Review

An update on primary hip osteoarthritis including altered Wnt and TGF-β associated gene expression from the bony component of the disease

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Abstract

The study of primary hip OA is continuing to redefine what was once considered a stagnant pathology as one of dynamic change, occurring over a long period of time involving the many composite tissue types of the joint including the bone. Examination of the inverse relationships evident between OA and fracture cohorts, including individuals with osteoporosis (OP), indicates an imbalance in formation and resorption in the bony component of both pathologies. This review contains an overview of primary OA followed by an assessment of differential gene expression and altered cellular characteristics identified in the bony compartments of primary hip OA, with a focus on the wingless mouse mammary tumor virus integration (Wnt) and TGF-β signalling pathways. The studies reviewed here suggest that OA is a systemic disease involving the bone and validate the assessment of molecular changes to further investigate this complex disease.

Key words: Hip osteoarthritis, Trabecular bone, Osteoblast, Gene, wingless MMTV integration (Wnt), TGF-β signalling.

The aetiology of primary OA

OA is currently classed as a collection of heterogeneous conditions rather than a single entity. The older conventions of an inevitably progressive, degenerative disease process have been revised in favour of a model whose progression involves a dynamic process of repair with heterogeneous results, including long periods of minimal change to tissue structure [1–3]. The disease can develop as a result of joint degeneration caused by injuries or a variety of other disorders, including inflammatory, neurological, developmental and metabolic ailments, a group of conditions referred to as secondary OA. Secondary OA caused by joint dysplasia, injury, infection, Legg-Perthes disease and haemophilia can occur in younger adults [4].

However, idiopathic or primary OA develops in the absence of any known cause of joint degeneration and rarely occurs in people <40 years. The whole joint is implicated in a disease process characterized clinically by hyaline cartilage fibrillation and loss, synovial inflammation, ligament laxity, muscle weakness and periarticular changes in the bone [3, 5–8]. These changes in the bone are determined by radiography and include asymmetric joint space narrowing, alongside increased bone density, increased thickness of the bony envelope (bony sclerosis) and bony outgrowths (osteoophytes) [3, 4, 6–10]. Clinically, OA is associated with regional pain, joint stiffness and dysfunction [11, 12].

Primary OA can occur in any synovial joint, although it rarely occurs in the ankle, wrist, elbow and shoulder, but it is common in the knee, hip, foot, spine and hand. Among these joints, the hip is the second most prevalent joint in which primary OA occurs, surpassed only by the knee [4, 11]. The pathophysiology of the joint degeneration in OA remains poorly understood [4].

The hip joint is a complex organ composed of different tissues including articular cartilage, subchondral bone, sensory nerve endings, the synovial membrane, the joint capsule and periarticular muscles [13, 14]. As such it has been established that the aetiology and progression of hip OA is not attributable to a single tissue, but is viewed as a failure of the entire joint, involving dynamic biological and biochemical processes [13, 15, 16]. Furthermore,
the development of primary OA has been attributed to systemic abnormalities [13]. To date, examinations have revealed changes concomitantly both in the cartilage and the bone [13, 14, 17, 18]. Characterization has established changes in chondrocyte biology in the progression and outcome of the disease [19]. Usually a loss of homeostasis in the cartilage, subsequent destruction and insufficient tissue repair are observed at the end stages of the disease [14]. Alongside these cartilaginous changes, a number of altered molecular, microarchitectural and physical properties have also been observed at the subchondral and intertrochanteric (IT) regions of the proximal femur in primary hip OA [20-23]. It is increasingly recognized that changes in the trabecular bone tissue distant from the affected joints are not easily explained as secondary changes, but may be a part of the primary disease process [15, 20, 24-26]. Examinations in sites such as the iliac crest and IT region have identified systemic changes that may potentially underlie the pathology [22, 25-27]. The focus of this review is an overview of primary OA followed by an assessment of systemic differential gene expression and altered cellular characteristics identified in the bony compartments of primary hip OA, including studies from regions of the femur such as the femoral head, femoral neck and IT region, as well as the iliac crest of the pelvis.

**Risk factors for primary OA**

Although a specific cause for primary OA has not yet been established, a number of risk factors are associated with the disease. The main intrinsic risk factors are ageing, genetic predisposition, female gender and increased bone density; extrinsic factors include obesity and joint laxity. Of these factors, the most dominant determinant associated with the pathology is age [4, 6]. In some populations, >75% of people over the age of 65 years have OA that involves one or more joints. After the age of 40 years the incidence of hip OA increases rapidly. The strong correlation between age and incidence indicates the number of people suffering from the disease is increasing rapidly [4]. Studies designed to evaluate genetic predisposition among siblings of patients who have undergone total joint replacement have shown 2- to 3-fold increases in the risk of hip OA relative to controls. Findings indicate that OA of the hip has a significant heritable component. Heritability estimates suggest that more than half the variation in susceptibility to this disease in the population is explained by genetic factors [28]. OA is generally more common in women than in men, particularly over the age of 40 years; heritability also appears to be greater in females [4, 28, 29]. Current studies suggest that the prevalence of the pathology is equivalent in both sexes [30]. However, there is a conflicting, significantly higher incidence of hip OA in females; this disparity may be due to differential survival and the greater reliability of incidence studies [30]. As such, the three most determining factors for the incidence of primary hip OA are age, genetic history and gender. In addition, OA of the hip is a negative risk factor for hip fracture [16]. Although critical risk factors for the occurrence of primary hip OA have been identified, no underlying cause has yet been found [4, 16].

### The inverse relationship between primary OA and fracture

The inverse relationship between OA and primary osteoporosis (OP) has been observed clinically for at least four decades [25, 31]. A number of more recent clinical observations support the concept of an inverse relationship between primary OA and OP [16, 24, 31]. The most notable aspects are the general absence of OA in the head of the femur excised during the treatment of fracture and the rarity of traumatic hip and spine fractures in OA cases. Patients with post-menopausal OA and those with OP appear to represent anthropometrically different populations [16]. Typical OA patients tend to be mesomorphic or obese, whereas typical OP type I and type II patients tend to be ectomorphic, trending towards a more fragile physique [25]. Many epidemiological, radiographic, BMD, zinc status, mechanical and mineralization studies have also validated an inverse relationship between OA of the hip and OP as well as fracture risk [23, 27, 32, 33]. The evidence for an inverse relationship between OA and OP is stronger at the axial skeleton (lumbar and femoral) than at the appendicular skeleton (hand and radius). It is likely that the association may be different for OA at different joints, and different between localized OA at a specific joint and primary OA [33]. The evidence for this inverse relationship comes mainly from cross-sectional studies. The associated bone and fragility differences have been attributed to an imbalance between bone formation and resorption in both pathologies [34]. These differences are further validated by observations at the molecular level both in the whole bone and some of its constituent cellular components [24, 34-37].

### Molecular changes in the bone of primary OA

There is a growing body of evidence for the systemic involvement of the trabecular bone at the molecular level in the pathogenesis of OA, including and beyond the localized cartilage/subchondral bone unit [9, 14, 38]. The genomics of OA have been classified into three main types: genetic alterations, functional genomics and differential gene expression [19]. The genetic alterations can be further divided into familial aggregation, twin, linkage and association studies. These studies represent the bulk of OA literature and have been reviewed previously [14, 39]. Currently, available data indicate that molecular regulators of signalling pathways directing joint formation and homeostasis or remodelling in adult bone are key molecular players in OA [22].

Several studies using molecular analyses applied to OA have generated strikingly consistent results. Molecular regulation in bone-forming osteoblasts influencing bone mass, as well as altered structure and function, may
contribute to the pathological process in OA [20, 40]. Several authors have also suggested that a primary osteoblastic defect might be implicated in the process leading to the breakdown of articular cartilage or that the process of cartilage deterioration is secondary to a primary bone disease in which concentrations of insulin-like growth factor 1 (IGF1), IGF2, IL-1 and IL-6 are increased [25, 41]. IGF receptors exist in the bone and in vitro work has suggested an anabolic effect of IGF1 on osteoblasts [33]. It has been proposed that increased levels of growth factors may stimulate bone formation, accounting for the inverse association between OA and OP. Higher growth factor levels may account for both higher bone density and osteophyte formation in OA. Findings of increased bone mass and BMD at sites in bony compartments distal to the site of disease may also be explained by these results. [33].

Osteoblasts sampled from the trabecular bone of the femoral head and neck proliferate faster in postmenopausal patients with OA compared with postmenopausal OP fracture cases during the first stage, and osteoprotegerin (OPG) protein secretion is also lower in OA than in OP [34]. Levels of receptor activator of nuclear factor kappa-B ligand (RANKL) mRNA expression and the RANKL/OPG mRNA ratio from the IT region were both found to be significantly lower in OA compared with a fracture cohort [24]. Similarly, both RANKL and the RANKL/OPG mRNA ratio were found to be lower in OA than in OP in response to 1,25-DihydroxyvitaminD (1,25D) and 17β-oestradiol as well as 1,25D alone. In both cohorts the main modification on the RANKL/OPG system induced by combinations of these hormones was found to be a net increase in RANKL mRNA expression [34]. This increase indicated that osteoblasts in women with hip OA were less sensitive to stimulation with these hormones, which could contribute to reduced osteoclastic activity during bone remodelling [34]. A further study reported higher expression of OPG in hip OA bone compared with an age-matched fracture cohort; RANKL was not examined in the study. The differential expression from the iliac crest is also consistent with an altered state of remodelling suppressing resorption [26].

It was also reported that the mRNA levels coding for MMP9 and OC were greater in bone sampled from the IT region of an OA group. Furthermore, the expression of cathepsin K, MMP9 and tartrate-resistant acid phosphatase (TRAP) relative to RANKL mRNA was significantly higher in the OA group [24]. Ratios of these bone resorption-related enzymes relative to the formation marker OC were lower in hip OA compared with a fracture group. Gene expression and the association between their mRNA levels pointed to higher bone resorption and bone formation in OA, differences in the balance between them and differences in the regulation of bone resorption in OA and OP bone [24].

It has been shown that individuals who have OA can be differentiated on the basis of the levels of eicosanoids such as PGE2, leukotriene B4 (CYP4F3) and IL-6 produced by their osteoblasts [41]. When normal articular cartilage was co-cultured with osteoblasts derived from subchondral bone of the femoral condyles in OA patients, an increase in the release of glycosaminoglycans from the cartilage matrix was observed; in contrast, co-culture with cells from normal bone had no effect [41–43]. More recently, it has been shown that the supernatant from cartilage cultures co-incubated with cells from OA bone contained more aggrecanase-generated metabolites [41, 42]. Therefore, cells from OA bone are able to modulate cartilage metabolism in a manner not seen with osteoblasts from patients who do not have joint disease. The resultant thinning of the articular cartilage might lead to initiation of further microdamage in the femoral head, neck and IT region of the bone and cartilage through a positive feedback mechanism, which can ultimately lead to complete loss of the articular cartilage associated with the end stages of the disease [41, 44].

Further observations include a significant difference in aromatase (CYP19A1) expression in trabecular bone of the femoral neck between patients with hip OA and patients with hip fracture after adjustment for sex and age [35]. Higher CYP19A1 expression was found not only in bone tissue samples from fracture patients, but also in primary osteoblasts grown in culture for several weeks after fracture, compared with hip OA [35]. The mechanisms responsible for the differences in CYP19A1 expression could be related to either intrinsic characteristics of the bone cells or external influences. Low expression of CYP19A1 in OA may result in lower local oestrogen availability, which in turn, could facilitate cartilage damage [35].

Collectively these observations suggest an altered state of remodelling in OA bone in comparison with control, OP and fracture cohorts, respectively, potentially contributing to changes in the trabecular bone associated with the end-stage pathology. This altered state appears to be driven by a number of differentially expressed molecules, some of which are very well-established markers of the process of bone remodelling. Other studies have specifically identified molecules from the wingless mouse mammary tumor virus integration (Wnt) and TGF-β signalling pathways as also being differentially expressed in bone from hip OA cases.

**Altered expression of Wnt molecules in primary OA**

Many of the genes involved in OA are associated with bone development and subsequent remodelling, and a number of molecular expression screens have identified Wnt-related molecules as involved in OA [15, 22, 37, 45, 46]. Examination of differentially expressed Wnt molecules in the cartilage has also revealed correlations with cartilage destruction [47]. Increased Wnt signalling post-developmentally may be deleterious for the joint cartilage, as Wnt signals induce the expression of MMPs that promote cartilage catabolism and degradation [37]. At the local level, aberrant Wnt signalling may be related to the bony scleroses and formation of osteophytes seen
in the affected joints. Systemically, a number of studies suggest that changes in the expression of Wnt pathway components are involved in the pathogenesis of OA, including increased BMD [22, 37, 45, 46].

The Wnts comprise a large family of secreted proteins, activating at least four intracellular signalling pathways distinguished by unique transcription factors at the end of each signalling cascade. Currently the types characterized include Wnt/calcium (Ca), Wnt/cyclic adenosine monophosphate (cAMP), Wnt/c-Jun NH(2)-terminal protein kinase (JNK) and Wnt/β-catenin, which regulate osteogenesis through a variety of mechanisms, among a range of cellular processes [40, 48, 49]. The Wnt pathways are generally assigned into two categories: the canonical, consisting of the Wnt/β-catenin pathway, and the non-canonical, consisting of all the others (Figs 1 and 2). Although some of the biological consequences of canonical Wnt signalling are established in the bone, the significance of the non-canonical pathways is not as well understood [48, 50, 51]. Wnt/β-catenin is of particular importance to bone biology and remains by far the most studied of the Wnt pathways; this pathway is defined by the cytoplasmic accumulation of β-catenin, its subsequent nuclear translocation and its activation of transcription factors [14, 40, 52, 53].

Regulation of Wnt signalling by secreted Wnt antagonists is critical to the normal development of osteoblasts and the associated bony tissue [54]. The extracellular regulators include secreted proteins such as Wnt inhibitory factors (WIFs), secreted frizzled-related proteins (sFRPs), dickkopfs (DKKs), sclerostin (SOST), rat homologue of the Xenopus-secreted WNT modulator (WISE) and connective tissue growth factor (CTGF) [48]. WIFs bind Wnt signalling molecules, sFRPs bind to frizzled (FZD) receptors and Wnt signalling molecules, DKKs, SOST and CTGF interact with low-density lipoprotein receptor-related proteins (LRPs). WIFs and sFRPs are known to inhibit all Wnt-activated pathways, while DKKs exclusively suppress canonical signalling [48].

The Wnt pathway is known to modulate bone mass through a number of mechanisms, including renewal of stem cells, stimulation of pre-osteoblast replication, induction of osteoblastogenesis and mineralization, inhibition of osteoblast and osteocyte apoptosis [40]. These studies have highlighted the significance of this pathway in the normal development of the primary osteoblast in the endochondral skeleton [51]. Data obtained from animal models and cell culture have shown that the activation of the canonical Wnt pathway has an anabolic effect on the bone as a consequence of stimulating bone formation [37].

It has been hypothesized that differences in osteocyte SOST expression in the cortical bone of the femoral neck might account for differences in osteonal bone-formation activity between patients with hip OA or hip fracture and controls. OA femora have normal calcar width, but have 18% fewer osteocytes per unit bone area than controls. Furthermore, there were fewer osteocytes in OA bone-expressed sclerostin than in controls, but wide variation in the osteocyte data was seen between individual subjects [46, 55]. In most OA patients, there was increased osteonal ALP staining and reduced sclerostin staining of osteocytes [46]. In fracture patients, newly forming osteons were similar in this respect to OA osteons, but with closure, there was a much sharper reduction in ALP staining that was only partly accounted for by the increased proportions of osteonal osteocytes staining positive for sclerostin. In OA, reduced sclerostin.

**Fig. 1** The canonical Wnt pathway and differentially expressed molecules from the bone of primary hip OA. (A) The canonical Wnt pathway in its activated state with a bound Wnt protein, the FZD and LRP, as well as downstream binding of axin-preserving β-catenin, which goes on to initiate transcription. (B) The canonical Wnt pathway in its inactive state. The FZD receptor is instead bound by a soluble frizzled-related protein (sFRP). The axin, glycogen synthase kinase 3 (GSK3) and APC complex then degrades β-catenin. (C) A list of differentially expressed molecules and downstream targets of the canonical Wnt pathway from the bone of primary hip OA cases (adapted from [22, 26, 37, 45, 46, 53]).
expression likely mediates increased osteoblastic activity in the intra-capsular cortex [46].

Microarray-based screening of hip OA cases using trabecular bone from the iliac crest revealed the differential expression of the genes four and a half LIM domains 2 (FHL2), v-akt murine thymoma viral oncogene homologue 1 (AKT1), dishevelled homologue 2 (DVL2) and MMP2 [26]. A similar screen utilizing microarray gene expression profiling of trabecular bone from the IT region obtained from a larger number of hip OA cases, hip OP cases and controls revealed a number of differentially expressed molecules. A substantial number of the top-ranking genes identified in the OA bone are known to be targets of the Wnt signalling pathway and have roles in osteoblasts, osteocytes and osteoclasts [22]. These genes included Wnt integration site family member 5B (WNT5B), LRP1, LRP3, FZD3, FZD8, sFRP5, axin 2 (AXIN2), adenomatosis polyposis coli (APC), dishevelled-associated activator of morphogenesis 1 (DAAM1), phosphatase and tensin homologue (PTEN), tax interaction protein 1 (TIP1) and transcription factor 20 (TCF20) [22]. These observations support altered Wnt signalling, leading to altered bone mass in hip OA. In some cases, additional association with the regulatory processes of osteogenesis further supports a potential role in bone formation and remodelling [22, 26].

Further study of Wnt-associated molecules in a similar OA disease cohort also from the IT region against controls revealed correlations with histomorphometric indices. Alterations in gene expression, structural indices and correlations between these were found in OA compared with control bone [45]. Significant correlations in control bone between \(\beta\)-catenin expression and formation indices osteoid-specific surface (OS/BS), osteoid surface (OS/BV) and osteoid volume (OV/BV) were absent in OA bone, indicating altered Wnt/\(\beta\)-catenin signalling and activity in the pathology. MMP25 expression and remodelling indices eroded specific surface (ES/BS), eroded surface (ES/BV) and eroded surface in the bone tissue volume (ES/TV) were correlated only in OA, pointing to aberrant bone remodelling in the pathology [45]. These findings alongside a number of other correlations indicated an altered state of osteoblast differentiation and function in OA driven by several key molecular regulators. In association with this differential gene expression, an altered state of both trabecular bone remodelling and resulting microarchitecture were also observed [45].

Cells of multiple lineages are present in bone tissue. In order to increase the understanding of gene expression specific to the osteoblast, primary cultures have also been examined [37]. Seven genes showed the most consistent evidence for differential expression, both in bone samples and osteoblast primary cultures from the trabecular bone of the femoral head. They included two membrane-associated Wnt receptor molecules, LRP5 and FZD5; a molecule that also binds Wnt ligands, sFRP3; a protein needed for Wnt action downstream of its receptors, DVL2; and three nuclear factors, B-cell CLL/lymphoma 9 (BCL9), E1A binding protein p300 (EP300) and TCF7-like 1 (TCF7L1) [37]. Up-regulation of the FZD5 gene in hip OA was found. FZD5 binds WNT7A and WNT5B and may have a more important role in the non-canonical than in the canonical pathway. Recently it has been demonstrated that sFRPs may enhance the Wnt-induced differentiation of osteoblastic precursors in mice [37], sFRP3 binds to FRZB, and it has been recently reported that the targeted disruption of the FRZB gene
promotes cartilage degradation in mice. BCL9 also binds //catenin and thus takes part in the formation of multimeric complexes of //catenin, TCFs, different co-activators and adaptors, which finally bind to conserved Wnt response elements in the DNA [37]. EP300 participates in the transduction of signals elicited by a number of regulatory factors, including TGF-β and Wnt [37]. The up-regulation of several genes in the Wnt pathway observed in OA in this study was accompanied by a parallel increase in Wnt activity, as revealed by higher expression of the Wnt target gene AXIN2, and associated TCFs T-cell factor/lymphoid enhancer factor (TCF/LEF). These differences suggest that genes in the Wnt pathway are up-regulated in the osteoarthritic bone, and may be involved in bony changes and also in cartilage degradation [37]. Further, molecular screens in the cartilage of secondary injury-driven OA have shown a number of differentially expressed molecules from the Wnt pathway, which may influence the cartilaginous repair response [56, 57].

A number of studies have clearly demonstrated a significant alteration in the expression of Wnt-associated molecules in the trabecular bone of hip OA patients. The altered expression of these molecules suggests systemic changes in the pathology, which, based on the function of the molecules and the pathway, have implications for the altered bone remodelling also observed in OA.

Specifically, the increased formation of hypomineralized bone, changes in microarchitecture and the production of degradative enzymes in hip OA may be attributable, at least in part, to the differential expression of Wnt-associated molecules in the bone.

Altered expression of TGF-β molecules in primary OA

A number of molecules involved in TGF-β signalling have been found to be differentially expressed in OA bone [15, 22, 26, 45]. The TGF-β signalling cascade is a known regulator of chemotaxis, proliferation of osteoblast precursors and differentiation into the mature osteoblast, as well as the synthesis of extracellular matrix and mineralization of the resulting matrix in the bone microenvir- 


doal [58–60]. Data from numerous in vitro experiments have demonstrated the role of TGF-β signalling mediated by TGF-β1 and cytokines in every stage of bone formation (Fig. 3) [58]. Most data support the following model: TGF-β1 increases bone formation in vitro mainly by recruiting osteoblast progenitors and stimulating their proliferation, thus expanding the pool of committed osteoblasts; it also promotes bone matrix production [58]. Once committed to osteogenesis, TGF-β1 increases the pool of osteoprogenitors by inducing their chemotaxis and

![Fig. 3](https://academic.oup.com/rheumatology/article-abstract/50/12/2166/1790141)
proliferation [61-63]. Most studies illustrate the mitogenic effect of TGF-β1 on osteoprogenitors and osteoblast-enriched cell culture [58, 64]. However, TGF-β1 blocks later phases of osteoblast differentiation and mineralization [65, 66]. These latter stages are regulated by other downstream growth factors such as bone morphogenetic proteins (BMPs) [59]. Apoptosis of osteoblasts is blocked by TGF-β1 during differentiation into osteocytes [58, 67]. It is generally concluded that TGF-β signalling inhibits mineralization of the matrix that it helps to produce [58, 66].

Bone turnover has been found to be reduced and increased concentrations of TGF-β have been found in the bone matrix of the iliac crest of OA cases, suggesting an altered ability to remodel compared with OP [25]. In a more recent microarray-based screening of OA against control trabecular bone from the IT region, TGF-β/BMP pathway components and modulators were found to be differentially expressed [22]. These were TGF-β1, BMP5, inhibin α (INHBA), follistatin (FST), TGF-β receptor 1 (TGFBR1), endoglin (ENG), activin A receptor, type I (ACVR1), latent TGF-β-binding protein 4 (LTBP4), SMAD mothers against DPP homologue 3 (SMAD3), SMAD4, inhibitor of DNA binding 1 (ID1), jun B proto-oncogene (JUNB), kruppel-like factor 10 (KLF10), histone deacetylase 4 (HDAC4), GLI-Kruppel family member (GLI3) and runt-related transcription factor 2 (RUNX2). This cohort of molecules was found to have potential effects on a number of processes including angiogenesis, chondrogenesis and osteogenesis, in general having both an agonistic and antagonistic effect on TGF-β signalling [22].

Further assessment of the expression of these molecules by quantitative PCR in a similar cohort also sampled from the IT region showed that SMAD3 was expressed significantly more highly in OA compared with controls [45]. SMAD3 is involved in TGF-β signal transduction and increased SMAD3 expression could therefore inhibit mature osteoblast differentiation and maintain an immature osteoblast phenotype. These findings are consistent with previous findings in OA, ultimately contributing to the observed increase in bone volume [45]. Negative correlations between SMAD3 and β-catenin expression as well as MMP25 in OA suggest the emergence of further dependencies not seen in the controls. Based on the roles of SMAD3 and β-catenin in signal transduction during osteoblastogenesis, this relationship also indicates irregular activity within the Wnt and TGF-β pathways in OA trabecular bone [45]. The negative correlation between MMP25 and SMAD3 expression may also contribute to the higher bone volume fraction observed in OA, as the inhibitory action of SMAD3 may be further augmented by a decrease in the turnover of the bone matrix. The positive correlations observed between SMAD3 and the CD14 molecule (CD14) in both the OA and control cohorts may represent conserved signalling pathways in cells of the granulocyte and monocytic lineages in both cohorts. The elevated expression of both these genes in OA is consistent with increased inflammatory cell activity in OA bone [45].

Comparisons between gene expression data obtained using oligonucleotide arrays from OA and fracture as well as a control cohort indicated differential expression of genes involved in bone cell functions in another group of OA patients [26]. Among the genes identified from the iliac crest were those associated with TGF-β signalling including v-FOS FBX murine osteosarcoma viral oncogene homologue (FOS), BMP1, TGF-β2, TGF-β3 and protease serine 11 (PRSS11) [26]. Higher BMP1 expression might contribute to systemic, increased bone collagen matrix formation in the disease. In OA trabecular bone, the expression of inhibitory molecules such as PRSS11 that block TGF-β signalling has been postulated as a compensatory mechanism in response to the elevated levels of TGF-β signalling in the pathology [26].

Primary osteoblastic cells from femoral bone with OA actively synthesize complex N- and O-glycan chains of bone cell glycoproteins, with quantitative differences between cell types [69]. TGF-β-induced cell differentiation and proliferation were found to have significant effects on both cell surface markers and glycosyltransferase activities of human osteoblasts and osteosarcoma cells. The changes induced by cytokines can result in altered cell surface functions, which may be of importance in OA [69]. Novel strategies for the treatment of OA may be aimed at controlling apoptosis by modification of glycosylation in bone cells [69].

The investigation of TGF-β1 in sections of developing bone and from bony osteophytes from osteoarthritic femoral heads revealed differential expression [68]. TGF-β1 expression was localized to osteoblasts apposed to bone or cartilage matrix, the intensity of expression correlating with matrix secretion. Chondroblasts and chondrocytes expressed lower, but significant levels of TGF-β1 mRNA; the expression was lost with the progression to calcifying cartilage [68]. TGF-β1 was differentially expressed most likely by mineralizing osteoblasts in a temporal and spatially regulated fashion leading to its incorporation in the extracellular matrix, with a potential role in the regulation of bone resorption [68]. Screening of cartilage from secondary injury-driven OA has also revealed the differential expression of TGF-β-associated molecules, potentially affecting the cartilaginous repair response [56, 57].

In summary, assessments of TGF-β signalling and its associated molecules in hip OA bone have revealed a complex multifaceted role for the pathway in the pathology. Given the significant role of this signalling pathway in the development and function of the osteoblast, the altered phenotype, the composition of the extracellular matrix and the process of mineralization observed in hip OA may also be driven in part by the differential expression of TGF-β molecules.

Conclusions

Primary hip OA is a complex disorder involving multiple tissue and cell types. Despite associated risk factors such as age, genetic history and gender, a cause remains to be established. Examination of the bony component of the
disease at the molecular level has revealed interplay between and within two central pathways controlling fundamental processes in the bone microenvironment, including osteoblast differentiation, the process of mineralization, and bone remodelling. Deregulation of the Wnt and TGF-β signalling pathways has been demonstrated in a number of studies utilizing bone from hip OA cases. Given the specificity of some of these molecules and their impact on the bone, these are attractive potential targets for therapy. However, functional knowledge about the role of both pathways in this disorder is still incomplete. In considering disease-modifying targets for OA, attention should be directed towards the correction of the underlying systemic abnormalities and addressing the failure of the joint components, including the bone. Most investigations have also been focussed on single skeletal regions. Given the similarities in the molecules and the pathways identified, further investigation in multi-regional studies from the same patient cohort may highlight systemic as well as localized changes in expression. The studies reviewed here suggest that OA is a systemic disease involving the bone and validate the assessment of molecular changes to further investigate this complex disease.

### Acknowledgements

The authors would like to thank Dr Egon Perilli and Dr Masakazu Kogawa for their support in the preparation of this review.

### Funding: This work was supported by the Disciplines of Anatomy & Pathology and Orthopaedics & Trauma at The University of Adelaide, as well as the National Health and Medical Research Council (NH&MRC), Australia.

### Disclosure statement: The authors have declared no conflicts of interest.

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