Osteoarthritis and molecular markers

A rheumatologist's perspective

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What is osteoarthritis

1. An evolutionary legacy or a disease?

OA is a common age-related condition in man, but it has a restricted inter and intra-articular distribution. It is rare before middle age, after which its prevalence rises steeply. However, only some joints are commonly affected—the distal interphalangeal and thumb base joints in the hands, medial tibiofemoral and lateral patello-femoral joints of the knees, and superior pole of the hip being particularly vulnerable in the peripheral skeleton. In other animals OA sometimes appears in older individuals, particularly in relation to trauma, but again, not all joints are affected. For example, the vulnerable joints in the horse appear to be those that have evolved most recently (Hutton 1994), and elderly rhesus macaque monkeys develop OA of the knees and distal interphalangeal joints, but not their thumb base (Lim et al. 1994).

These observations have led to the hypothesis that OA is an evolutionary legacy (Hutton 1987, Dieppe 1995). This paradigm of OA suggests that the condition is the result of two features of the evolution of our species—the change in posture and usage of the skeleton, and the development of a long "post-reproductive" life span. As man evolved from the apes he adopted a bipedal gait and a prehensile grip and changed his usage of the musculoskeletal system. It has been suggested that with the reduction in evolutionary pressure on those members of the species with less physical prowess certain joints remain "underdesigned" for the job now asked of them. Thus the superior pole of the hip and thumb base in the hand are mal-adapted for man's standing posture and prehensile grip, for example. This problem may then be exacerbated by our longevity. It is unusual for members of a species to live long after their reproductive period, but the human female may live as long after her menopause as before it. Whereas there has been great evolutionary investment in reproduction, there has been less investment in cell and tissue repair (Schachter et al. 1993). Injury to the tissues accumulates with age, especially in vulnerable (or "underdesigned") areas of the system, and the repair process becomes increasingly unable to cope as age advances. Thus OA can be seen as an age-related disorder of evolution, featuring aberrant repair.

2. Disease(s) or disease process(es)?

An alternative paradigm to the evolutionary theory of OA suggests that it is a specific disease, or disease process. However, OA is a very variable condition, and any comprehensive account of the disorder must accommodate this heterogeneity. It could occur because OA includes many different diseases with a similar outcome, or because there are final common pathways that follow any form of joint damage. Currently, many authors view OA as a group of conditions (the "osteoarthritic diseases") that can be differentiated by the joint site(s) involved, but all of which feature a common pathological process that can lead to joint failure (Dieppe and Kirwan 1994).

3. Genetic or environmental?

Some diseases are purely genetic, some, such as certain traumatic events, purely environmental. In the past, some have thought that OA is largely secondary to joint trauma. However, the recent discovery that subtle abnormalities of the COL2A1 gene can lead to premature OA (Knowlton et al. 1990) has helped rekindle the belief that it could be a genetic disorder. It seems unlikely that the majority of cases of sporadic age-related OA can be ascribed to a specific genetic abnormality, especially as the joint distribution seen in common OA is quite different from that of the more generalised disease seen with genetic abnormalities and in cases secondary to metabolic disorders such as ochronosis. However, there is a lot of evidence for a genetic component to sporadic OA (Hutton and Dieppe 1989). Similarly, there is a lot of

evidence to support an important role of trauma in the aetiology of OA (Radin et al. 1991). But OA is not simply a traumatic disorder. As an example, it has been shown that the development of knee OA following menisectomy (a clear example of "secondary" or "post-traumatic" OA) depends on the age and sex of the individual, and on the presence of hand OA—a surrogate sign of a generalised or genetic predisposition (Doherty et al. 1983). The current consensus, therefore, is that most cases of OA are due to a complex interaction of multiple genetic and environmental (including traumatic) factors.

4. Inflammatory or degenerative?

OA has often been classified as a non-inflammatory or degenerative form of arthritis. However, there is very active tissue turnover in an OA joint, many of the cardinal features of the condition being due to the (aberrant) repair process rather than the associated tissue damage (Hutton 1989). In addition, inflammatory changes are always present in both the synovium and subchondral bone in advanced cases (Revell et al. 1988). Inflammation may not be amongst the earliest or most critical features of OA, but it may contribute extensively to disease progression and outcome. It is both inaccurate and misleading to classify OA as either a degenerative disease or one with no inflammatory component.

5. A cartilage or a bone disease?

OA is characterised by focal areas of damaged articular cartilage associated with remodelling of the subchondral bone and marginal osteophyte formation. There has been much discussion concerning the earliest events in OA—which tissue is affected first? However, OA is probably a disease of the whole joint organ, in which there is linked dysregulation of matrix turnover in all tissues, including ligaments, menisci and synovium, as well as the bone and cartilage. Some recent animal model data suggest that changes at the interfaces between bone and cartilage, and ligament and cartilage, may be particularly important in the early evolution of the condition (Billingham and Meijers 1994).

6. Mechanical or biochemical?

Much recent research has focused on two quite different approaches to the aetiology of OA: some groups concentrating on the induction of joint damage by trauma or biomechanical changes, whereas others emphasise the early biochemical events and mediators of tissue damage and repair. These two avenues are now being brought together in two ways: first the effects of mechanical stimuli on the activity of both chondrocytes and osteocytes is being explored, secondly it has been appreciated that the risk factors for OA include a mixture of both generalised, systemic influences, and local, biomechanical factors (Dieppe 1991). The joint is a mechanical organ, responding to mechanical stimuli to maintain its normal integrity. But it is through biochemical pathways that matrix turnover and shape changes in the joint are controlled and mediated.

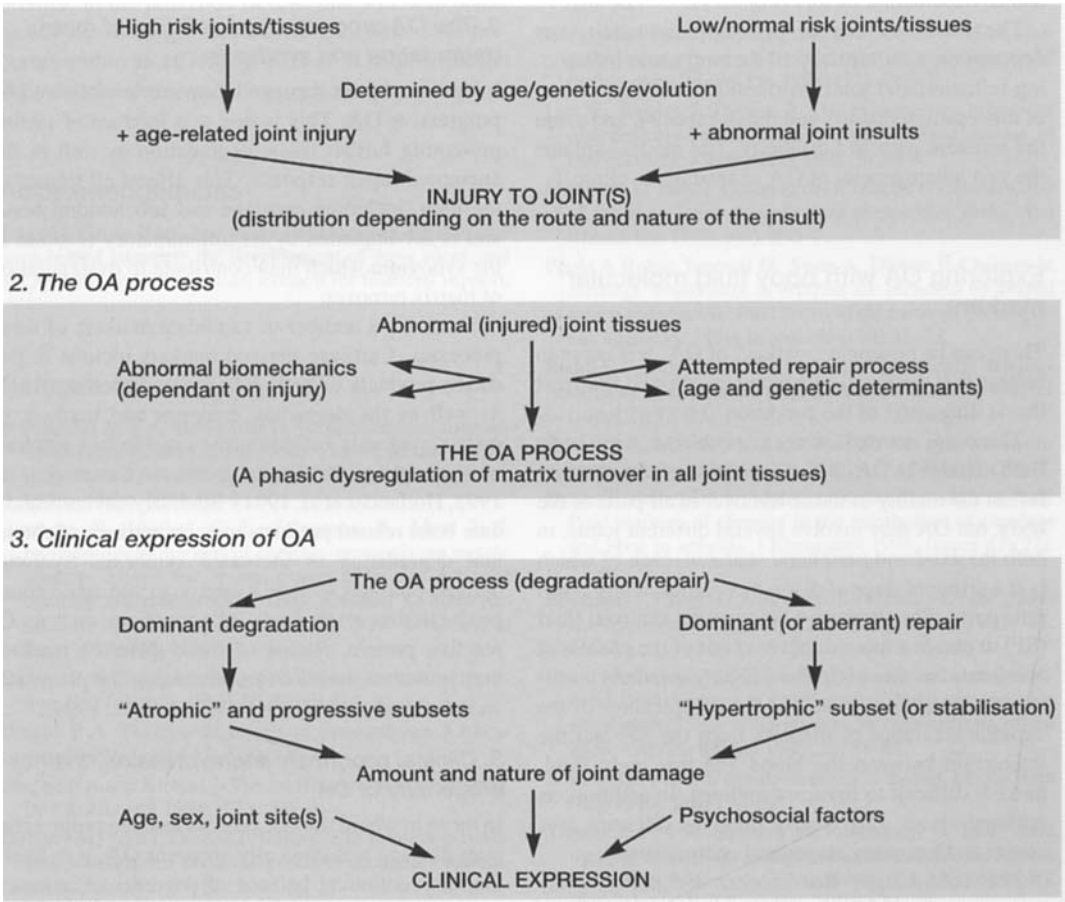
7. Progressive or non-progressive?

The observation that not all cartilage lesions progress to OA is of fundamental importance to our understanding of the condition (Youngman et al. 1987). It suggests that there may be two quite different processes involved, which may have different genetic and environmental risk factors: first the initiation of joint damage, and secondly the progressive process leading to the clinical expression of OA. Furthermore, it is now clear from longitudinal clinical studies that some established OA stops progressing, in spite of significant joint damage (Massardo et al. 1989), implying that the balance of degradative and reparative processes involved in progressive, established OA can lead to a "victory" for repair, and stabilisation of joint damage. An extension of this concept suggests that OA may progress in phasic bursts of matrix turnover dysregulation.

A rheumatologist's view of the aetiopathogenesis of OA

One model of the aetiopathogenesis of OA, which attempts a resolution of the questions and answers outlined above, is shown in Figure 1. This suggests that the OA process involves several steps, which can be conveniently broken down into three stages:

1. Initiation of joint damage: There are two main routes to joint damage: first through abnormal trauma or damage to normal tissues or joints (so-called "secondary" OA), and secondly through age-related accumulation of damage to normal tissues. The second route is most likely to occur in tissues that are rendered susceptible through a specific genetic abnormality (damage to the COL2A1 gene for example) or in those joints which are least well adapted to modern usage (through the evolutionary legacy). Secondary OA is likely to be confined to damaged joints, whereas OA arising because of genetic or metabolic disorders will be widespread or "generalised". Sporadic OA, initiated by age-related damage to underdesigned joints will feature the slow accumulation of joint sites with age, but in the restricted distribution (certain areas of the hands, knees and hips) which is characteristic of much of the OA seen in our communities.



2. *The progressive OA process:* The OA process develops and progresses in a proportion of those with joint injury. This is mediated by two main factors: first joint injury can alter biomechanics, which may lead to further damage, secondly, it stimulates an attempt at tissue repair. In some people, younger age groups especially, this repair process may succeed in limiting joint damage, in part by altering the biomechanics, resulting in stabilisation of the disorder. However, in others, particularly the elderly, the repair process is either sufficiently ineffective or aberrant to result in a worsening of the condition. Either way, the attempt at repair is an intrinsic part of the process and its outcome, and the dysregulation of matrix turnover, with dominance of either synthesis or degradation, a main feature of the process. The dependence of this process on a variety of factors, including age, sex and genetics, helps further explain the heterogeneity of the condition.

3. *Clinical expression and heterogeneity:* The clinical expression of the condition depends in part on age, sex and the joint site(s) involved, as outlined above. The degree of bone response that occurs in response to joint injury is one of the most striking features clinically, leading to the differentiation of OA joints into those that are "hypertrophic" and those that are "atrophic" (Solomon 1976). This phenomenon is associated with patient age, and with other features indicative of a greater or lesser ability to mount an attempted repair response. Thus the hypertrophic joint tends to be more stable and to have a better outcome than the atrophic form, which is often unstable

and rapidly progressive (Ledingham et al. 1993). In addition, the pain and disability that result from joint damage depend on a complex set of psycho-social and environmental factors (Figure 1).

The final outcome or patient presentation thus depends on a multiplicity of factors, some influencing initiation and joint distribution, some the nature of the resulting process and repair capacity, and some the resultant pain and disability. The model explains the vast heterogeneity of OA as seen in the clinic.

Exploring OA with body fluid molecular markers

There can be no single "marker" of OA. It is naive to believe that there will be a blood or synovial fluid test that is diagnostic of the condition.

There are several intrinsic problems with body fluid markers in OA. Blood or urine markers can only reflect the totality of tissue turnover in all parts of the body, but OA may involve several different joints, in both the axial and peripheral skeleton, each of which is at a different stage of disease evolution at any given time point. The alternative is to use the synovial fluid (SF) to obtain a more direct read out of the process at one joint, but this body fluid is only regularly available from the knee joint, and the complexities of the variable clearance of markers from the SF, and the interaction between the blood and this body fluid, make it difficult to interpret findings. In addition, as outlined above, OA clearly involves different processes and has many stages and components.

The contribution that marker technology may make, other than in providing important research tools, is in helping identify and quantify different aspects of the disease process as outlined above:

1. Tissue susceptibility and the initiation of joint damage

As outlined above, genetic or metabolic abnormalities may render the musculoskeletal system of some individuals to be more susceptible to OA to those of others. Molecular markers might reflect this. It has been suggested, for example, that high serum levels of keratan sulphate epitopes might reflect a generalised increase in connective tissue turnover and an increased susceptibility to OA (Thonar et al. 1993), although it should be stressed that there is no direct evidence to support this hypothesis.

According to the OA paradigms outlined above, damage to the normal integrity of the joint is essential to trigger off the OA process. It may be that this can be identified, through the release of some specific component of joint tissues. For example, fragments of type 9 collagen might be released early on in the initiation of cartilage damage (Wooten et al. 1995).

2. The OA process, dysregulation of matrix degradation and synthesis:

Initiation of joint damage is sometimes followed by progressive OA. This is due to a mixture of factors promoting further tissue degradation as well as the attempted repair response. This affects all tissues of the joint, including cartilage and subchondral bone, and is accompanied by an inflammatory reaction in the synovium which may contribute to dysregulation of matrix turnover.

There are a number of candidate markers of these processes. Cartilage derived markers include degradation products of both collagen and proteoglycans, as well as the degrading enzymes and markers of matrix synthesis including the chondroitin sulphate neo-epitopes and collagen products (Caterson et al. 1992, Hollander et al. 1994). Similarly, several candidate bone related products may be markers of abnormal degradation or increased synthesis. Synovial derived products include hyaluronan and acute phase products that result from inflammation, such as C-reactive protein. Ratios of these different markers may provide a useful way of assessing the process in an individual patient or joint (Poole et al. 1994).

3. Clinical prognosis and expression, the heterogeneity of OA

In those in whom the OA process leads to progressive joint damage and clinically apparent OA, it is likely that the continuing balance of degradative, aberrant reparative and inflammatory processes will directly affect outcome, in which case the marker profile might be expected to have prognostic value. Similarly, the number and types of joint involved might affect the marker profiles in blood and urine, and the tendency for there to be a "hypertrophic" or "atrophic" response in the joint might be reflected by a different balance of synthetic and degradative products in body fluids. Some recent data suggest that serum levels of both hyaluronan (Sharif et al. 1995) and cartilage oligomeric matrix protein (Saxne and Heinegard 1995) may be predictive of the outcome in OA.

Conclusions

OA remains an enigma. However, it can be conveniently split into three phases: the initiation of joint damage, the development of a process of degradation

and attempted repair, and the clinical expression of the disease. While there can be no single body fluid test for OA, molecular marker technology is showing promise in the provision of tests that will help detection of joint damage, delineation of the balance of processes within an affected joint, and in helping predict the outcome of this very heterogeneous condition.

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