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Chondrocyte genomics: implications for disease modification in osteoarthritis

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Advances in genomic technologies have made genome-wide-association and gene-expression studies a reality. Despite technical and analytical challenges, the application of genomic technologies to osteoarthritis research will lead to a better understanding of the disease at the molecular level. Functional genomics will identify genes involved in the chondrocyte response to cartilage injury and cartilage repair, and will help clarify the role of chondrocytes in arthritis onset, progression and outcome. Systems biology will enable researchers to develop a full portrait of osteoarthritis, a complex and multifactorial disease that involves not only articular cartilage but also synovium, synovial fluid, subchondral bone and peripheral blood. Ultimately such an approach will result in novel diagnostic and therapeutic targets and better disease management.

Osteoarthritis (OA) is the most common form of arthritis and affects ~12% of the population in the West. Despite the high prevalence of OA, to date no treatment can prevent, alter or halt the progression of the disease. Therapy mainly involves symptom management [1]. Early stage OA is often managed with nonpharmacological therapies, such as exercise, weight control and supplements such as glucosamine sulfate and chondroitin sulfate. Intermediate OA is treated with simple analgesics, with nonsteroidal anti-inflammatories such as ibuprofen, with intra-articular injection of either steroid or hyaluronic acid-like products, or with arthroscopic treatment. Severe or late-stage OA is usually managed surgically with reconstructive surgery [1].

Obstacles to the development and evaluation of disease-modifying drugs for OA (DMOADs) include a lack of early OA diagnostic tools that can identify early OA, the stage at which disease-modifying drugs are most likely to be effective. The lack of outcome measures that are more sensitive than radiography makes it difficult to assess drug efficacy in a sensitive and timely manner. We also lack validated therapeutic targets for OA, a complex disease of unknown etiology and largely unknown pathogenesis [2].

Loss of articular cartilage is the hallmark of OA. Cartilage integrity is maintained by only one cell type, the chondrocyte, which plays a crucial role in maintaining cartilage matrix homeostasis. The current hypothesis of OA pathogenesis is that the disease occurs as the result of an imbalance between chondrocyte anabolic and catabolic activities. OA progression involves not only articular cartilage but also other tissues in the joint, such as the synovium and subchondral bone. A complete knowledge of OA will involve understanding the contribution from these tissues (Figure 1).

Recent advances in genomic technologies have shifted the focus of OA research from biochemical aspects of articular cartilage matrix destruction, and from analysis of one or a few genes at a time, to chondrocyte genomics or 'chondrogenomics'. In fields such as cancer, genomics, especially functional genomics using gene profiling, has provided important insights [3–5]. We have reason to be optimistic that genomic approaches will similarly provide insights, at the molecular level, to OA. This review will focus on genomic technologies, the genetics of OA, the status of chondrogenomics and on challenges and the future.

Genomic technologies

Completion of the first draft of the human genome raised expectations that genomic technologies would lead to better health management and improve the treatment of disease. Two major genomic approaches are currently used for studying complex diseases such as OA (Figure 1). The first of these, the genetic approach, characterizes the genetic basis of a disease phenotype.

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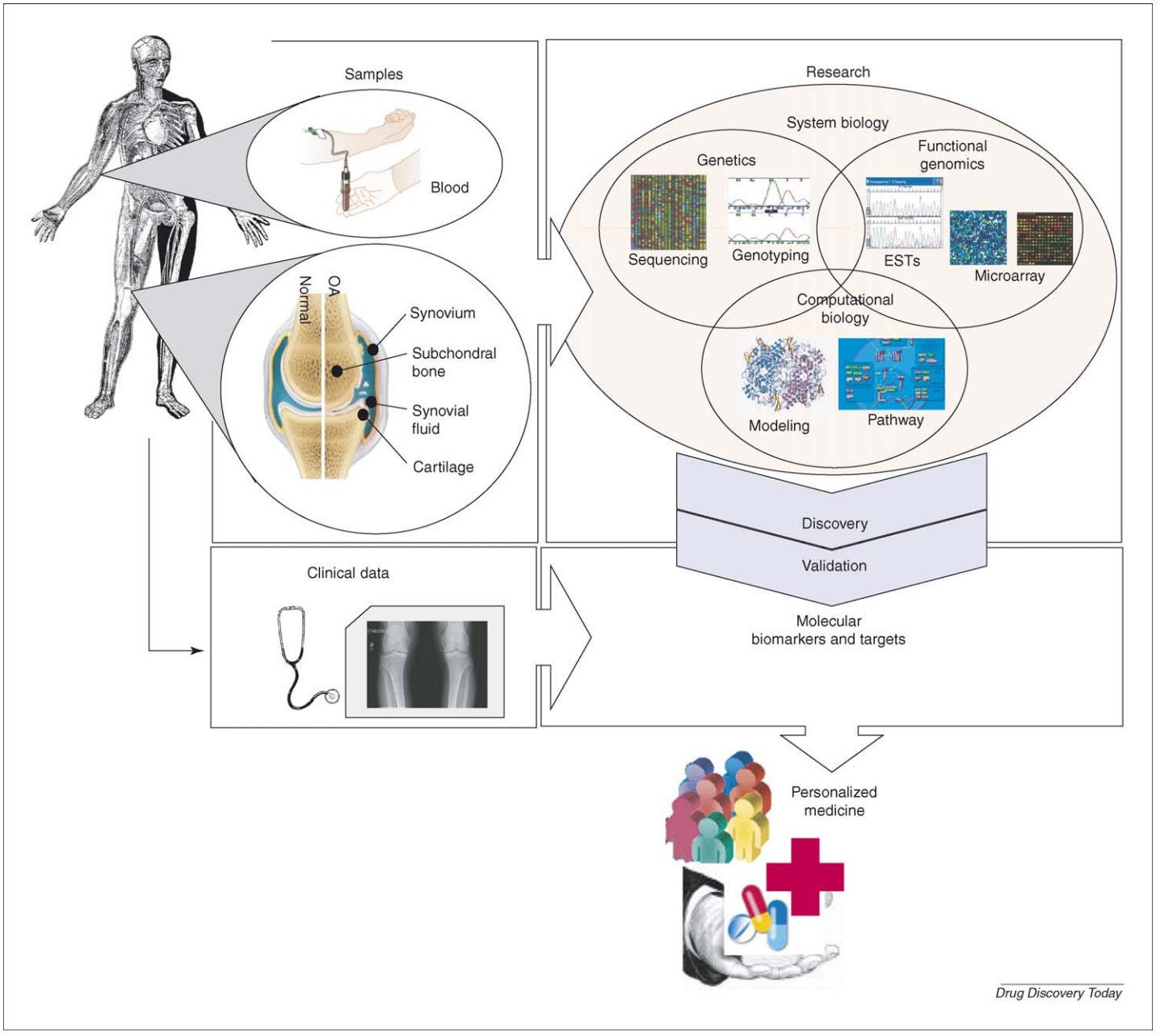

FIGURE 1

Schematic representation of comprehensive genomic approaches for arthritis. Normal or osteoarthritis (OA) samples (including peripheral blood, articular cartilage, synovium and subchondral bone) can be analyzed with genetic (sequencing, genotyping) and functional-genomic approaches [expressed sequence tags (ESTs) and microarray]. Data processing and computational biology tools will be applied to interpret such data, gaining insights into biological process and mechanisms of OA. In conjunction with the clinical data of the patients, these molecular elucidations of identified targets will drive the identification of new molecular biomarkers for diagnosis or disease subtyping, and novel candidates for disease-modifying drugs. Ultimately, this systems biology approach will allow personalized medicine to become a reality in the future.

Methods include linkage studies that involve estimation of the recombination between two loci [observed and unobserved (the disease locus)] and association studies that test whether single-locus alleles or genotype frequencies differ between cases and controls. The deposition of millions of single nucleotide polymorphisms (SNPs) into public databases, combined with rapidly improving genotyping technology, has made genome-wide-association studies possible [6]. Issues regarding these methods, such as power, efficiency, and data interpretation, are discussed and reviewed by Hirschhorn and Daly [7].

The second approach, functional genomics, studies the expressed genome of a tissue of interest. It is estimated that ~23,000 genes are represented in the human genome [8]. Functional genomics poses questions about which genes are expressed in which tissue, and the differences in gene expression level that can be found in different physiological and pathological states of the tissue.

The functional genomic approach that is widely used involves the use of expressed sequence tags (ESTs) and microarray technology. The EST approach involves constructing a cDNA library to obtain single-pass sequences from randomly picked cDNA clones.

The ESTs represent the gene transcript population and reflect transcript abundance (according to EST frequency in the library) [9]. In addition, genes differentially expressed can be identified by comparing relative EST frequencies in normal and diseased tissues, or different disease stages. The derived cDNA clones can also be used for downstream validation and functional studies.

Microarray technology measures the expression levels of thousands of genes simultaneously. Two types of microarrays (cDNA and oligonucleotide) are available, with genome-wide oligonucleotide arrays being currently more of a standard. cDNA microarrays use PCR-derived elements: aliquots from two mRNA samples are fluorophore-labeled and used to probe the target elements in a competitive hybridization reaction. The ratio between the two fluorophores detected for any given element defines the relative mRNA amount in the original two samples. Affymetrix oligonucleotide arrays are fabricated by *in situ* synthesis of oligonucleotides. Biotinylated cRNA is synthesized from total RNA, and labeled cRNA is quantified by hybridization to the GeneChips®. To facilitate the sharing of microarray data, the Microarray Gene Expression Data (MGED) Society has established standards for microarray data annotation and exchange, referred to as MIAME – minimum information about a microarray experiment (http://www.mged.org/miame) [10]. The two platforms have recently been reviewed [11,12].

ESTs and microarray analysis can generate comprehensive lists of differentially expressed genes. The challenges are to identify the relationships between and among genes, to recognize functional pathways, and to relate or compare genomic findings with publicly available data. To address these challenges, web tools have been developed to facilitate data interpretation, some of them being discussed in this paper. The Gene Ontology Consortium develops controlled vocabularies to describe gene attributes (biological processes, cellular components and molecular functions), so that the data from different species can be compared (http://www.geneontology.org) [13]. The database for annotation, visualization and integrated discovery 2.0 (DAVID 2.0) ranks functional categories, based on co-occurrence, with sets of genes in a gene list. This tool can rapidly identify biological processes, molecular functions and pathways that are over-represented in a gene list, relative to the representation within the proteome of a species (http://apps1.niaid.nih.gov/david/upload.asp) [14]. PubGene 2.5™ database and analysis software (http://www.pubgene.com/products.htm) [15] identifies ways in which genes or proteins of interest are related (network browser module). New generation tools include: Reactome, a curated resource of core pathways and reactions in human biology (http://www.reactome.org) [16]; HumanCyc (http://www.humancyc.org), a database for human metabolic pathways; and PANTHER (protein analysis through evolutionary relationships) (http://www.pantherdb.org/), a database with 83 pathways. These tools will help identify disease-relevant genes and pathways, and prioritize targets.

Genetics of osteoarthritis

Over the past few years, several genes have been associated with various types of OA (Table 1), including most recently asporin (ASPN), frizzled-related protein (FRZB) and estrogen receptor 1 (ESR1). Asporin, first characterized by Lorenzo *et al.* [17], is highly expressed in osteoarthritic cartilage. Asporin is a component of the extracellular matrix (ECM), and it acts as a negative regulator of chondrogenesis by inhibiting transforming growth factor-β via direct contact [18]. A case-control association study, by Kizawa *et al.* [18], of asporin in a population of Japanese knee OA patients showed that an allele with 14 aspartic acid repeats (D14) was significantly overrepresented in OA as compared with the allele with 13 aspartic acid residues at the N-terminus (D13). The study also showed that D14 frequency increased with disease severity [18]. The same research group found 19 asporin SNPs by screening 48 Japanese OA patients over a 33.4 kb genomic region [19]. The frequency of genotypes identified was determined by genotyping 96 Japanese OA patients. Five haplotypes comprised three SNPs (i-ASPN-5, i-ASPN-21 and i-ASPN-17) covering 90% of the studied population [19]. A UK study, by Mustafa *et al.* [20], of 1995 Caucasians found that the D14 allele of asporin was more common in OA patients, but was only significant in men with hip replacements. Rodriguez-Lopez *et al.* [21] studied the genetic association (found by Kizawa *et al.*) in a population of Spanish Caucasians, including patients who had undergone joint-replacement surgery for primary OA of the hip (n = 303) or knee (n = 188), as well as 233 patients with hand OA and 294 controls. No significant difference in the OA-associated allele reported by Kizawa and aspartic acid residues of asporin between OA and non-OA in European Caucasians was found [21]. A study of D-polymorphisms of ASPN in a Greek population determined that a D15 allele could be a risk factor for OA [22]. The findings of these three European studies suggest that D14 polymorphism might not be the major OA susceptibility factor in European Caucasians.

TABLE 1

Examples of known genetics of osteoarthritis

Symbol	Chromosomal location	Disease phenotype	Expression in osteoarthritis	Therapeutic target
ASPN	9q21.3-q22	Osteoarthritis (OA) of the knee and hip [17]	Upregulated [17]	Possible
COL2A1	12q13.11-q13.2	OA with mild chondrodysplasia [56–58]	Upregulated [59]	NA
ESR1	6q25.1	Knee OA [24]	No change [60]	Possible
FRZB	2q31-q33	Hip OA in females [23]	NA	Possible
IL1R1	2q12	Distal interphalangeal OA [61]	NA	Yes
MATN3	2p24-p23	Hand OA [62]	NA	NA
MMP13	11q22.3	OA [63]	Upregulated [31]	Yes

Abbreviations: ASPN, asporin; COL2A1, collagen type II alpha 1; ESR1, estrogen receptor 1; FRZB, frizzled-related protein; IL1R1, interleukin-1 receptor type I; MATN3, matrilin-3; MMP13, matrix metalloproteinase 13 or collagenase 3; NA, not available.

Another gene, *FRZB*, which encodes for secreted FRZB (also known as sFRP3), is involved in skeletal development and negative regulation of the Wnt receptor signaling pathway, the inhibition of which is important for maintaining the integrity of the cartilage–bone junction [23]. A variant of FRZB, R324G, could lead to the development of occult structural hip dysplasia, which manifests later in life as hip OA [23]. In an SNP-association study, an Arg324Gly substitution (R324G) at the C-terminus of FRZB was associated with hip OA in females. Furthermore, a combination of the R324G SNP and a mutation of another highly conserved Arg residue, Arg200Trp (R200W), was reported as a strong risk factor for primary hip OA in females [23].

ESR1 is expressed in articular chondrocytes and bones, and has several known DNA variants. Bergink *et al.* [24] conducted an association study exploring the links between three ESR1 allele haplotypes (px, PX and Px) and radiographic knee OA. The group found the PX haplotype was significantly more frequent in radiographic OA ($p < 0.01$) [24]. These intriguing genetic association studies indicate several future targets for disease modification (Table 1).

Functional genomics

Expressed sequence tag approach

Although the EST approach has passed its prime time, large-scale single-pass sequencing of randomly selected cDNA clones from specific libraries is a powerful approach for gene identification, and has provided valuable information for gene expression in specific tissues. Today, >6,000,000 human ESTs have been deposited into the dbEST division of GenBank (http://www.ncbi.nlm.nih.gov/GenBank/index.html).

Kumar *et al.* [25] were first to report on normal- and osteoarthritic-cartilage cDNA libraries. This group analyzed 10,000 ESTs (5000 ESTs from each library) and reported several interesting findings. First, two novel homologs of the known proteins were identified in this study: procollagen C-proteinase enhancer protein-2 (PCPE-2) and GalNAc transferase. PCPE-2 is related to PCPE, which acts as an enhancer for bone morphogenetic protein (BMP) 1 during collagen type I–III C-terminal processing, and is probably involved in type II collagen processing in cartilage. GalNAc transferase might be involved in the O-linked transfer of *N*-acetyl galactosamine to proteoglycans. The group also identified, in cartilage, several known genes whose expression had not been previously reported in cartilage, including connective tissue growth factor (CTGF), CTGF-ligand and clusterin. Finally, of the 20 genes most abundantly expressed in normal and osteoarthritic cartilage, six ECM genes were found in normal and osteoarthritic cartilage. Three of the six ECM genes were upregulated (more-abundant in relative EST copy number) in osteoarthritic cartilage; they are cartilage oligomeric matrix protein, fibronectin and proline–arginine-rich end leucine-rich repeat protein (PRELP). This study demonstrates that in-depth sequencing of ESTs can identify known, as well as novel, genes that could have a role in OA, and it shows that comparing gene expression in normal and osteoarthritic cartilage could identify novel diagnostic and therapeutic targets [25].

In a recent, similar but more comprehensive, set of studies of human cartilage, a database was established of ~117,000 ESTs sequenced from fetal cartilage [9], normal cartilage and surgically well-characterized mild and severe osteoarthritic cartilage [26]. In a study in fetal cartilage, several genes involved in cartilage development were identified, including insulin-like growth factor-II, its receptor, its binding proteins, CTGF and fibroblast growth factors. In the normal and osteoarthritic cartilage EST study, we reported that fibronectin and PRELP were upregulated in OA, as reported by Kumar [25].

Following the development of a transcriptome map, it was estimated that between 13,000 and 16,000 genes were expressed in human cartilage. The study identified several genomic regions that are transcriptionally 'hot' (chromosomes 3 and 15) or 'cold' (chromosomes 14, 19, 22 and Y) in cartilage. We have proposed two possible mechanisms of chromatin domain-specific transcriptional control: histone-deacetylase-mediated chromatin repression and Swi/Snf-mediated chromatin activation in cartilage. This study was the first comprehensive mapping of human-cartilage-expressed transcripts to the human genome and should prove useful in elucidating the biology of cartilage and the pathogenesis of arthritis [27].

Other recent EST efforts have also provided interesting results. Tagariello *et al.* [28] generated 4748 clones from a human growth plate cartilage cDNA library; the candidate genes identified will be of value for the diagnosis and treatment of skeletal disease. Another study by Jung *et al.* [29] established a set of >2000 genes expressed in a human chondrocyte HCS-2/8 cell line, thereby providing a framework for understanding chondrocyte growth and differentiation. Meng *et al.* [30] reported a group of novel genes upregulated in early- and late-stage experimentally induced temporomandibular joint (TMJ) OA. These genes include aquaporin 3, secreted phosphoprotein 2, nephroblastoma overexpressed gene, dickkopf homolog 3 and Egl nine homolog 3 [30]. Because the TMJ is not a typical diarthrodial joint, for the reason that the articulating surfaces are fibrocartilaginous rather than hyaline, the genes identified in this study might be peculiar to TMJ OA progression, rather than showing the common response of hyaline cartilage to OA. Each of these studies has contributed greatly to our understanding of chondrocyte biology and pathology in OA.

Microarray approach

Since the mid-1990s, EST databases and cDNA clones have provided the raw material for cDNA microarray technology. The early 2000s saw the beginning of cartilage functional genomics research. Aigner and colleagues [31] published the first cDNA microarray study in OA. This group screened 1000 genes in normal and osteoarthritic cartilage and found that, of the matrix metalloproteinases (MMPs), MMP-3 was strongly expressed in normal and early degenerative cartilage and was downregulated in the late stages of disease; MMP-13 and MMP-2 were only significantly detectable in late-stage osteoarthritic cartilage samples [31].

Stokes *et al.* [32] provided another example of the cDNA microarray approach to the study of chondrocytes. In a study of human fetal epiphyseal chondrocytes (HFCs) the group found that transcription factors, twist homolog 1 (TWIST) and hypoxia-inducible factor-1 α (HIF-1α), and a cellular adhesion protein gene, cadherin 11, were markedly regulated in response to differentiation and dedifferentiation. HIF-1α was upregulated in differentiated HFCs, whereas TWIST and cadherin 11 were upregulated in

dedifferentiated HFCs. These genes were also expressed by normal and osteoarthritic adult cartilage and chondrocytes. In addition, the HFC gene expression profile also identified many genes that, at the time, were not known to be expressed by chondrocytes [32].

Our laboratory constructed an in-house cDNA microarray (ChondroChip™) using cDNA clones derived from our four human cartilage cDNA libraries (described previously). The array was used to study the effect of β-2 microglobulin (B2M) on chondrocytes. B2M is a molecule that was identified from a previous EST study [33]. It was found that B2M upregulated several genes potentially implicated in OA pathogenesis, including chitinase 3-like 2 (YKL-39), collagen type III, lumican and manganese superoxide dismutase [33]. The cDNA microarray approach to degenerative arthritis research was recently reviewed by Aigner *et al.* [34].

The Affymetrix GeneChip®, the most widely used microarray platform, has also been applied to cartilage and OA research, so far mainly in animal models. Affymetrix U34A was used in a rat model to compare diaphyseal femoral fractures healing with intramedullary nail fixation and internal plate fixation. Cartilage, cell division, inflammation and the acetylcholine receptor transcripts were significantly upregulated in the nails-treated group [35]. In another example, the Affymetrix canine 23,836 probeset GeneChip® identified 528 genes that were significantly upregulated or downregulated in response to mechanical damage [36]. One of these genes, *mig-6* which encodes a protein involved in signal transduction (known as ErbB receptor feedback inhibitor 1), was found to be increased fourfold in cartilage in response to mechanical impact *in vitro*, as assessed by quantitative real time (RT)–PCR. Furthermore, the transcription level of *mig-6* was fourfold higher in canine hip degenerated cartilage than in disease-free cartilage [37]. This finding implies that *mig-6* might be involved in mechanically induced OA.

In a human Affymetrix HG-U95Av2 array study, Shi *et al.* [38] investigated the mechanisms underlying the differential effect of interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) on gene expression in the human chondrosarcoma cell line SW1353. The expression pattern of proIL-1β, MMP-1 and MMP-13 in chondrocytes was differentially regulated when stimulated with proinflammatory cytokines. Moreover, IL-1, but not TNF-α, induces IL-6, BMP-2 and cyclooxygenase-2 (COX-2) expression [38].

Most recently, Sato *et al.* [39] profiled human knee osteoarthritic cartilage samples using Affymetrix GeneChip® technology. With five pairs of intact and five pairs of damaged regions of osteoarthritic cartilage, 151 transcripts were commonly expressed and showed at least twofold differences in expression. Genes expressing proteins such as sex-determining region Y-type high mobility group box 11 (SOX11), TNF-α-induced protein 6 (TNFAIP6 or TSG6) and transforming growth factor β induced 68 kd (TGFBI) were highly expressed in damaged regions, and genes such as *chordin-like 2* were significantly downregulated in damaged regions [39].

Challenges

Complexity of osteoarthritis

The American College of Rheumatology defines OA as a 'heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins'. To distill one molecular gene signature from these several OA conditions is a challenge.

Differences in cartilage samples from various patients will affect data interpretation; matching a sample with its phenotype is crucial. Biological variability hinders statistical evaluation and the establishment of a common gene signature. However, clustering analysis of enough control and disease profiles might enable important clinical subtypes to be identified, which, in turn, can be used to predict responders and nonresponders of defined therapeutic regimens, establishing cohorts for clinical trials. Gene expression monitoring by microarrays was used to distinguish acute myeloid leukemia and acute lymphoblastic leukemia [40]. This study showed that gene expression signature can identify subsets of diseases and it would be hoped that, in a similar manner, one might be able to identify disease subsets in OA.

Lack of early and sensitive diagnostic tools

Diagnosis, especially at early disease stages, has long been an issue in osteoarthritic cartilage degeneration research and patient management. The development of new disease-modifying drugs will be facilitated by early diagnostic and OA-progression biomarkers. Early diagnosis and treatment are the goals of the Osteoarthritis Initiative Program sponsored by the NIH. Despite intensive research efforts, current biomarkers are not reliable for clinical diagnostic use [41].

New emerging technologies, however, are beginning to show promise for early diagnosis – improved magnetic resonance imaging (MRI) techniques [42] and a blood-based gene expression biomarker set recently proposed by our laboratory [43]. A blood gene signature was demonstrated to be capable of distinguishing individuals with early OA from control subjects (Figure 2a) [43]. Nine biomarkers have been validated that, in combination, yielded receiver operating characteristic (ROC) curve areas of $\geq$0.90 (Figure 2b) [43]. Three of the nine biomarkers have previously been linked to osteoarthritic cartilage biology: TNFAIP6 (TSG6) [44], IL-13 receptor α [45] and early growth response 1 [46]. This study indicates that the panel of nine genes expressed by peripheral blood cells could have clinical utility for detecting early knee OA.

Genomic technologies

Although microarray technology for gene expression analysis is widely used, issues remain that still need to be addressed. Reproducibility across platforms, for example reproducibility between oligonucleotide GeneChips® and spotted cDNA arrays, has yet to be resolved. A recent report from Larkin and colleagues [47] showed encouraging consistent results for >90% of the genes that were common to Affymetrix GeneChip® and cDNA arrays. Important factors that will improve the reproducibility include: (i) recent advances in the two platforms; (ii) a consistent annotation method; (iii) a log2 ratio of gene expression; and (iv) amplified RNA as a starting material [48]. Although discrepancies exist in gene expression analysis between laboratories and across platforms, most biological themes and pathways identified could be reproducible if standardized methods were followed [49–51].

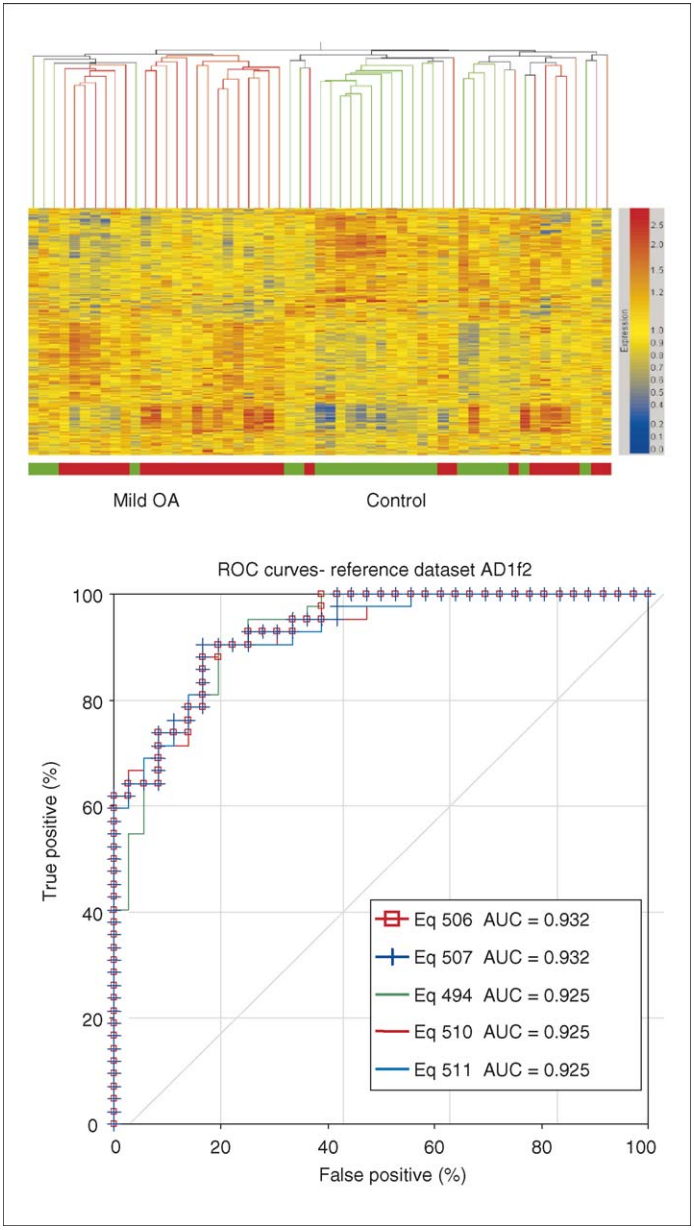

FIGURE 2

Blood gene expression profiling identifies mild knee osteoarthritis. **(a)** Comparison of blood gene expression profiles from 25 controls and 32 mild knee osteoarthritis (OA) subjects. **(b)** Nine biomarker combinations give receiver operating characteristic (ROC) areas >0.90 in a training set with 78 samples [43]. This figure presents the top five ROC curves for biomarker combinations that successfully discriminate mild OA (n = 42) from control samples (n = 36) in the reference dataset AD1f2. Abbreviation: AUC, area under the curve.

Data analysis methodology represents another significant issue. Important aspects of microarray analysis have been reviewed by Allison *et al.* [52]. The key consensuses for microarray experiment design are replicates, sufficient sample size and avoiding confounding extraneous factors. Robust multiarray analysis (RMA) and its modification, GC-RMA, are considered better methods for the Affymetrix GeneChip® than other alternatives. Fold change alone is not valid for data interpretation, and application of a false-discovery rate is recommended. Cross-validation should be considered for classification. How microarray data are validated is still in dispute; issues are concerned with what to validate, measurement error or sampling variability, and criteria for validation of a finding [52]. In summary, further advances in genomic technology are required to realize the full potential of this technology in biomedical research.

Systems biology

Systems biology is an evolving concept that will enable us to have increased understanding of a complex disease such as OA. OA is not a disease of cartilage alone. It is a disease of the whole joint, and interactions between, and among, the joint components all contribute to pathogenesis. OA could be a systemic disease, with the joint being the site where the disease manifests itself (Figure 1). Our current molecular understanding of OA synovium and subchondral bone (at the molecular level) is limited. The study of the synovium is hampered by the heterogeneity of the cell types involved in the synovial tissue. For example, Oehler *et al.* [53] showed significant T cell and B cell infiltration in OA synovium, suggesting a distinct pathogenetic role for the synovium in osteoarthritic cartilage degeneration. The study of subchondral bone is not practical because it is almost impossible to obtain samples. Compared with cartilage and synovium, peripheral blood is, however, readily available. We have shown that peripheral blood profiling promises new insights for disease diagnosis, disease staging and for monitoring therapeutic efficacy. The challenge for the blood approach is to understand the biology of the blood molecular signature and its relation to local and possibly systemic joint disease.

Another challenge for OA systems biology is to correlate disease phenotype (symptoms) to structural changes (through imaging, e.g. X-ray or MRI) and to molecular gene signatures. Furthermore, interpretation of genetic findings in OA, in relation to functional genomics findings, is needed. A recent study by Hubner *et al.* [54] showed that integration of genome-wide transcriptional profiling and linkage analysis could be another approach to identify genes for an underlying disease. Asporin is an example for OA. Certain asporin SNPs have been shown to be a risk factor for OA (or a subset of OA) and the expression level of asporin has been found to be upregulated in OA [17–22]. However, a study has yet to show the correlation of a positive asporin SNP allele with its expression level in disease.

Conclusions and future

We need disease-modifying drugs for the treatment of OA. Structure-modifying drugs are now targeting catabolic pathways, for example MMPs [55]. Despite the challenges posed by genomic technologies, knowledge gained from functional genomic studies of chondrocytes and synovium in combination with a systems biology approach will help us to identify novel targets for disease modification, as well as better targets for symptom modification. Understanding information generated from chondrogenomics and synovium genomics should lead to more and better targets for local intra-articular disease-modifying therapy. Furthermore, the recent application of peripheral blood gene expression in early OA diagnosis holds the promise of allowing earlier diagnosis than the current X-ray imaging technology allows, possible differentiation of OA subpopulations, and prediction of therapeutic responses. Advances in early diagnosis,

disease subgroup identification, prediction of responders to therapeutic regimen and discovery of novel targets for disease modification hold the hope for future personalized medicine for OA (Figure 1).

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