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REVIEW

Gene Expression Profiling Studies Using Microarray in Osteoarthritis: Genes in Common and Different Conditions

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Abstract

Osteoarthritis (OA), which is characterized mainly by cartilage degradation, is the most prevalent joint disorder worldwide. Although OA is identified as a major cause of joint pain, disability, and socioeconomic burden, the etiology of OA is still not clearly known. Recently, gene microarray analysis has become an efficient method for the research of complex diseases and has been employed to determine what genes and pathways are involved in the pathological process of OA. In this review, OA study results over the last decade are summarized for gene expression profiling of various tissues, such as cartilage, subchondral bone, and synovium in human OA and mouse OA models. Many differentially expressed genes, which mainly involve matrix metabolism, bone turnover, and inflammation pathways, were identified in diseased compared with "normal" tissues. Nevertheless, rare common genes were reported from studies using different tissue sources, microarray chips, and research designs. Thus, future novel and carefully designed microarray studies are required to elucidate underlying genetic mechanisms in the pathogenesis of OA as well as new directions for potential OA-targeted pharmaceutical therapies.

Keywords Osteoarthritis · Gene expression profiles · Articular cartilage · Subchondral bone · Synovium

Introduction

Osteoarthritis (OA), an incurable disease (except by arthroplasty in its symptomatic end-stage), is the most common form of arthritis and as such is the primary cause of knee, hip, and hand joint pain and inflammation in aged people worldwide (Glyn-Jones et al. 2015; Loeser 2017; van der Kraan 2012). OA has been reported to affect more than 37% of people over 60, and is predicted to be the single greatest cause of disability in the general population by 2030 (Dillon et al. 2006; Thomas et al. 2014). Pain and loss of joint function can be debilitating for OA patients and the socioeconomic burden of OA is large (Hiligsmann et al. 2013).The total economic burden for OA was estimated to be 1–2.5% of the gross domestic product in western countries and will rise substantially as the prevalence of OA increases with a greater proportion of the population living longer (Bitton 2009). Despite its high prevalence and substantial public health consequences, the etiology of OA needs to be better understood.

A number of studies have shown that OA is a multi-factorial disease with a strong genetic component; reported heritability estimates range 40–65% depending on the tissue type

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(Jordan et al. 2004; Kraus et al. 2007; Spector et al. 1996). Recently, gene expression profiling (GEP) using microarray has been identified as a promising method to identify changes occurring in the initiation and progression of complex diseases, such as rheumatoid arthritis (RA) and OA (Bauer et al. 2009; Haupl et al. 2010). The identification of gene expression profiles associated with OA can help us to learn more about the pathophysiological mechanisms and related pathways involved in this disease (Tsezou 2014).

This review summarizes findings from GEP studies using microarray technology and based on joint tissue types in OA for the last decade (Table 1) that provide some novel knowledge about the role of genes in the pathogenesis of OA.

Search Strategy and Selection Criteria

We searched PubMed with the search term "osteoarthritis" in combination with the terms "cartilage", "subchondral bone", "synovium", "gene expression profile", and "microarray". We focused on publications between January 2001 and December 2018. Emphasis was placed on articles addressing OA of the knee and hip joints. Review articles were cited to provide readers with a detailed discussion of the topic of this review.

GEP Study in Cartilage of Knee and Hip Joints

During the initial and progressive stages of OA, morphological and histopathologic alterations principally occur in the articular cartilage, including crack formation and cartilage erosion (Pritzker et al. 2006). Thus, the majority of GEP studies were largely focused on articular cartilage samples of OA.

To elucidate the molecular mechanisms underlying cartilage degeneration in OA, Sato et al. (2006) compared differences in gene expression profiles of chondrocytes between intact and damaged regions of cartilage from the same knee in OA patients using high-density oligonucleotide array. Their study demonstrated that 114 differentially expressed genes (DGEs) were commonly detected in all five OA-paired samples with 35 DGEs that were expressed in damaged > intact, while 79 DGEs were expressed in damaged < intact cartilage. Moreover, DGEs such as *SOX11, CCND1, PSAT, P4HA3, UCP2, GALNTL1, TNFAIP6, S100A4, DSCR1, TREM1, TGFBI, CRLF1* (Table 2) that relate to cell proliferation, interstitial collagen synthesis, and degradation inhibition were highly expressed in damaged cartilage compared to intact cartilage. When compared with the results of comparisons between normal and OA cartilage obtained from different individuals in previous gene-related studies, at least seven common genes (*TNFIP6, PRSS11, PTGES, S100A4, FN1, TGFBI, and COL1A2*; Table 2) were highly expressed in the damaged region of OA cartilage (Sato et al. 2006). This result suggested that genetic changes could be observed before any apparent damage to cartilage during the progression from normal cartilage to degenerated cartilage in OA (Aigner et al. 2001; Bayliss et al. 2001; Hu et al. 1998; Li et al. 2005).

Another large-scale GEP study was performed based on 78 samples from human femoral condyles using a custom-made complementary DNA array covering > 4000 genes (Aigner et al. 2006). DGEs were detected and compared between four classification groups (18 normal, 20 early degenerated, 21 mild OA and 19 moderate/severe OA cartilage specimens). A number of anabolic and catabolic matrix genes were found to be upregulated, including *COL1A1*, *COL1A2*, *COL6A1*, *COL9A2*, *COL11A1*, *COL5A1* and *COL15A1* (Table 2), among them, *COL5A1* and *COL15A1* were not known to be expressed in OA before. Another surprising finding was the prominent down-regulation of genes for *SOD2*, *SOD3*, *GPX3*, *tob1* and *btg2* that would significantly increase oxidative stress and cell damage due to an accumulation of oxidatively damaged molecules and changes in phenotype stabilization, all of which could be observed in OA chondrocytes (Bos et al. 2008; Tiku et al. 1999).

To better characterize the cellular events and regulatory pathways involved in OA-induced cartilage destruction, a genome-wide microarray containing 54,613 probe sets was used by Karlsson et al. (2010) to survey gene expression patterns in OA and normal cartilage. One of the first reported comprehensive GEP studies, it demonstrated that 111 genes displayed differential expression in skeletal development and extracellular matrix (ECM) formation between OA and normal cartilage. Besides a higher number of genes increasingly expressed in accordance with results from other reports, the study also identified some new candidate genes that display significantly higher expression, including genes (*CLEC3A*, *CLEC3B*, *CDH11*, *GPNMB*, *CHST11*, *MSX1*, *MSX2*) involved in the bone formation process and genes (*COL13A1*, *COL14A1*, *COL8A2*) encoding collagens in OA cartilage (Aigner et al. 2006; Geyer et al. 2009).

Snelling et al. (2014) sought to avoid the influences of inter-individual or age-related confounding factors, by designing a GEP study to identify OA relevant genes and pathways in damaged and undamaged cartilage from the same knee of patients with anteromedial gonarthrosis, a specific form of knee OA. In their study, 754 DGEs (> twofold, $P < 0.05$ not FDR corrected) were identified, of which 11 genes (e.g., *IL11*, *SOX11*, *DNER*, *GFRA2* and *FGF18*) showed > fivefold up-regulation and 38 genes (e.g., *LAMB1*, *SPARCL1*, *SFRP4* and *MMP13*) showed > fivefold down-regulation in damaged cartilage. Analysis of gene ontology

Table 1 Overview of GEP studies presented in the current review

References	Subject	Tissue type	Control	Samples/confirming methods	Platform/chips
Sato et al. (2006)	Human OA of knee	Cartilage from the same joint	Damaged vs. intact cartilage groups	9 paired samples, 5 paired for microarray/**4 paired for *RT-qPCR***	Affymetrix/Human U133A and U133B array
Aigner et al. (2006)	Human OA, femoral condyle of knee	Cartilage from different patients	OA vs. normal cartilage groups	78 samples, 18 normal cartilage, 20 early, 21 mild, 19 severe degeneration/**10 selected genes for RT-qPCR**	Fuji (Tokyo, Japan) BAS 5000 system/custom-made probes
Karlsson et al. (2010)	Human OA of knee	Cartilage from different patients	OA donors vs. normal donors vs. healthy cartilage	18 samples, 5 OA donors, 5 normal donors, 8 healthy donors/**7 genes were verified RT-qPCR and 2 genes were verified by IHC**	Affymetrix/HG-U133plus2.0
Snelling et al. (2014)	Human OA, medial tibial plateaus of knee	Cartilage from the same joint	Damaged vs. undamaged cartilage groups	16 paired samples, 10 paired for microarray,/**6 paired for RT-*qPCR* validation**	Agilent/G2159F
Ramos et al. (2014a, b)	Human OA of knee and hip	Cartilage from the same joint	Affected vs. preserved Cartilage groups	33 paired samples, 22 paired hips, 11 paired knees/**27 paired for RT-qPCR**	Illumina/Human HT-12_v3
Ramos et al. (2014a, b)	Human OA	Blood from different patients	OA vs. healthy control groups	139 samples, 139 for microarray/**19 for *RT-qPCR* validation 2 for IHC**	Illumina/Human HT-12 v3
Xu et al. (2012)	Human OA of hip	Cartilage from different patients	OA hip vs. NOF cartilage groups	19 samples, 10 NOF donors, 9 hip OA donors/**6 for RT-qPCR**	Illumina/HumanHT-12 v3
Wang et al. (2016)	Human OA of hip	Cartilage from different patients	OA hip vs. NOFH cartilage groups	24 samples, 4 pairs for microarray/**9 pairs for *RT-qPCR* validation**	Agilent/Human 4×44 K
Zhang et al. (2012)	Rat model OA of knee	Subchondral bone from different rats	Experimental vs. Sham-operated groups	90 samples, 30 for microarray 30 for histological analysis/**10 for *RT-qPCR* validation 1 for IHC**	Agilent/4×44 K, G4131F
Chou et al. (2013a, b)	Human OA, of knee	Subchondral bone from different patients	OA vs. non-OA groups	25 samples, 20 human OA donors, 5 non-OA controls/**64 for RT-qPCR**	Agilent/4×44 K,
Kato et al. (2007)	Human OA of knee	Synovium from different patients	OA vs. RA vs. non-OA/non-RA groups	61 samples, 43 OA patients, 10 RA patients, 8 non-OA/non-RA patients/**No RT-qPCR or IHC**	Microarray System Generation III scanner/self-designed chips
Lambert et al. (2014)	Human OA of knee	Synovium From the same joint	Inflamed vs. normal/reactive groups	12 paired samples, 12 inflamed synovium, 12 normal/reactive synovium/**Western blot and IHC**	Illumina/Human HT-12 v4

Table 1 (continued)

References	Subject	Tissue type	Control	Samples/confirming methods	Platform/chips
Remst et al. (2014)	Human and experimental mice synovial fibrosis and OA	Synovium and synovial fibroblasts from human and mice	Human synovial fibroblasts vs. experimental mice OA synovium vs. mice induced fibrosis synovium vs. human OA synovium groups	39 simples, 8 synovial fibroblast patients, 4 experimental OA synovium and induced fibrosis synovium mice, 7 end-stage OA patients/**RT-qPCR and IHC**	Affymetrix/GeneChip Genome 430 2.0 array
Endo et al. (2018)	Knee in rat OA models	Articular cartilage and menisci	Induced OA verse normal rats	Six cruciate ligament transection and six sham-operated rats/**not known**	Data not available
He et al. (2018)	Patients with OA	Articular cartilage from human OA patients	Human healthy controls	Two sets: five patients with OA for Genome-wide DNA methylation and three patients with OA for mRNA expression/**no RT-qPCR or IHC**	Illumina/Infinium HumanMethylation450 BeadChip

NFO neck of femur fracture, *NOFH* non-traumatic osteonecrosis of femoral head, *RA* rheumatoid arthritis

(GO) and enriched pathways for DGEs showed 67 GO groups and three major dysregulated pathways including those associated with cell signaling, ECM formation, and inflammation. Moreover, a number of genes previously unreported in OA were differentially expressed, such as *RARRES3*, *ADAMTSL2*, *DUSP10*, and genes previously identified were also confirmed including *SFRP3*, *MMP3* and *IFG1* (Aigner et al. 2006; Lories et al. 2007).

A similar study of hip cartilage was carried out by Ramos et al. (2014b), in which DGEs were determined in paired samples of OA-affected cartilage and intact cartilage from the same joint (22 hips, 11 knees). The results showed that 19 (14 upregulated, 5 down-regulated in affected compared to preserved cartilage) of 1717 unique genes were differentially expressed with two fold-changes and higher, including *TNFAIP6, CRLF1*, *FRZB*, *NGF*, *COL9A1*, *CD55*, *PTGES* etc.) Furthermore, use of the online tools DAVID and STRING (Huang et al. 2009; Szklarczyk et al. 2011) demonstrated significant enrichment for genes involved in both skeletal development and ECM organization pathways (e.g., *FRZB*, *TNFRSF11B*, *DCN*, *COL1A2*, *COL2A1*, *COL3A1*), and *FN1* as the central gene in protein–protein interaction. The fact that genes *FRZB* and *TNFRSF11B* are involved in skeletal development is in accordance with the observation of Xu, who compared normal cartilage with OA cartilage, suggesting that skeletal development is a common pathway in OA initiation as well as ongoing OA and confirming the hypothesis that chondrocytes lose their maturational arrested phenotype in OA pathogenesis (Gebauer et al. 2005; Xu et al. 2012).

Interestingly, in another study exploring gene expression profiles of peripheral blood from osteoarthritis patients, Ramos et al. (2014a) found 86 DEGs expressed with at least a 1.5-fold difference, and that new candidate genes *ATF4*, *GPR18*, *H3F3B* were the top genes identified ($P < 4.5 \times 10^{-8}$). Furthermore, the apoptosis pathway was found to be enriched in DGEs, including the well-known genes *CASP3*, *FADD*, and genes less well known to be involved in the apoptosis process such as *SIAH1* and *GPR18* in the blood of OA patients compared to controls (Takenouchi et al. 2012; Xu et al. 2006). None of these findings was detected in their previous study and this fact may imply that systemic factors in the blood could contribute to precipitate apoptosis of chondrocytes during micro-trauma, leading to the subsequent onset of OA (Ramos et al. 2014a; Zamli and Sharif 2011).

In addition to knee joints, the gene expression profile of end-stage OA hip cartilage ($n = 9$) was defined by Xu et al. (2012) by comparing normal hip cartilage ($n = 10$) to those taken from patients with femoral head fractures. A total of 998 DEGs (fold change $\geq$ I ± 1.5I, $P \leq 0.01$) were identified and were found to be enriched within 71 canonical pathways between the two groups of samples, including a number of

Table 2 List of important genes associated with OA in different studies

References	Genes identified as importance for osteoarthritis
Sato et al. (2006)	*SOX11, CCND1, PSAT, P4HA3, UCP2, GALNTL1, TNFAIP6, S100A4, DSCR1, TREM1, TGFBI, CRLF1*
Sato et al. (2006)	*TNFIP6, PRSS11, PTGES, S100A4, FN1, TGFBI, and* ***COL****1A2*
Aigner et al. (2006)	***COL****1A1,* ***COL****1A2,* ***COL****6A1,* ***COL****9A2,* ***COL****11A1*, ***COL****5A1* and ***COL****15A1*
Bos et al. (2008) and Tiku et al. (1999)	*SOD2, SOD3, GPX3, TOB1* and BTG*2*
Aigner et al. (2006) and Geyer et al. (2009)	*CLEC3A, CLEC3B, CDH11, GPNMB, CHST11, MSX1, MSX2*
Aigner et al. (2006) and Geyer et al. (2009)	***COL****13A1,* ***COL****14A1,* ***COL****8A2*
Snelling et al. (2014)	*IL11, SOX11, DNER, GFRA2* and *FGF18*
Snelling et al. (2014)	*LAMB1, SPARCL1, SFRP4* and ***MMP****13*
Snelling et al. (2014)	*RARRES3, ADAMTSL2, DUSP10*
Snelling et al. (2014)	*SFRP3,* ***MMP****3* and *IFG1*
Ramos et al. (2014b)	*TNFAIP6, CRLF1, FRZB, NGF,* ***COL****9A1, CD55, PTGES*
Ramos et al. (2014b)	*FRZB, TNFRSF11B, DCN,* ***COL****1A2,* ***COL****2A1,* ***COL****3A1*
Ramos et al. (2014a)	*ATF4, GPR18, H3F3B*
Ramos et al. (2014a)	*CASP3, FADD*
Xu et al. (2012)	*ADAMTS1, ADAMTS5,* ***MMP****1,* ***MMP****3,* ***MMP****23, SOD2*
Wang et al. (2016)	***COL****5A1, OGN, ANGPTL4, CRIP1, NFIL3, METRNL, ID2* and *STEAP1*
Zhang et al. (2012)	*ALP, lGF1, TGFβ1, POSTN,* ***MMP****3, TNFSF11, ACP5, BMP5, ASPN* and *IHH*
Chou et al. (2013b)	*POSTN, ASPN,* ***COL****6A3,* ***COL****3A1, OGN, DIO2* and *TNFSF11*
Kato et al. (2007)	*PPP2R5C, PGK1, SORD, EXT1, HS6ST, HARSL, LIMK2, GSTT1, FN1, FBLN3,* ***COL****3A1 and CXCL2*
Aigner et al. (2001)	*FBLN3, IL1R1, LIMK2,* ***COL****3A1, CXCL2, FN1 and GSTT1*
Aigner et al. (2001)	*PPP2R5C, EXT1, HS6ST*
Aigner et al. (2001)	*PCBP1*and *GSTT1*
Lambert et al. (2014)	*IL6, IL8, CXCL5, CXCL6, CECL2, CECL1, TREM-1* and *S100A9*
van Lent et al. (2012)	*HSD11B1, SLCO, MIR1275*
van Lent et al. (2012)	*CRIP2, LOXL1*
Remst et al. (2014)	*PLOD2, LOX,* ***COL****1A1,* ***COL****5A1* and *TIMP1*
Kato et al. (2007)	***COL****1A1,* ***COL****3A1,* ***COL****5A1,* ***MMP****3* and ***MMP****9*

Common genes among different studies are colored

genes (*ADAMTS1*, *ADAMTS5*, *MMP1*, *MMP3*, *MMP23*, *SOD2*) that are consistent with data from previous studies (Davidson et al. 2006; Scott et al. 2010; Swingler et al. 2009). When compared to the knee GEP dataset described by Karlsson et al. (2010), only 229 genes were found to be similarly differentially expressed, although remarkably 34 canonical pathways overlapped between the two studies. Furthermore, differences between the two studies in "*O-Glycan* Biosynthesis" in hip and "*IGF-1* signaling" in knee OA were observed, suggesting that the molecular mechanisms underpinning the cartilage destruction observed in hip and knee OA may have some unique and location-specific differences (Karlsson et al. 2010).

A recent study compared gene expression profiles of hip OA with those from specimens of patients with non-traumatic osteonecrosis of the femoral head (Wang et al. 2016). As in OA, non-traumatic osteonecrosis of the femoral head is primarily characterized by progressive cartilage degeneration and avascular bone necrosis (Ikeuchi et al. 2015). In Wang's study, eight common DEGs (*COL5A1*, *OGN*, *ANGPTL4*, *CRIP1*, *NFIL3*, *METRNL*, *ID2* and *STEAP1*) and ten common significant GO terms that are mainly implicated in apoptosis and development processes of chondrocytes were identified in the two groups. In addition, they also observed that both the ECM–receptor interaction and the focal adhesion pathways were enriched in the DEGs of both non-traumatic osteonecrosis of femoral head (NOFH) and hip OA. Taken together these results imply that some mechanisms might be shared in the pathogenesis of NOFH and hip OA.

Although the results described above have identified many DEGs between OA cartilage and "normal cartilage" separately, common DEGs between them were rare. The main DEGs reported in most of the studies include *COL*, *SOX*, *MMP*, and *SOD* gene families, which involve cartilage collagen catabolic and anabolic metabolism, tissue

remodeling, matrix degradation, and oxidative cellular defense of chondrocytes. Sustaining these biological processes is essential for homeostasis of normal cartilage, thus any homeostatic disruption may result in the occurrence of OA. There are three potential explanations for the difference in DEGs identified among these studies. One is that sampling strategies adopted by the investigators were different. Some studies included OA and "normal" cartilage samples from the same diseased joint of OA patients, whereas some obtained OA cartilage from the joints of OA patients and "normal" cartilage from the corresponding joints of normal controls. A second explanation might be that the diseased joint location varied between studies. For example, some studies targeted knee joints, while others targeted hip joints. Another difference is that the microarray platforms used for gene expression profiling differed among studies. Early in the development of this approach, microarray platforms contained only a small portion of the genes in the genome due to limitations of then-current technology, such as the Affymetrix oligonucleotide microarray HG-U133 plus 2.0. However, more recent studies have utilized genome-wide microarray platforms such as the Agilent Human 4 × 44 K Microarray chip.

GEP Study in Subchondral Bone of Human and Mice Model

OA was long considered to be a primary articular cartilage disorder; however, it is now known to be a complex condition affecting the whole joint (Lohmander 2000). The role of subchondral bone is currently considered to be of particular importance in the pathogenesis of OA (Castaneda et al. 2012; Goldring and Goldring 2010; Hayami et al. 2006). During OA progression, subchondral bone undergoes structural changes including micro-fractures, increased bone turnover, angiogenesis, and bone sclerosis in its later stages (Burr 2004; Goldring 2009). Kraus et al. (2009) demonstrated that subchondral bone texture could be a biomarker predicting severity of the knee OA. Thus, identification of the genetic mechanisms underlying changes of subchondral bone may improve our understanding about their roles in the pathogenesis of OA.

Zhang et al. (2012) conducted a GEP study using microarray technology in subchondral bone. As it is impossible to obtain adequate subchondral bone samples from humans with early-stage OA, they used a rat model with meniscectomy and medial collateral ligament transection to investigate the time course of genetic changes in the subchondral bone during the early stages of experimental OA. The authors identified 2,234 DEGs at 1 week, 1,944 DEGs at 2 weeks and 1,157 DEGs at 4 week post-surgery in the experimental group compared to the sham-operated group. They then further analyzed the dysregulated genes and found that the events underlying subchondral bone remodeling in OA occur sequentially, and in a time-dependent manner at the gene expression level. Moreover, some identified dysregulated genes, including *ALP*, *lGF1*, *TGFβ1*, *POSTN*, *MMP3*, *TNFSF11*, *ACP5*, *BMP5*, *ASPN* and *IHH*, may have roles in bone development and remodeling, and might influence osteoclast and osteoblast differentiation and function in this rat model. These data provide add to existing evidence that the altered phenotype of osteoblasts and osteoclasts in the subchondral bone of OA-affected joints contributes to pathogenesis of OA (Appleton et al. 2007; Logar et al. 2007; Sanchez et al. 2008).

To detect genetic alterations in the subchondral bone of patients with OA, a method was developed by Chou et al. (2013a) to precisely obtain a particular type of specimen from specific regions of the joint. In comparisons of osteoarthritic and normal subchondral bone, differences were observed in gene expression profiles, which was the first GEP study in the subchondral bone of human subjects (Chou et al. 2013b). In their report, RNA was isolated from subchondral bone OA ($n = 20$) and non-OA ($n = 5$) from the lateral and medial tibial plateaus of the knee and was used to perform a whole-genome GEP study using an Agilent microarray platform. In general, a total of 972 DEGs (fold change $\geq \pm 2$, $P \leq 0.05$) were identified in subchondral bone between the lateral and medial tibial plateaus. The most significantly dysregulated DGEs included up-expressed genes such as *POSTN*, *ASPN*, *COL6A3*, *COL3A1*, *OGN*, *DIO2* and *TNFSF11* as well as down-expressed genes such as *LEP* and *APOB*, which was similar to the results of Zhang's study and indicated that these have same roles in OA bone formation and pathogenesis as described in previous studies (Loeser et al. 2012; Meulenbelt et al. 2008; Zhang et al. 2012). Moreover, the software *Ingenuity Pathway Analysis* was used to detect canonical pathways in DEGs and a total of 279 canonical pathways, including two novel pathways *Periostin* and *Leptin*, were identified in this study. Dysregulated *Periostin* and *Leptin* could change the bone-remodeling rate through inhibiting or increasing phosphorylation of the *AKT* pathway in early- or late-stage OA. The abnormal bone remodeling generated by osteoblasts and osteoclasts, and the increased osteoid collagen matrix identified may be involved in the hypo-mineralization of subchondral bone and formation of osteophytes observed in OA progression (Martel-Pelletier and Pelletier 2010).

In these two GEP studies of subchondral bone from OA joints, the researchers reported only a few expressed DEGs in common including *POSTN*, *ASPN and TNFSF11*, but the rest of DEGs were different from each other. The possible explanation is that one study focused on a mouse model, whereas the other examined subchondral bone of human joints. Also, two diverse microarray platforms were used (agilent whole rat genome microarray, 4644 K, and the G4131F/agilent whole human genome 44 K microarray chips). Of these three common expressed genes, only *TNFSF11* has been identified as a DEG similarly reported by Ramos for cartilage tissue (Ramos et al. 2014b). This phenomenon indicates that there may be little overlap between the molecular mechanisms for the observed changes in cartilage and subchondral bone tissues in OA.

GEP Study in Synovium of OA Joints

Besides cartilage breakdown and abnormal subchondral bone remodeling, other manifestations of OA include synovial inflammation and synovial fibrosis that are directly associated with OA disease progression and clinical symptoms such as joint pain, swelling, and joint dysfunction (Sellam and Berenbaum 2010). Inflammation of the synovium can be observed in both early- and late-stage OA, and some evidence suggests that synovitis has an independent effect on initiation and progression of OA (Atukorala et al. 2016; Felson et al. 2016). Several GEP studies have been reported to focus on the synovial molecular mechanisms underlying the pathogenesis of OA.

A large-scale GEP study, which aimed to identify the DGEs between synovium samples from 43 OA patients, 10 RA patients, and 8 non-OA/non-RA patients, was performed by Kato et al. (2007). In their study, only 21 DGEs (e.g., *PPP2R5C*, *PGK1*, *SORD*, *EXT1*, *HS6ST*, *HARSL*, *LIMK2*, *GSTT1*, *FN1*, *FBLN3*, *COL3A1 and CXCL2*), which could be grouped into seven categories according to the previous study, were detected as expressed with significant differences between all three groups simultaneously (Kumar et al. 2001). Seven of the DGEs (*FBLN3*, *IL1R1*, *LIMK2*, *COL3A1*, *CXCL2*, *FN1* and *GSTT1*) were implicated in the pathogenesis of arthritis by previous studies, such as *FN1*, which was described by Aigner et al. (2001) as a major regulator of the matrix turnover of cartilage in OA. The linear discriminant analysis showed that these DGEs could be used to distinguish the OA, RA, or non-OA/non-RA groups from each other, supporting the use of this strategy to detect biomarkers that are uniquely expressed in OA synovium. Furthermore, a linear trend test based on a one-way ANOVA showed that there were increasing or decreasing trends between the expression levels of genes (*PPP2R5C*, *EXT1*, *HS6ST*)/gene (G*STT1*) detected in synovium and the severity of OA. They also reported that two genes (*PCBP1* and *GSTT1)* were found to be associated with the occurrence of synovitis in OA patients, while the gene *COMP*, which is one of the molecules associated with clinical synovitis in knee OA patients, was not found in microarray chips in this study. Thus, further study of the relationship of these genes and OA and their role in the generation of synovitis is warranted.

To diminish the bias in observed levels of gene expression, experimental and control samples have been obtained from different individuals with wide clinical heterogeneity. Lambert et al. (2014) collected normal and inflamed synovial membrane tissues, which were characterized according to macroscopic criteria, from the same knee joints of different patients ($n = 12$) with late-stage OA. In addition, gene expression profiling was performed using microarray and the results compared for inflamed and normal groups. Their research demonstrated that 896 DGEs expressed in inflamed and normal synovial membranes were mainly involved in four molecular pathways which related to inflammation, cartilage metabolism, *Wnt-5* signaling, and angiogenesis. Moreover, many cytokine and chemokine genes such as *IL6*, *IL8*, *CXCL5*, *CXCL6*, *CECL2, CECL1*, *TREM-1* and *S100A9* were confirmed as upregulated in the inflammatory pathway. *S100A9*, a member of the *alarmin* family, encoded a key protein in synovial inflammation and cartilage destruction in OA as found in a previous study (van Lent et al. 2012). *MMP3* and *MMP9* were observed to significantly upregulate in inflamed vs. normal synovial membranes, suggesting that synovitis could accelerate the destruction of cartilage in the OA process. Furthermore, a series of genes that have not been associated with OA pathogenesis were found to be differentially expressed between the inflamed and normal synovial membrane in their study. These genes included upregulated *HSD11B1*, *SLCO, and MIR1275* and downregulated *CRIP2 and LOXL1*. Further research on the roles of these genes may lead to a better understanding of OA pathogenesis.

Synovial fibrosis, another major characteristic of OA, is an important cause of joint stiffness and dysfunction in OA patients (Krieg et al. 2007). Several previous studies have shown that *TGFβ*, which is elevated in the serum of OA patients, is a key gene in the onset of fibrosis of synovial membranes (Leask and Abraham 2004; Punzi et al. 2003).

However, because *TGFβ* is involved in the normal metabolic homeostasis of cartilage and other joint tissues, it is not an appropriate to block *TGFβ* to prevent the synovial fibrosis. Consequently, Remst et al. (2014) analyzed gene expression profiles in *TGFβ*-induced OA synovial fibroblasts, the synovium of mice with fibrosis or experimental OA, and in the synovium of patients with OA using microarray. Their results showed that five *TGFβ*-inducible genes (*PLOD2*, *LOX*, *COL1A1*, *COL5A1* and *TIMP1*) were significantly upregulated in all four groups of samples compared to controls. It was hypothesized that the elevated level of TGFβ stimulated the upregulated expression of downstream genes *PLOD2, LOX, COL1A1, COL5A1* and *TIMP1* in synovium tissue in vivo. The subsequent expression of *COL1A1* and *COL5A1* increased the synthesis of collagen, while *LOX*, *PLOD2*, and *TIMP-1* inhibited the degradation of collagen through reducing matrix metalloproteinases (MMPs) activity, resulting in fibrosis. Interestingly, only the gene *PLOD2* could be used as a suitable and promising target gene for interfering with synovial fibrosis in OA because of the crucial functions of the other four genes in normal physiological processes in joints (Lopez et al. 2010).

Similar to what was observed in the previous studies with cartilage and subchondral bone, commonly expressed DEGs in synovium were rare in these three reports. Except for the different microarray platforms used, the primary reasons might be the distinct phenotype of diseased synovium (e.g., synovitis/synovial fibrosis in each condition), and/or different study designs and subjects. For instance, Kato et al. (2007) compared the synovium of OA, RA, and non-OA/non-RA patients, whereas Lambert et al. (2014) compared normal and inflamed synovium from the same knee joint of OA patients. Interestingly, these studies found higher expression of the *COL* gene family and matrix metalloproteinase genes in OA synovium, such as *COL1A1, COL3A1, COL5A1, MMP3* and *MMP9*. Some genes encode collagens or metalloproteinases that are involved in the metabolism of cartilage matrix and were also detected as DEGs in OA cartilage and subchondral bone in the previous studies, indicating that there are some common pathological pathways/molecular mechanisms shared by chondrocytes, subchondral bone, and synovium in the pathogenesis of OA.

More Recent Studies of GEP in Osteoarthritis

Several new reports published during the revision of this manuscript. Most of these reported altered expression levels of the genes mentioned above. Some revealed new sets of genes through whole-genome expression analysis. In particular, Endo et al. (2018) found that the up-regulation of Adamts2, 4, Mmp 2, 12, 13, 14, 16, extracellular matrix genes including versican (Vcan), lumican (Lum), syndecan 1 (Sdc1), and prostaglandin endoperoxide synthase 2 (Ptgs2) in menisci but not in cartilage. In an attempt to identify significantly changed genes and functional pathways in osteoarthritic cartilage using integrative genomic analyses, He et al. (2018) identified 1265 differentially methylated genes; 145 of these were associated with significant changes in the expression of genes that included DLX5, NCOR2 and AXIN2. These genes have not been identified in previous studies.

Recent Results from RNA-Seq Confirmed Some Key Genes and Provide New Tools

By analysis of RNA-seq in human knee cartilage tissue collected from 18 normal and 20 OA subjects, Fisch et al. (2018) identified eight transcription factors (TFs) that target large numbers of dysregulated genes in OA and are suppressed in OA. These TFs are UN, EGR1, JUND, FOSL2, MYC, KLF4, RELA, and FOS. However, none of these genes have been identified from microarray studies. Both microarray and RNA-Seq analyses have some technical limitations. A recent study by Mandelboum et al. (2019) indicated that genes that are exceptionally long or short are overrepresented in RNA-Seq datasets, which can lead to misinterpreted results. It is important in the future to understand the similarities and differences between the data from microarray and RNA-Seq technologies.

Limitations of the Current Studies and Suggested Future Directions

Although recent GEP studies have made considerable progress in identifying differences in expression of genes between OA and normal samples from different joints of humans and mouse models,there were still several limitations of these studies. These limitations may result in gene expression profiles identified in one study that are not consistent with results of other studies of even the same joint tissue (cartilage, subchondral bone, or synovium), and thus reported DGEs may show little overlap among studies. The few human GEP studies conducted to date have also been characterized by small numbers of tissue samples and subjects. Another limitation of some studies was lack of control for heterogeneity of OA etiology among the OA patients studied (e.g., aging, joint injury obesity).

Moreover, most human tissue specimens were obtained from late-stage OA patients who were undergoing joint arthroplasty surgery, usually due to the difficulty of obtaining joint tissue from early-stage OA patients. These specimens did not represent the pathological conditions of the initiation and progression of OA. Furthermore, most studies could not completely eliminate potential confounding factors such as age, gender, and ethnic/genetic background of patients in different sample groups. In addition, these GEP studies mainly evaluated gene expression levels, which do not always reflect the amounts of their corresponding proteins because of translational control and post-translational processing.

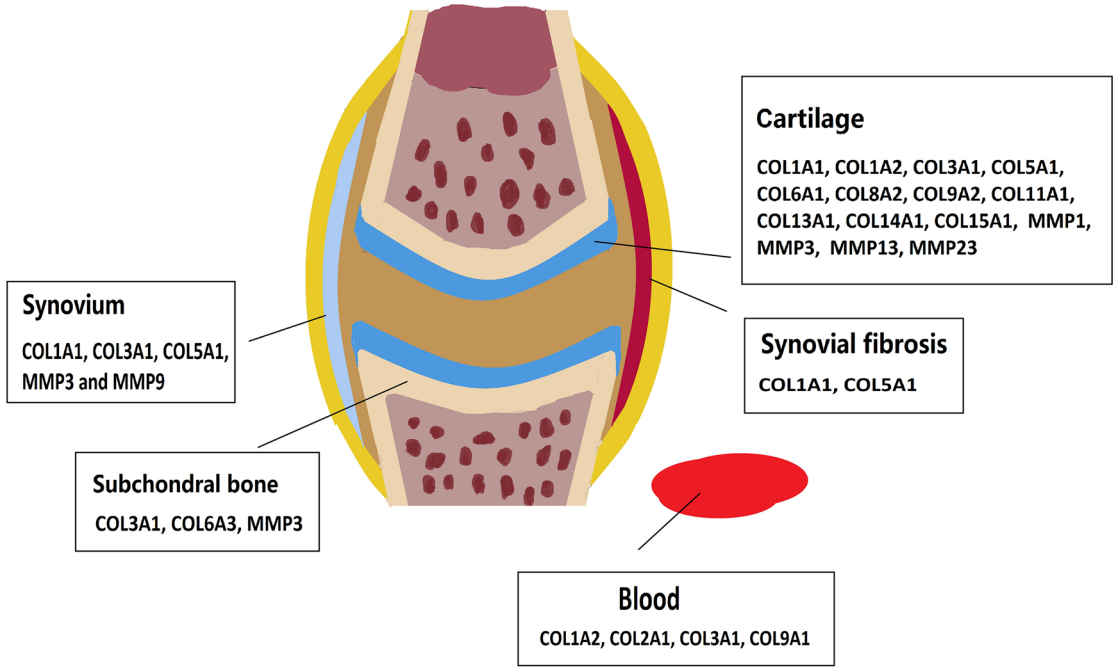
An important limitation in these studies is that the cell types found in the tissues themselves are quite heterogeneous. Sanjurjo-Rodríguez et al. (2016) assessed chondrocytes and subchondral bone cells simultaneously and finding that only one common upregulated gene (in damaged areas) was found in both cartilage and bone cells. Combined with Aigner's and Remst's studies, COL1A1 is upregulated in both cartilage and OA synovial fibroblasts cells. Therefore, the large number of genes from different studies may be due to cell and/or tissue heterogeneity.

Variation in microarray platforms may also account for some inconsistent results. Several different microarray platforms, including Agilent, Affymetrix, Illumina, and Generate (Table 1) were used in these studies. However, even with the same platform data were not consistent among studies, reflecting the complexity of the analysis, tissues, and disease. Furthermore, studies using other genome resources and technologies such as proteomics, methylations, and microRNA to confirm data from gene expression profiles generated by microarray will help to address this issue and further our understand of the molecular mechanisms of osteoarthritis. In addition, animal models may help clarify data inconsistencies. Tissues or cells can be collected from homogenous groups of animals at precise times under controlled conditions. However, we also should keep in mind that animal models cannot replace human studies and in many cases are not accurately representative of the human disease condition.

Therefore, future studies should adopt the same genome-wide microarray approach to detect DEGs with more samples included similar conditions across studies. The research subjects should be divided into subgroups to ameliorate influences varying etiologies of OA. Moreover, the role of DEGs and their downstream pathways should be compared among different tissues. Finally, the use of proteomics should further uncover pathophysiological functions of DGEs in the pathogenesis of OA.

Conclusion

Over the past decade, much knowledge about the roles of genes and their downstream pathways in the pathological processes of OA has been gained from studies with retrieved human joint tissues and animal models. In general, in response to aberrant mechanical or aging-induced oxidative stress, the expression of some catabolic genes is upregulated, while genes responsible for normal homeostasis are down-regulated in articular cartilage. Chondrocytes thus produce a variety of matrix-degrading enzymes such as metalloproteinase and a disintegrin and metalloproteinase with thrombospondin-like motifs (e.g., *MMP1*, *MMP13*, *ADAMTS4*, *ADAMTS5*), resulting in degradation of the extracellular matrix and loss of cartilage (Ding et al. 2010; Loeser et al. 2016). Furthermore, the presence of articular cartilage debris may stimulate upregulated expression of inflammatory-related genes in synovium, resulting in the release of cytokines and chemokines such as *TNFα*, *IGF-1*, *IL-1* and *TGFβ* into the joint cavity. These inflammatory mediators not only contribute to the onset and progression of synovitis, but also can conversely drive progressive cartilage degeneration via positive feedback, forming a vicious spiral (Scanzello and Goldring 2012). Meanwhile, mechanical stimulation and degradative cytokines could alter the normal expression pattern of genes in osteoblasts and osteoclasts, resulting in abnormal remodeling, vascular infiltration, and formation of osteophytes and cysts in subchondral bone (Sanchez et al. 2012). This pathological cascade could correspond to the findings of those studies in this review. Figure 1 summarizes the genes from variety of studies. Figure 1a shows the common genes in different tissues. Figure 1b shows the number of genes in different functional categories. In particular, the 32 genes in skeletal development are listed. Genes in other categories are listed in our supplementary data (Supplementary materials 1). These data represent tremendous effort in the studies of understanding of molecular mechanism of osteoarthritis. Moreover, despite some defects in and limitations of these studies, the identification of new genes and pathways could provide a basis for further studies on their single and intersectional functions in OA pathogenesis and inform potential pharmaceutical treatments in OA treatment.



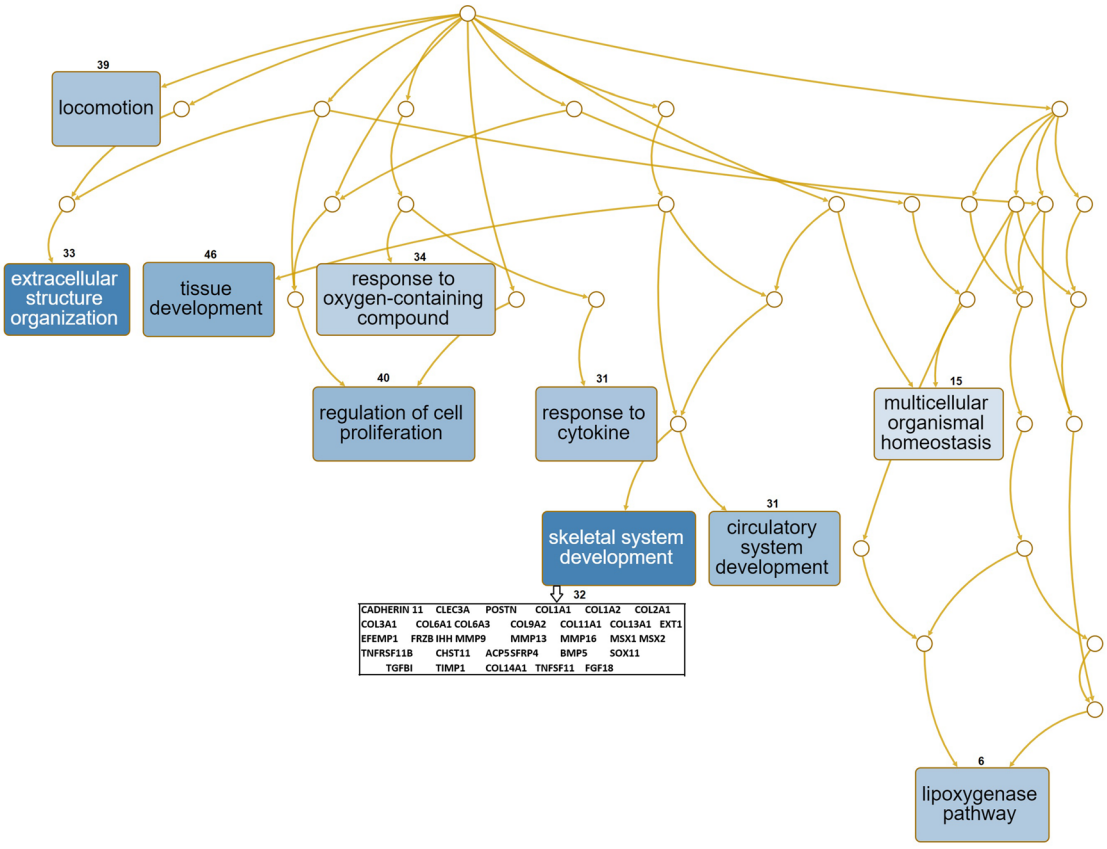


Fig. 1 Summary of Important genes for osteoarthritis from variety of studies. **a** Identified common genes from different tissues. **b** Genes in different functional categories

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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