Molecular markers for joint and skeletal diseases

Notes from the general discussion

Paul Dieppe

Bristol University, Bristol Royal Infirmary, Rheumatology Unit, Marlborough St., Bristol BS2 8HW, UK. Tel +44-117 928 2983. Fax +44-117 928 3841.

1. What does the basic or clinical scientist want markers for ?

"Markers" may provide a valuable measure of a variety of physiological or pathological processes within the different tissues of the musculoskeletal system. An understanding of the tissue specificity and metabolism of the putative marker is therefore important.

In the case of bone and joint disease, molecular markers offer an important opportunity to probe disease processes and help our understanding of disease pathogenesis. In the case of bone disease they can, for example, help us explore the coupling of bone formation and resorption, whereas in joint disease, they may help us understand the relationships between inflammation and joint damage, and the linkage between changes in bone, cartilage and synovial disease.

2. What does the practicing clinician want markers for ?

Disease "markers" might be of clinical value in four quite different situations: for the diagnosis of a disease, for assessing disease activity or severity, to predict the prognosis of the condition, or to predict or measure responses to therapy. In the case of the developing field of molecular markers for bone and joint disease, new assays have so far proved more promising for the assessment of disease activity and prognosis, or of treatment responses, than they have for the diagnosis of specific diseases. It may be unrealistic to expect body fluid markers to be diagnostic of joint diseases, where early changes may affect a small part of only a single or a few of the 200 or so joints in the musculoskeletal system.

A marker of progressive joint damage would be particularly valuable in clinical work with both rheumatoid and osteoarthritis. This is because it is difficult to assess whether a joint is undergoing active destruction with any of the currently available clinical, imaging of serological measures of disease.

New molecular markers are not needed for aspects of joint disease that can be assessed well in other ways such as synovial inflammation.

3. How can the clinical value of a marker be validated ?

There are many different aspects of the validity of a test. To the biologist, face validity may be of most importance (i.e. the biological rationale of the assay), but to the clinician, criterion validity is crucial (i.e. whether the test measures what you think it should be measuring). It is already clear that face validity and criterion validity do not necessarily coincide. For example, assays of keratan sulfate (KS) have been shown to be a "marker" of cartilage degradation in a variety of in vitro situations and animal models. However, serum KS levels do not predict loss of cartilage in human arthritis.

The need for a marker of progressive joint damage presents special problems with criterion validity - i.e. the lack of a good "gold-standard" to which the measure can be related. Radiographic changes are insensitive and very slow to change. Developments in MRI may aid the validation of body fluid markers as measures of joint damage.

Once a measure has been shown to have criterion validity—as a measure of joint damage for example—the construct and content validity (change with disease change, and generalisability of the test) become important, as does the discriminant ability of the test, i.e. its sensitivity and ability to detect small changes.

In order to explore the validity of new markers, it is important to make careful selections of patient groups for study, and to design clinical protocols that can

answer specific questions. Human disease situations in which a major change in a condition is induced may be particularly valuable, such as investigating patients before and after an intervention such as osteotomy, or trauma as in the anterior cruciate ligament rupture model of osteoarthritis. The widespread application of molecular marker assays to groups of patients, without standardization of methodology or specific hypothesis testing is likely to cause more harm than good.

4. The need for standardization of molecular marker assays

Many new marker assays have been developed over recent years, and they are being used in many different clinical studies. In addition to the need for the clinicians to standardize their outcome measures, and to design careful, hypothesis driven protocols, it is important that the assays themselves are standardized.

In the future, we will need to use similar approaches to those that have helped standardize some of the immunological assays used in bone and joint disease. Protocols for the collection and storage of body fluid samples are needed, and standard antibodies will need to be produced. Different laboratories can then compare the results of their assays, using aliquots of standard body fluid samples.

Before this is worthwhile, basic and clinical scientists need to collaborate in the selection of markers. Factors to be taken into account will need to include face validity, knowledge of marker metabolism and clearance, the clinical needs, and preliminary clinical data. Similarly, the appropriate assay techniques and antibodies to be used in clinical studies need to be carefully selected through collaborative meetings and work.