

Increased disease by increased load	Increased disease by loss of joint mechanoprotection	Reduced disease by mechanical joint offloading
Overuse (e.g. cotton pickers' (hand), coal miners' (back), farmers' (hip) OA)	Acute destabilizing injuries (e.g. cruciate/meniscal tears)	Polio and CVA patients have reduced disease on immobilized side
Obesity	Loss of gait reflexes with age	Disease arrest following high tibial osteotomy
Acute articular cartilage trauma (e.g. intra-articular fracture)	Chondrodysplasias (weak cartilage matrix)	Disease modification following surgical joint distraction
Joint malalignment	Joint damage due to previous inflammatory arthritis	Animal are protected from experimental OA with joint immobilization
	Loss of joint support through muscle weakness (e.g. age)	

Table 1

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