Osteoarthritis: An Old Disease Cast in a New Light through Greater Understanding of the Human Genome

Rachel Bevan (Meds 2012) and Jason Essue (Meds 2011)
Faculty Reviewer: Dr. Andrew Leask

The successful mapping of the human genome offers the potential to greatly advance our understanding of various disease processes. Osteoarthritis is a disease of particular interest because there is significant morbidity and societal burden associated with this condition. Furthermore, the prevalence of this disease is expected to rise dramatically with the aging of the baby-boomer generation (individuals born between 1946 and 1964), with a concomitant elevation in health care costs in Canada and abroad. Osteoarthritis was previously viewed as a commonplace disease resulting from environmental ‘wear and tear’, that was an inevitable part of aging. However, new advances have demonstrated that osteoarthritis is a surprisingly complex multi-factorial disease that is affected by both environmental and genetic variables. This review discusses some of the environmental and genetic factors that influence the progression of osteoarthritis. Recent advances in biomarkers that are associated with increased disease risk are also discussed. Finally, the potential impact of genetics on both early diagnosis of disease, and prediction of how a patient will respond to a particular pharmacological treatment is presented.

Introduction

Ever since the discovery of the three-dimensional structure of DNA\(^1\) the field of genetics has intrigued both scientists and the general public alike for its potential impact on disease diagnosis. Indeed, the concept of genetics as a primary player in the role of diseases is assumed by most of the lay public today. One of the goals of understanding genetic influences in the disease process is to aid in treatment of patients through the development of a personalized medical approach. Predictive genetic testing is one area that has garnered great interest in the past decade, especially since the sequencing of the human genome.\(^2\) The goal of predictive genetic testing is to determine if an individual is likely to develop a disease state based upon the presence/absence of particular genes or biomarkers. Although challenging, determining how best to treat a patient based on their genetic make-up is simplified in the cases where a particular gene or mutation is the direct cause of particular disease. For example, cystic fibrosis is an autosomal recessive disease; for the disease to occur, each copy of the CFTR gene must have a mutation that renders the resultant protein non-functional.\(^3,4\)

However, in many cases the disease process is not straightforward; the presence of a particular genetic variant doesn’t necessarily lead to the disease. Instead, diseases, especially those of a chronic nature, are multi-factorial, resulting from a complex set of interactions among many different genetic and environmental factors. In general, there is no single gene that causes the disease, but genetic factors are likely to contribute to an increased probability of developing the condition. Thus, it is imperative to develop methods to identify individuals at risk.

Osteoarthritis (OA) is one example of a multi-factorial disease that is influenced by genetic and environmental variables. OA was previously viewed as a commonplace disease resulting from environmental ‘wear and tear’ that was an inevitable part of aging.\(^5\) However, new
advances have demonstrated that OA is a surprisingly complex multi-factorial disease that is affected by both environmental and genetic variables. This review discusses some of the environmental and genetic factors that influence the progression of OA. Recent advances in biomarkers that increase disease risk are also discussed. Finally, the potential impact of genetics on both early diagnosis of disease, and prediction of how a patient will respond to a particular pharmacological treatment are presented.

**Disease Burden of Osteoarthritis**

OA affects 10-12% of the adult population in North America and is a leading cause of pain, physical disability, and use of health care services. OA is a degenerative disease characterized by the early deterioration of articular cartilage from within the joint, and later by complete loss of articular cartilage, damage to the subchondral bone, severe deformities, and disabling pain. The consequences of disease are detrimental to overall quality of life in many ways, including fatigue, reduced income due to impaired labour force engagement, hospitalization, surgery, medication side effects, family instability, and decreased social participation. Alarming, the number of people affected by OA is expected to increase dramatically as the baby-boomer generation ages. For instance, in Canada approximately 3 million people are currently living with OA. This figure is expected to rise to 5 million by the year 2026. Unless better methods are developed to diagnose and treat OA, the direct and indirect costs associated with caring for such individuals will rise substantially with broader implications for the overall economic burden.

**Risk Factors for Osteoarthritis**

The risk factors for OA can be classified as either systemic or local-mechanical. The local-mechanical risk factors are then further classified as intrinsic or extrinsic to the joint in question. In accordance with this model, OA is widely believed to be the result of local risk factors acting within the context of systemic susceptibility. The intrinsic local-mechanical risk factors for OA include joint alignment, muscle weakness, and proprioception. Extrinsic local-mechanical risk factors include physical activity, occupations involving strenuous repetitive motions, obesity, and joint injury. A number of systemic risk factors have been reported, including age, sex, ethnicity, bone density, nutritional factors, and genetic factors.

**Biomarkers in Osteoarthritis: Targets for Personalized Medicine**

At present, the best way to characterize OA involves measuring joint space narrowing on radiographs, evaluating clinical symptoms suggestive of OA (i.e. pain), and direct arthroscopic visualization of the articular surfaces within the joint capsule (particularly in the case of knee OA). However, these methods are often only able to detect OA after irreparable joint damage has occurred. Thus, there is a need to identify more sensitive methods to detect OA prior to irreversible joint damage, in order to improve morbidity outcomes. In particular, there is great interest in identifying specific biological markers that will reflect the biological changes that occur within the joint during the early phases of the OA disease process. Since OA primarily affects bone, cartilage, and synovial tissue, it is logical to consider the structural molecules derived from these tissues as potential biological markers of OA. Notable candidate biological markers include:

1. N-terminal cross-linked telopeptide of type I collagen (NTX-I) as a marker of bone degradation;
2. C-terminal cross-linked telopeptide of type II collagen (CTX-II) as a marker of cartilage degradation;

It should also be noted that the biomarkers described above represent the net outcome of disease and do not indicate how the disease originated, nor do they represent targets for drug intervention in OA. However, these biomarkers...
are useful to clinicians to stage the disease process in patients. Furthermore, biological markers may enable clinicians to differentiate patients based on risk of experiencing rapid progression of OA as these individuals will be in greatest need of targeted early intervention.\textsuperscript{16} Biomarkers are also expected to advance the process of drug development by providing cost-effective and sensitive indicators of a drug’s effectiveness.\textsuperscript{15} Unfortunately, a single specific biological marker has yet to emerge to fulfill these lofty objectives, and it seems likely that it will be necessary to use a combination of markers in order to adequately characterize OA. Additionally, practical issues such as tissue specificity, clearance rates, potential circadian variations,\textsuperscript{14} and differences due to gender, ethnicity, and age need to be resolved prior to widespread acceptance of candidate biological markers.

It is also important to highlight that recent genome-wide linkage studies have identified several gene variants that appear to predispose to OA.\textsuperscript{14,17} In these studies, researchers relied upon microarrays capable of assessing 300,000 or more single-nucleotide polymorphisms (SNPs) in a given DNA sample. These microarrays examined interpersonal differences in inherited genetic variability by comparing the prevalence of gene variants among patients who have a given disease with controls who do not have the disease.\textsuperscript{18}

Several chromosome regions and genes have been identified that are associated with OA prevalence (FRZB, BMP2, CD36, PTGS2, and NCOR2) or OA progression (CILP, TNFRSF11B, and ESR1; ADAM12 is associated with both prevalence and progression).\textsuperscript{14,17} Most of the genes identified encode proteins that are involved in signal-transduction pathways.\textsuperscript{14} This work should help to clarify the relationship between genetic susceptibility, the genomic expression of aberrant genes that predispose to OA via biological markers, and the actual manifestation and rate of onset of the disease process. More significantly, further clarification of such pathways in preclinical and clinical models of OA will lead not only to the identification of new clinically relevant biological markers, but help achieve the ultimate goal of OA researchers in both academia and industry, which is to develop novel drug targets and therapies to combat this debilitating condition.\textsuperscript{14,15,17}

**Predictive Genetic Testing**

OA is a good example of a multi-factorial disease with a large societal burden for which predictive genetic testing could play a role in the future. In general, the goal of predictive genetic testing is to identify asymptomatic individuals at risk for disease based on particular biomarkers and/or genes that have been linked to predisposition to a particular disease. This differs from the majority of current medical tests, which are diagnostic, and thus seek to determine the etiology of a patient’s *current* disease state. Thus, there is a fundamental uncertainty as to whether or not the disease state will develop and how severe the disease will manifest if it does in fact develop. This is especially true in complex multi-factorial diseases such as OA where it is difficult to make accurate predictions due to the influence of environmental factors.\textsuperscript{2}

**Pharmacogenomics**

Genetic diagnosis and biomarker testing is important not only for current and future disease states, but also in predicting how an individual might respond to particular medications. The study of the genetic basis of differential drug response has been termed ‘pharmacogenomics’. In general, many genes play a role in pharmacokinetics and pharmacodynamics of various drug responses. Pharmacogenomics research seeks to elucidate the genetic basis of how individuals or sub-populations respond to different drugs in terms of side-effects, toxicity, and drug efficacy. Such knowledge can lead to the development of biomarker tests to predict which individuals will respond well to particular drugs.\textsuperscript{19,20} It might also help in targeting drug development to specific sup-populations that may be more likely to respond to a particular therapy.\textsuperscript{21} In general, knowledge of the genetic factors that relate to drug response will provide a powerful tool for treatment in the future.\textsuperscript{19,20}
However, the development of detailed genetic tests that can be linked to a population-specific drug response is quite complex. A number of steps are involved, including:

1. Identification of genes that are involved in the drug response (e.g. pharmacokinetics and pharmacodynamics of the drug);
2. Determining differing variants of these genes;
3. Determining whether or not these different genetic variants correlate with a differential drug response.

One recent success of the field is the drug warfarin, whereby specific variants of particular genes were found to correlate with response to warfarin at particular doses.\(^{22}\) As of August 2007, the FDA has updated prescribing information for warfarin to include the information that the genetic make-up of a patient may influence how they respond to warfarin.\(^{23}\) However, it is not clear that the benefits out-weigh the costs. In a recent study on non-valvular atrial fibrillation, it was determined that there is little benefit to genetic testing for warfarin dosing, based on an estimated cost of $400 (US) per genetic test, except in patients at the highest risk for hemorrhage.\(^{24}\) This is likely to change as the costs of genetic testing decrease with the advancement of sequencing technologies\(^{25}\), however it does call into question the cost-effectiveness of personalized medicine.\(^{26}\)

**Personalized Medicine: Is it Realistic?**

The goal of personalized medicine is to provide individualized treatment to patients, based partially on the knowledge of the genetic profile of an individual (including genes/biomarkers of disease state) and knowledge of how patients might respond to different medical treatments.\(^{27,28}\)

The complexities of moving towards a personalized medicine approach are immense. Cost-effective genome sequencing techniques\(^{25}\), methods for analyzing genome-wide gene/protein/mRNA expression profiles and interaction related to disease states\(^{23}\), and the complete human haplotype mapping project (the HapMap project which provides a complete listing of human SNPs)\(^{27,30}\) will help in the acquisition of knowledge about the genetic basis for human disease. However, even these advanced techniques are not sufficient to deal with problems like incomplete penetrance, whereby presence of the disease allele(s) does not necessarily mean that that disease will occur.\(^{31}\) Furthermore, models for the genetic basis of disease should account for the effect of epigenetic control of gene expression.\(^{24}\) Epigenetic control of gene expression (and problems with epigenetic control) have been shown to play a fundamental role in both Prader-Willi and Angelman diseases\(^{33}\), and is thought to be implicated in the disease process for many diseases, including auto-immune diseases and psychiatric disorders\(^{34}\).

Realizing the full benefits of personalized medicine and predictive genetic testing is still far in the future.\(^{29}\) Nonetheless, it is important to be aware of these rapidly evolving fields as they hold the potential to revolutionize medicine.

**References**

7. Cunningham LS, Kelsey JL. Epidemiology of musculoskeletal impairments and associated