

REVIEW

Osteoarthritis from evolutionary and mechanistic perspectives

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Abstract

Developmental osteogenesis and the pathologies associated with tissues that normally are mineralized are active areas of research. All of the basic cell types of skeletal tissue evolved in early aquatic vertebrates. Their characteristics, transcription factors, and signaling pathways have been conserved, even as they adapted to the challenge imposed by gravity in the transition to terrestrial existence. The response to excess mechanical stress (among other factors) can be expressed in the pathologic phenotype described as osteoarthritis (OA). OA is mediated by epigenetic modification of the same conserved developmental gene networks, rather than by gene mutations or new chemical signaling pathways. Thus, these responses have their evolutionary roots in morphogenesis. Epigenetic channeling and heterochrony, orchestrated primarily by micro-RNAs, maintain the sequence of these responses, while allowing variation in their timing that depends at least partly on the life history of the individual.

KEYWORDS

channeling, epigenetics, evolution, microRNA, osteoarthritis

1 | INTRODUCTION

The diarthrodial joint appeared in the early ancestors of bony fishes, first in the jaw articulation, followed by fin function against the resistance of the water medium (Askari et al., 2016). The basic cell types associated with skeletal tissues (cartilage, bone, dentine, and enamel/enameloid) also were present, together with their associated transcription factors and signaling pathways (Apschner, Schulte-Merker, & Witten, 2011).

To illustrate the deep conservation of these earliest innovations, a teleost, the zebrafish (*Danio rerio*), has emerged as an important model for osteogenesis research

that complements mammalian models and human clinical research (Apschner et al., 2011). When vertebrates began to colonize the terrestrial environment, these aquatic life adaptations were subjected to marked changes in mechanical loading (related to gravity), for which some joints may have been “designed” poorly (Hutton, 1989). This discussion explores some of the important aspects of how these ancient innovations play out in normal morphogenesis and in the clinical disease osteoarthritis (OA). Figure 1 presents the overall scheme, to this end.

2 | SKELETAL ADAPTATIONS: WHAT IS EVOLVING?

The evolutionary model for the vertebrate joint is a complex system termed the osteochondral unit (Stender, Carpenter, Regueiro, & Ferguson, 2016). Decker, Kogama, and Pacifici (2014) described the morphogenesis

Abbreviations: AGE, advanced glycation end products; BMP, bone morphogenetic protein; ECM, extracellular matrix; FGF-2, fibroblast growth factor 2; miRNA, micro-RNA; NF-κB, nuclear factor kappa B; OA, osteoarthritis; ROS, reactive oxygen species; SOX-9, Sry-related high mobility group box 9; Wnt, wingless-type mouse mammary integration rate.

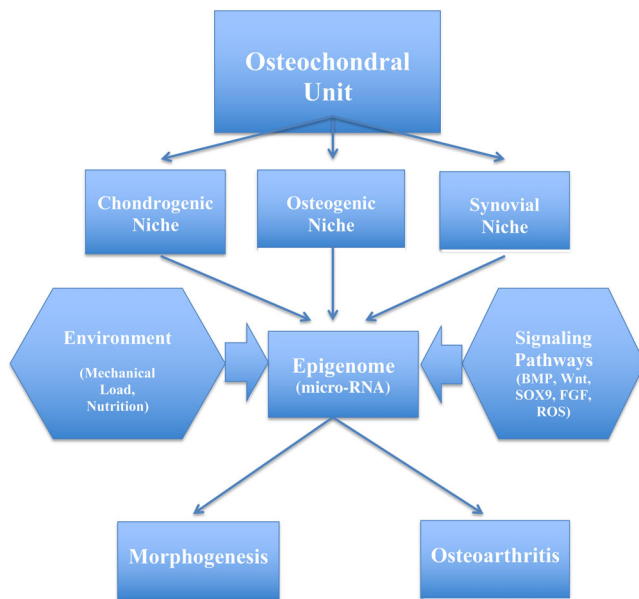


FIGURE 1 Flow diagram of the principle ideas presented in the text

of this unit as including the same mesenchymal stem cells that give rise to chondrocytes in both the articular cartilage and the growth plate chondrocytes. What ensues is an ontogenic process of controlled differentiation and phenotypic expression at specific developmental times in specific cell niches. During ontogeny, as well as during adult life, all bony structures are subject to mechanical stress. Their responses (microscopic and gross) to the magnitude and direction of stress vectors entrain an orderly adaptive process of remodeling to maintain bone and joint function (Frost, 2004; Goldring & Goldring, 2016).

From the evolutionary perspective, it is critical that phenotypic variation exists among all living populations, to permit the action of natural selection. No selection is possible on genes that are not segregating in a population. Clearly, however, variation will be confined within certain limits to prevent collapse of vital and conserved subcellular, cellular, tissue, organ, and organ system functions. Variants that risk these functions risk the organism, and if conserved, would in turn risk the population and the species. In this report, we are concerned with deeply conserved homologies arising from ancient gene networks that transformed gill arches to jaws, and fins to quadruped limbs (McCune & Schimenti, 2012).

Phenotypic diversity eddies within the broad stream of homologous networks and characterizes the adaptation and remodeling of the osteochondral unit. Important features of these processes, as summarized by Young and Badyaev (2007), include: (a) ontogeny and remodeling that are influenced by internal and external stressors;

(b) development and remodeling that entail orderly transitions from stem cell proliferation to differentiation; (c) phenotypic variation that results from changes in the timing of developmental transitions, or heterochrony; (d) adaptation that can arise quite rapidly; and (e) an “environmental sensitivity” and adaptability of this complex system that is mediated by epigenetic modification of gene networks, rather than by gene mutations or constant evolution of entirely new signaling pathways over geological time. This last point has been illustrated by various studies (Fathollahi, Aslani, Jamshidi, & Mahmoudi, 2019; Reppe, Datta, & Gautvik, 2017; Van Meurs, Boer, Lopez-Delgado, & Riancho, 2019; Vrtacnik, Mare, & Ostanek, 2014).

3 | EPIGENETICS OF THE OSTEOCHONDRAL UNIT: BIOLOGY OF MICRORNAS

The three major epigenetic mechanisms (DNA methylation, histone modification, and noncoding RNA) have roles in joint health and disease. For example, DNA methylation of the gene *dnmt3b* results in catabolism and terminal differentiation of chondrocytes that contribute to inflammation and osteophyte formation (Shen et al., 2017). Chromatin-related (histone) modification of the *EZH2* gene decreases the population of mesenchymal cells and accelerates osteoblast differentiation, thereby affecting skeletal patterning (Dudacovik et al., 2015).

It has become recognized that micro-RNA (miRNA), a large family of noncoding RNA that is present in all multicellular life, has profound structural, enzymatic, and regulatory governance effects on the osteochondral unit (Ambros, 2004). By binding to mRNA, miRNAs regulate posttranscription protein synthesis. Furthermore, one miRNA can bind to more than one mRNA, and one gene can be targeted by more than one miRNA. In the context of bone tissue, this versatility maintains the pluripotency of stem cells and regulates the commitment and stability of stem cell derivatives to specific phenotypes (Hassan, Tye, Stein, & Lian, 2015).

With respect to the joint, the biogenesis and activity of miRNAs respond to mechanical load (Guo et al., 2015; Le, Swinger, & Clark, 2013), aging of mesenchymal stem cells (He, Eberhart, & Postlethwait, 2009), and hypoxia (Nallamshetty, Chan, & Loscalzo, 2013). These properties appear to facilitate the “micromanagement” of the vertebrate skeleton in all species from fish to mammals (Dong, Yang, Guo, & Kang, 2012; He et al., 2009). Periods of rapid evolutionary change, such as at the origins of vertebrates and placental mammals, are believed to include significant proliferation and activity of miRNA (Hertel et al., 2006). Once integrated into cellular

chemistry, miRNAs and their functions rarely are lost subsequently (Heimberg, Sempere, Moy, Donoghue, & Peterson, 2008).

The acquisition of new families of miRNAs over time reflects vertebrate complexity and plasticity, as well as broader taxonomic hierarchy (Heimberg et al., 2008; Sempere, Cole, McPeck, & Peterson, 2006). Moreover, there is some evidence to support the hypothesis that morphologic novelty is enabled, in part, by miRNA-mediated epigenetic activity (He et al., 2009; Heimberg et al., 2008; Sempere et al., 2006). For example, vertebrates have nearly triple the number of cell types compared to invertebrates, as well as having 41 additional miRNA families. These changes occurred largely at the beginning of vertebrate radiation, with the new miRNAs being acquired *before* the split from jawless fishes but *after* the divergence from invertebrate chordates. Thus, vertebrate complexity (including a mineralized endoskeleton and the diarthrodial joint) may well have been enabled by a rapid and unprecedented rate of miRNA acquisition (Heimberg et al., 2008; Sempere et al., 2006).

Cellular signaling includes a stunningly sophisticated epigenetic network of chemical messengers that mediate the communication within and between cells during morphogenesis and remodeling (Allori, Saito, & Warren, 2008). These recognized pathways are orchestrated largely by miRNA activities (Zhao et al., 2013). At least five of these pathways, important in bone and joint biology, have been characterized in detail:

1. Bone morphogenetic proteins (BMPs) are highly conserved in the animal kingdom, regulating bone and cartilage formation, among a wide variety of other processes (Chen, Zhao, & Mundy, 2004). In the joint, BMPs can increase extracellular cartilage matrix (ECM) and increase chondrocyte differentiation (Van der Kraan, Davison, & van den Berg, 2010). Furthermore, some of the same BMPs that function in the osteochondral unit also regulate endocrine function, a coupling that can result in strong and rapid positive natural selection (Ahmad, Ahmad, Adeel, Asif, & Du, 2018). In the mammalian female, BMPs are expressed in granulosa cells, theca cells, and oocytes, where they regulate folliculogenesis by increasing follicle stimulating hormone, increasing estradiol, and decreasing progesterone (Rossi et al., 2015). In the male, BMPs maintain spermatogenesis, prevent epididymis degeneration, and regulate cell proliferation in the developing prostate (Lamm et al., 2001; Zhao, Liaw, & Hogan, 1998).
2. Wingless-type mouse mammary integration rate (Wnt) tightly regulates bone formation/regeneration and embryonic joint development, but also is involved in

many nonskeletal processes (Lewiecki, 2014; Monteagudo & Lories, 2017). Expression of Wnt pathway proteins can elicit dramatically different functional outcomes, depending on life stage (embryo or adult), or location within the osteochondral unit (subchondral bone or articular cartilage) (Sassi et al., 2014).

3. Sry-related high-mobility group box 9 (SOX-9) is expressed by progenitor mesenchymal cells and is essential to the survival of chondrocytes undergoing chondrogenesis (Jo et al., 2014). By promoting the synthesis of cartilage-specific matrix proteins, SOX-9 supports chondrocyte maintenance (Zhang, Thelena, Lagrisse, & Weng, 2019). Positive selection also may impact this pathway, owing to the role of SOX-9 in testis formation and sex determination (Jo et al., 2014).
4. Fibroblast growth factor 2 (FGF-2) plays an important role in the formation of the joint cavity in the embryo (Kavanaugh et al., 2006).
5. Reactive oxygen species (ROS), the free radicals that are generated by many normal and abnormal cellular processes, act as modifiers of miRNA structure (Jaksik et al., 2014). Oxidized miRNA in turn can result in misrecognition of cell signals, thus leading to aberrant gene expression. The biological consequence can be defective protein synthesis and altered cell fate programs (Nunomura et al., 2012; Wang et al., 2015).

The microecological environment of the osteochondral unit is influenced by many factors, including nutrition, mechanical load, oxygen availability, temperature, hydration, and spontaneous gene mutation (Wu, Shen, & Tang, 2009). Given the ecological complexity, the stability of a species phenotype in the face of a fluctuating microenvironment or macroenvironment is termed *canalization* (Posadas & Carthew, 2014; Wu et al., 2009). Canalization is yet another conserved attribute of all organisms. MiRNAs perform this evolutionary function by incomplete binding to their target mRNA, thus limiting translation to some specific threshold (Ebert & Sharp, 2012). This is termed a “weak buffer” of phenotype (Posadas & Carthew, 2014; Wu et al., 2009).

Another somewhat more hypothetical pathway involves both upregulation and repression via a chemical mediator that is termed an “incoherent feed-forward loop” (Posadas & Carthew, 2014). The overall effect of this metabolic pathway that is relevant to ontogeny is the regulation of miRNAs and their targets, to conserve irreversible mammalian cell differentiation (Tsang, Zhu, & van Oudenaarden, 2007). It is stunning that miRNAs not only regulate phenotype within a species, but also can canalize along a lineage of descendent species (interspecies canalization). This latter process also is a product of strong conservation through natural selection. For

example, studies have shown that the divergence of a given phenotype is less for miRNA-targeted genes than for nontarget genes; thus, miRNA buffers gene expression in a phylogenetic lineage (Cui, Yu, Purisima, & Wang, 2007).

Gould (2002) presented a detailed discussion of the evolutionary theory behind this sort of historical constraint, termed “channeling.” Such constraint imposes obvious negative structural limits on natural selection (zebras can never sprout wings to elude lions, to cite Gould’s facetious example). However, there exist also the positive consequences of constraint as “*promoters, suppliers, and causes of evolutionary direction and change*” (italics in the original Gould, 2002).

4 | OA AND THE OSTEOCHONDRAL UNIT

OA is a multifactorial degenerative disease involving one or more joints (Koszywska, Hawranek, & Nowak, 2014). Some contributing factors are classified as unmodifiable, examples including aging and genetics linked to specific OA phenotypes (Fathollahi et al., 2019; Roberts et al., 2016; Van der Kraan & van den Berg, 2008; Warner & Valdes, 2016). Others are classified as modifiable, such as obesity, repetitive mechanical stress with damage, inadequate muscle support, changes in bone alignment, and nutritional metabolites such as advanced glycation end products (AGEs) (Jackson, Wlecka, Teichtau, Morris, & Cicuttini, 2004; Koszywska et al., 2014; Saudek & Kay, 2003; Wang & He, 2018).

To understand the pathophysiology of OA, it is useful to consider the osteochondral unit as being composed of distinct yet interacting microenvironments, or niches (Williams, Edwards, Cooper, & Oreffo, 2013). The articular cartilage and its ECM constitute the chondrogenic niche. Transmembrane mechanoreceptor proteins (integrins) respond to overloading by initiating intracellular signaling cascades leading to the production of catabolic and inflammatory cytokines (Ramage, Nuki, & Salter, 2009). The induction of proinflammatory genes is mediated largely by nuclear factor kappa B (NF- κ B) (Agarwal et al., 2004), and results in degradation of the ECM, thus shifting the homeostatic anabolic/catabolic balance toward catabolism (Roberts et al., 2016; Williams et al., 2013). By contrast, moderate, intermittent loading is necessary for normal cartilage maintenance and homeostasis (Guilak, 2011).

The proinflammatory impact of the various risk factors noted above is accompanied by excess generation of ROS in pathways such as chondrocytes $\rightarrow$ mitochondrial damage $\rightarrow$ activation of endoplasmic reticulum pathways $\rightarrow$ initiation of cell apoptosis (Feng, Chen, Pengcheng, Zhang, &

Wang, 2019; Wu et al., 2016). Apoptosis, or programmed cell death, evolved early in eukaryotes and shares many molecular pathways with innate immunity, suggesting a process of coevolution (James & Green, 2002; Zmasek & Godzik, 2013). Moreover, the mitochondrial apoptosis pathway is present in all metazoans (Green & Fitzgerald, 2016). On the other hand, the normally low oxygen tension in this niche has an anabolic effect that tends to mitigate the impact of inflammatory cytokines (Pattappa, Johnstone, Zellner, Docheva, & Angele, 2019), thus creating a mechanism for metabolic balance within necessary limits.

A unique response by the chondrogenic niche is formation of osteophytes, “a fibrocartilage-capped bony outgrowth” (Van der Kraan & van den Berg, 2007). Mechanical stress, growth factors, and cytokines stimulate proliferation of periosteal mesenchymal stem cells at the joint margin, where cartilage meets bone (Junker et al., 2016). These stimulated stem cells differentiate into osteophytic chondrocytes, leading to endochondral ossification, a process induced and supported by BMPs (Gelse et al., 2012). Steinberg et al. (2018) compared the gene expression pattern in osteophytic chondrocytes (transient phenotype) to that of articular chondrocytes (a permanent phenotype), and found differential expression of 56 genes. Thus, osteophytic chondrocytes recapitulate the conserved pathway of endochondral ossification, which in the instance of OA may represent an attempt to heal the joint (Steinberg et al., 2018).

The subchondral bone represents the osteogenic niche, consisting of a subchondral bone plate with underlying trabecular bone. The plate layer is sufficiently porous, especially in high stress areas, to allow vascular communication with the overlying articular cartilage (Li et al., 2013). Coincident with the degradation of ECM collagen network, mechanosensors in osteoblasts respond to excessive stress by upregulating a variety of genes expressing alkaline phosphatase, collagen protein, growth factors, and inflammatory cytokines via NF- κ B (Sharma, Jagga, Lee, & Nam, 2013; Williams et al., 2013). The homeostatic balance between resorption and deposition is shifted, resulting in increased bone turnover, development of subchondral sclerosis, increased calcification of cartilage, and decreased diameter of trabeculae (Aho, 2017). The increased vascularity and the presence of microcracks increases the interaction with the overlying articular cartilage via signaling molecules (Sharma et al., 2013).

The synovial membrane and the synovial fluid constitute the synovial niche (Scanzello & Goldring, 2012). The semipermeable membrane regulates the balance of synovial fluid at a number of molecular levels, including high molecular weight molecules (lubricin, hyaluronic acid) and low-molecular-weight molecules (growth factors, cytokines, electrolytes, osmolytes). Normal synovial fluid

in turn regulates the physiological homeostasis of the articular cartilage (Scanzello & Goldring, 2012). Dysregulation of various aspects of the synovial fluid molecular balance is an important component of OA onset. For example, the activation of the Wnt signaling pathway in inflamed synoviocytes contributes to an increase in matrix metalloproteinases that take part in cartilage destruction (Lambert et al., 2014).

Synovial fibroblast response to mechanical stress is critical during the initial stages of OA (Schroder et al., 2019; Van den Bosch, 2019). In addition, the accumulation of AGEs over time and the low oxygen tension that occurs early in the inflammatory process promote the generation of ROS and oxidative stress (Franke et al., 2009; Ng et al., 2010). As the synovial fluid is the source of nutrients to chondrocytes, the resulting inflammatory changes in the synovial niche in turn promote degeneration of cartilage (Franke et al., 2009).

5 | EPIGENETICS OF OA

Epigenetic changes in gene expression are the focus of several recent reviews of the pathophysiology of OA (Fathollahi

et al., 2019; Van Meurs et al., 2019; Zhang et al., 2019). It is remarkable that the five signaling pathways described for morphogenesis and remodeling also are central players in OA development, and that these pathways are regulated in part or in whole by miRNAs: BMPs (Deng, Li, Gao, Lei, & Huard, 2018), Wnt (Xu, Gao, Zhang, Piao, & Dong, 2019), SOX-9 (Martinez-Sanchez, Dudek, & Murphy, 2012), FGF-2 (Boehme & Rolauffs, 2018), and ROS (Portal-Nunez, Esbrit, Alcaraz, & Longo, 2016). Furthermore, owing to the presence of damage-associated molecular patterns such as ECM secondary breakdown products and accumulated AGEs, inflammatory signaling pathways will become engaged early in cartilage degeneration and OA, via cytokines and NF- κ B (Chang et al., 2019; van den Bosch 2019).

Among the approximately 30 miRNAs that are expressed differentially in OA (Asahara, 2016; Zhang, Lygrisse, & Wang, 2017), miRNA-140 has the highest expression, regulating cartilage homeostasis, inhibiting inflammatory pathways, and modulating SOX-9 (Karlson, deSouza, Odegaard, Eugebretsen, & Brinchmann, 2016; Yu, Chen, & Wang, 2011; Zhang, Ma, & Yao, 2013). It is considered to be cartilage-specific (articular and growth plate) and highly conserved among all vertebrates (Zhang et al., 2013).

TABLE 1 Key signaling pathways

Signaling pathway	Role in morphogenesis	Role in osteoarthritis	References
BMPs	All phases of chondrogenesis and endochondral ossification.	Repair of damaged cartilage. Stimulation of chondrocyte degeneration.	Van der Kraan et al. (2010)
Wnt	Senses mechanical stress to control joint patterning and chondrocyte maturation.	Regulates cartilage degradation and osteophyte formation. Activated by inflammatory cytokines. Crosstalk with BMPs.	Papathanasiou, Malizos, and Tsezou (2012), Sassi et al. (2014), Brunt, Begg, Kague, Cross, and Hammomd (2017), and Zhou, Wang, Hamilton, and Chen (2017)
SOX-9	Stem cell proliferation and differentiation in cartilage.	Downregulated in adult but expressed in new progenitor cells in late-stage OA	Moskalewski, Hye, Jankowska-Steifer, and Osieka-Iwan (2013), Kim, Park, and Im (2013), and Koelling et al. (2009)
FGF-2	Formation of joint cavity (cavitation)	Activated by injury: Increases chondrocyte proliferation, induces catabolism. Increases gene expression of inflammatory mediators and SOX-9	Kavanaugh et al. (2006), Chong et al. (2013), Shi, Wang, Acton, Eckert, and Trippel (2015), and Boehme and Rolauffs (2018)
ROS	Regulates chondrogenesis and differentiation. Regulates endochondral ossification	Excess ROS induced by injury and aging. Diffuses into all niches. Oxidative stress causes cytotoxicity, apoptosis, inflammation.	Ziskoven et al. (2010), Bai, Gong, Dom, Cao, and Dong (2019), and Lepetsos, Papavassiliou, and Papavassiliou (2019)

Abbreviations: BMPs, bone morphogenetic protein; FGF-2, fibroblast growth factor 2; ROS, reactive oxygen species; SOX-9, Sry-related high mobility group box 9; Wnt, wingless-type mouse mammary integration rate.

6 | EVOLUTION OF OA PATHOBIOLOGY

While OA is a prominent subject in mammalian clinical medicine and research, like osteogenesis itself, this condition has its counterpart in reptiles (Philbey, Lawrie, Alleson, & Taylor, 2006; Wolfe, Stringer, Krauss, & Trout, 2015) and birds (Degernes, Lynch, & Shivaprasad, 2011; Rothschild & Panza, 2007). Additionally, as demonstrated in the zebrafish model, the changes in morphology and gene expression in mammalian OA are present in fish at different developmental stages from larva to old age (Hayes et al., 2013; Mitchell et al., 2013). Furthermore, the five selected epigenetic pathways have been described in the zebrafish model: BMP (Meinecke et al., 2018), Wnt (Martin & Kimmelman, 2012), SOX-9 (Plavicki et al., 2014), FGF (Row et al., 2018), and ROS (Zancan et al., 2015).

The osteochondral unit, especially the chondrogenic niche, is well-adapted for fitness during the reproductive life stage (Van der Kraan & van den Berg, 2008). Any significant loss of function would compromise reproductive success. Population effects would include (a) lower position within a dominance hierarchy and reduced reproductive capacity (natural selection), and/or (b) adverse effect on competition for mate choice (sexual selection) (Prum, 2017). These consequences could be considered to be a sort of genomic programming, because the elements of the osteochondral unit appear to have become firmly established in cell and tissue lines during mammalian evolution (Ahmad et al., 2018). For example, BMPs 2, 6, and 7 participate in signaling in the ovary and pituitary gland as well as in bone/cartilage regeneration (Deng et al., 2018; Lochab & Extavour, 2017; Shimisaki, Moore, Otsuka, & Erikson, 2004).

Any effect of joint responses would tend to manifest during later life stages of the individual. Postreproductive negative selection then could “appear” to be silent to the differential reproductive success that drives Darwinian evolution. The actual effect may have been creation of an increasingly complex biological spectrum that, at least at times, seems to act independently of clinically evident outcomes.

Tissue repair also recapitulates tissue morphogenesis. Repair and regeneration revive “old tools” that enabled embryonic morphogenesis of that same tissue (Ferguson, Miclau, Hu, Alpera, & Helms, 2006; Martin & Pankhurst, 2004; Sen & Ghatak, 2015). Table 1 summarizes key signaling pathways as they appear in morphogenesis or tissue repair. One important difference involves induction of inflammatory pathways (cytokine signaling) during injury response. As stated by Houard, Goldring, and Benenbaum (2013), recapitulating the morphogenetic

program causes a shift in chondrocyte phenotype, “leading to matrix remodeling, inappropriate hypertrophy-like maturation, and cartilage calcification.” Thus, miRNAs (especially miRNA-140) exert dual control of both fetal development and the pathogenesis of OA (Miyaki et al., 2010; Sen & Ghatak, 2015; Tuddenham et al., 2006).

Channeling is a third function that constrains and directs the path of particular evolutionary patterns (Gould, 2002). MiRNAs are crucial agents of this constraint in the conserved body plan. Peterson, Dietrich, and McPeck (2009) made two evolutionary observations: (a) miRNAs have been added to the metazoan genome continuously over geological time, resulting in less variability of traits as a clade evolves; (b) the earlier-established miRNAs acquire more robust activity over time. Furthermore, heterochrony is coupled to epigenetic channeling. In this context, heterochrony represents changes in the timing of maturation and differentiation of stem cells in bone and articular cartilage (Decker et al., 2014; Smith, 2001). One important gene example, *Lin-28*, is conserved broadly in spatiotemporal terms (heterochronic) and is expressed in mouse and chick limb buds (Yokoyama et al., 2008). *Lin-28* regulates developmental timing and articular cartilage thickness. MiRNAs in the *let-7* family are associated with the expression of this gene (Kobayashi & Kozlova, 2018).

7 | CONCLUSIONS

Osteoarthritic pathology is conserved across taxa. Within a clade, the observed homologous responses to injury and age are programmed for the osteochondral unit (and its niches). We know that these responses have their evolutionary roots in morphogenesis. Epigenetic channeling and heterochrony, orchestrated primarily by miRNAs, maintain the sequence of these responses, while allowing variation in their timing that depends at least partly on the life history of the individual.

At the basis of all this ferment lies nature's irreducible complexity. Organisms are not billiard balls, propelled by simple and measurable external forces to predictable new positions on life's pool table. Sufficiently complex systems have greater richness. Organisms have a history that constrains their future in myriad, subtle ways. (Gould, 1980)

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REFERENCES

- Agarwal, S., Deschner, J., Long, P., Verma, P., Hofman, C., Evans, C. H., & Piesco, N. (2004). Role of NF- κ B transcription factors in antiinflammatory and proinflammatory actions of mechanical signals. *Arthritis and Rheumatism*, 50(11), 3541–3548.
- Ahmad, H. I., Ahmad, M. J., Adeel, M. M., Asif, A. R., & Du, X. (2018). Positive selection drives evolution of endocrine regulatory bone morphogenetic protein system in mammals. *Oncotarget*, 9(26), 18435–18445.
- Aho, O.-M. (2017). Subchondral bone histology and grading in osteoarthritis. *PLoS One*, 12(3), e0173726. <https://doi.org/10.1371/journal.pone.0173726>
- Allori, A. C., Sailon, A. M., & Warren, S. M. (2008). Biological basis of bone formation, remodeling, and repair—Part I: Biochemical signaling molecules. *Tissue Engineering Part B*, 14(3), 259–273. <https://doi.org/10.1089/ten.teb.2008.0082>
- Ambros, V. (2004). The functions of animal microRNAs. *Nature*, 431, 350–355.
- Apschner, A., Schulte-Merker, S., & Witten, P. E. (2011). Not all bones are created equal—Using zebrafish and other teleost species in osteogenesis research. *Methods in Cell Biology*, 105, 239–255.
- Asahara, H. (2016). Current status and strategy of microRNA research for cartilage development and osteoarthritis pathogenesis. *Journal of Bone Metabolism*, 23, 121–127.
- Askari, A., Smeeton, J., Paul, S., Schindler, S., Brasch, I., Ellis, N. A., ... Crump, J. G. (2016). Ancient origin of lubricated joints in bony vertebrates. *eLife*, 5, e16415. <https://doi.org/10.7554/eLife.16415>
- Bai, Y., Gong, X., Dom, C., Cao, Z., & Dong, S. (2019). Redox control of chondrocyte differentiation and chondrogenesis. *Journal of Free Radicals in Biology & Medicine*, 132, 83–89.
- Boehme, K. A., & Rolauffs, B. (2018). Onset and progression of osteoarthritis—Can growth factors, inflammatory cytokines, or differential miRNA expression concomitantly induce proliferation, extracellular matrix degradation, and inflammation in articular cartilage? *International Journal of Molecular Sciences*, 19, 2282. <https://doi.org/10.3390/ijms19082281>
- Brunt, L. H., Begg, K., Kague, E., Cross, S., & Hammomd, C. L. (2017). Wnt signaling controls the response to mechanical load during zebrafish joint development. *Development*, 144(15), 2798–2809.
- Chang, S. H., Mori, D., Kobayashi, H., Mori, Y., Nakamoto, H., Okada, K., ... Saito, T. (2019). Excessive mechanical loading promotes osteoarthritis through the gremlin-1-NF- κ B pathway. *Nature Communications*, 10, 1442. <https://doi.org/10.1038/s41467-019-19491-5>
- Chen, D., Zhao, M., & Mundy, G. R. (2004). Bone morphogenetic proteins. *Growth Factors*, 22(4), 233–241.
- Chong, K.-W., Channalaris, A., Burleigh, A., Jen, H., Watt, F. E., Saklatvala, J., & Vincent, T. L. (2013). Fibroblast growth factor 2 drives changes in gene expression following injury to murine cartilage in vitro and in vivo. *Arthritis and Rheumatism*, 65(9), 2346–2355.
- Cui, Q., Yu, Z., Purisima, E. O., & Wang, E. (2007). MicroRNA regulation and interspecific variation of gene expression. *Trends in Genetics*, 23(8), 372–375.
- Decker, R. S., Kogama, E., & Pacifici, M. (2014). Genesis and morphogenesis of limb joints and articular cartilage. *Matrix Biology*, 39, 5–10.
- Degernes, L. A., Lynch, P. S., & Shivaprasad, H. L. (2011). Degenerative joint disease in captive waterfowl. *Avian Pathology*, 40(1), 103–110.
- Deng, Z. H., Li, Y. S., Gao, X., Lei, G. H., & Huard, J. (2018). Bone morphogenetic proteins for articular cartilage regeneration. *Osteoarthritis and Cartilage*, 26, 1153–1161.
- Dong, S., Yang, B., Guo, H., & Kang, F. (2012). MicroRNAs regulate osteogenesis and chondrogenesis. *Biochemical and Biophysical Research Communications*, 418(4), 587–591.
- Dudacovik, A., Camilleri, E. T., Xu, F., Riester, S. M., McGee-Lawrence, M. E., Bradley, E. W., ... van Wijnen, A. J. (2015). Epigenetic control of skeletal development by the histone methyltransferase Ezh2. *The Journal of Biological Chemistry*, 290(4), 27604–27617.
- Ebert, M. S., & Sharp, P. A. (2012). Role for microRNAs in conferring robustness to biological processes. *Cell*, 149, 515–524.
- Fathollahi, A., Aslani, S., Jamshidi, J., & Mahmoudi, M. (2019). Epigenetics in osteoarthritis: Novel insight. *Journal of Cellular Physiology*, 234, 12309–12324. <https://doi.org/10.1002/jcp.28020>
- Feng, K., Chen, Z., Pengcheng, L., Zhang, S., & Wang, X. (2019). Quercetin attenuates oxidative stress-induced apoptosis via SIRT1/AMPK-mediated inhibition of endoplasmic reticulum stress in rat chondrocytes and prevents progression of osteoarthritis in a rat model. *Journal of Cellular Physiology*, 234, 18192–18205. <https://doi.org/10.1002/jcp.28452>
- Ferguson, C. M., Miclau, T., Hu, D., Alpera, E., & Helms, J. A. (2006). Common molecular pathways in skeletal morphogenesis and repair. *Annals of the New York Academy of Sciences*, 857(1), 33–42.
- Franke, S., Sommer, M., Ruster, C., Bondeva, T., Martiche, J., Hofmann, G., ... Wolf, G. (2009). Advanced glycation end products induce cell cycle arrest and proinflammatory changes in osteoarthritis fibroblast-like synovial cells. *Arthritis Research & Therapy*, 11, R136. <https://doi.org/10.1186/ar2807>
- Frost, H. M. (2004). A 2003 update of bone physiology and Wolff's law for clinicians. *The Angle orthodontist*, 74(1), 3–15.
- Gelse, K., Ekici, A. B., Cipa, F., Swoboda, B., Carl, H. D., Olk, A., ... Klinger, P. (2012). Molecular differentiation between osteophytic and articular cartilage—Clues for a transient and permanent chondrocyte phenotype. *Osteoarthritis and Cartilage*, 20, 162–171.
- Goldring, S. R., & Goldring, M. B. (2016). Changes in the osteochondral unit during osteoarthritis: Structure, function, and cartilage-bone crosstalk. *Nature Reviews Rheumatology*, 12(11), 632–644.
- Gould, S. J. (1980). *The Panda's thumb* (p. 16). New York, NY: WW Norton and Company.
- Gould, S. J. (2002). The integration of constraint and adaptation (structure and function) in ontogeny and phylogeny. In *The structure of evolutionary theory* (pp. 1025–1039). Cambridge, MA: The Belknap Press of Harvard University Press.

- Green, D. R., & Fitzgerald, P. (2016). Just so stories about the evolution of apoptosis. *Current Biology*, 26, R620–R627.
- Guilak, F. (2011). Biomechanical factors in osteoarthritis. *Best Practice & Research. Clinical Rheumatology*, 25, 815–823.
- Guo, Y., Wang, Y., Liu, Y., Zeng, Q., Zhao, Y., Zhang, X., & Zhang, X. (2015). MicroRNA-218, microRNA-191, microRNA-3070a, and microRNA-33 are responsive to mechanical strain exerted on osteoblastic cells. *Molecular Medicine Reports*, 12(2), 3033–3038.
- Hassan, M. Q., Tye, C. E., Stein, G. S., & Lian, J. B. (2015). Non-coding RNAs: Epigenetic regulators of bone development and homeostasis. *Bone*, 81, 746–756.
- Hayes, A. J., Reynolds, S., Nowell, M. A., Meaken, L. B., Habicher, J., Leden, L., ... Hammond, C. L. (2013). Spinal deformity in aged zebrafish is accompanied by degenerative changes to their vertebrae that resemble osteoarthritis. *PLoS One*, 8(9), e75787. <https://doi.org/10.1371/journal.pone.0075787>
- He, X., Eberhart, J. K., & Postlethwait, J. H. (2009). MicroRNA and micromanaging the skeleton in disease, development, and evolution. *Journal of Cellular and Molecular Medicine*, 13(4), 606–618.
- Heimberg, A. M., Sempere, L. F., Moy, V. M., Donoghue, P. C. J., & Peterson, K. J. (2008). microRNAs and the advent of vertebrate morphologic complexity. *Proceedings of the National Academy of Sciences of the United States of America*, 105(8), 2946–2951.
- Hertel, J., Lindemeyer, M., Missal, K., Fried, C., Tanzer, A., Flamm, C., ... Stadler, P. (2006). The expansion of the metazoan microRNA repertoire. *BMC Genomics*, 7(25), 25. <https://doi.org/10.1186/1471-2164-7-25>
- Houard, X., Goldring, M. B., & Berenbaum, F. (2013). Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. *Current Rheumatology Reports*, 15, 325. <https://doi.org/10.1007/s11926-013-0375-6>
- Hutton, C. W. (1989). Osteoarthritis: The cause not the result of joint failure? *Annals of the Rheumatic Diseases*, 48, 958–961.
- Jackson, B. D., Wlecka, A. E., Teichtau, A. J., Morris, M. E., & Cicuttini, F. M. (2004). Reviewing knee osteoarthritis—A biomechanical perspective. *Journal of Science and Medicine in Sport*, 7(3), 347–357.
- Jaksik, R., Lalik, A., Skonieczna, M., Ciesler-Pobada, A., Student, S., & Rzeszowska-Wolny, J. (2014). MicroRNAs and reactive oxygen species: Are they in the same circuit? *Mutation Res/Genet Toxicol Environ Mutagenesis*, 764–765, 64–71.
- James, E. R., & Green, D. R. (2002). Infection and the origins of apoptosis. *Cell Death and Differentiation*, 9, 355–357.
- Jo, A., Denduluri, S., Zhang, B., Wang, Z., Yin, L., Yan, Z., ... Haydon, R. C. (2014). The versatile functions of Sox9 in development, stem cells, and human diseases. *Genes & Diseases*, 1, 149–161.
- Junker, S., Krumbholz, G., Frommer, K. W., Rehart, S., Steinmeyer, J., Rickert, M., ... Neumann, E. (2016). Differentiation of osteophyte types in osteoarthritis—Proposal of a histological classification. *Joint, Bone, Spine*, 83(1), 63–67.
- Karlson, T. A., deSouza, G. A., Odegard, B., Eugebretsen, L., & Brinchmann, J. E. (2016). microRNA-140 inhibits inflammation and stimulates chondrogenesis in a model of interleukin 1 β -induced osteoarthritis. *Molecular Therapy. Nucleic Acids*, 5, e373. <https://doi.org/10.1038/mtna.2016.64>
- Kavanaugh, E., Church, V. L., Osbourne, A. C., Lamb, K. J., Archer, C. W., Francis-West, P. H., & Pitsillides, A. A. (2006). Differential regulation of GD-5 and FGF-2/4 by immobilization in ovo exposes distinct roles in joint formation. *Developmental Dynamics*, 235, 826–834.
- Kim, K.-I., Park, Y.-S., & Im, G. I. (2013). Changes in the epigenetic status of the SOX-9 promoter in human osteoarthritic cartilage. *Journal of Bone and Mineral Research*, 28(5), 1050–1060.
- Kobayashi, T., & Kozlova, A. (2018). Lin28a overexpression reveals role of Erk signaling in articular cartilage development. *Development*, 145, dev162594. <https://doi.org/10.1242/dev.162594>
- Koelling, S., Kruegel, J., Irmer, M., Path, J. R., Sadowski, B., Miro, X., & Miosage, N. (2009). Migratory chondrogenic progenitor cells from repair tissue during later stages of human osteoarthritis. *Cell Stem Cell*, 4, 324–335.
- Koszywska, A., Hawranek, R., & Nowak, J. (2014). Osteoarthritis—A multifactorial disease. *Rheumatologia*, 52(5), 319–32539.
- Lambert, C., Dubuc, J.-E., Montell, E., Verges, J., Munuaut, C., Noel, A., & Henrotin, Y. (2014). Gene expression pattern of cells from inflamed and normal areas of osteoarthritic synovial membrane. *Arthritis and Rheumatism*, 66(4), 960–968.
- Lamm, M. L. G., Polasek, C. A., Barnett, C. A., Lee, J., Clemens, J. Q., Hebner, C. M., & Bushman, W. (2001). Mesenchymal factor bone morphogenetic protein 4 restricts ductal budding and branching morphogenesis in the developing prostate. *Developmental Biology*, 232, 301–314.
- Le, L. T. T., Swinger, T., & Clark, I. M. (2013). The role of microRNAs in osteoarthritis and chondrogenesis. *Arthritis and Rheumatism*, 65(8), 1963–1974.
- Lepetsos, P., Papavassiliou, K. A., & Papavassiliou, A. G. (2019). Redox and NF- κ B signaling in osteoarthritis. *Free Radical Biology & Medicine*, 132, 90–100.
- Lewiecki, E. M. (2014). Role of sclerostin in bone and cartilage and its potential as a therapeutic target in bone diseases. *Therapeutic Advances in Musculoskeletal Disease*, 6(2), 48–57.
- Li, G., Yin, J., Cheng, T. S., Pavlos, N. J., Zhang, C., & Zeng, M. H. (2013). Subchondral bone in osteoarthritis: Insight into risk factors and microstructural changes. *Arthritis Research & Therapy*, 15, 223. <https://doi.org/10.1186/ar4405>
- Lochab, A. K., & Extavour, C. G. (2017). Bone morphogenetic protein (BMP) signaling in animal reproductive system development and function. *Developmental Biology*, 427, 258–269.
- Martin, B. L., & Kimmelman, D. (2012). Canonical Wnt signaling dynamically controls multiple stem cell fate decisions during vertebrate body formation. *Developmental Cell*, 22(1), 223–232.
- Martin, P., & Pankhurst, S. M. (2004). Parallels between tissue repair and embryo morphogenesis. *Development*, 131, 3021–3024.
- Martinez-Sanchez, A., Dudek, K., & Murphy, C. L. (2012). Regulation of human chondrocyte function through direct inhibition of cartilage master regulator SOX9 by microRNA-145 (miRNA-145). *The Journal of Biological Chemistry*, 287(2), 916–924.
- McCune, A. R., & Schimenti, J. C. (2012). Using genetic networks and homology to understand the evolution of phenotypic traits. *Current Genetics*, 13, 74–84.
- Meinecke, L., Sharma, J. C., Du, H., Zhan, L., Nie, Q., & Schilling, T. F. (2018). Modeling craniofacial development reveals spatiotemporal constraints on robust patterning of the mandibular arch. *PLoS Computational Biology*, 14(11), e1006569. <https://doi.org/10.1371/journal.pcbi.1006569>
- Mitchell, R. E., Huitema, L. F. A., Skinner, R. E. H., Brunt, L. H., Severn, C., Schulte-Merker, S., & Hammond, C. L. (2013). New

- tools for studying genetics in zebrafish. *Osteoarthritis Cartilage*, 21, 269–278.
- Miyaki, S., Sato, T., Inoue, A., Otsuki, S., Ito, Y., Yokoyama, S., ... Asahara, H. (2010). MicroRNA-140 plays dual roles in both cartilage development and homeostasis. *Genes & Development*, 24, 1173–1185.
- Monteagudo, S., & Lories, R. J. (2017). Cushioning the cartilage: A canonical Wnt restricting matter. *Nature Reviews. Rheumatology*, 13, 670–681. <https://doi.org/10.1038/nrrhum.2017.171>
- Moskalewski, S., Hye, A., Jankowska-Steifer, E., & Osieka-Iwan, A. (2013). Formation of synovial joints and articular cartilage. *Folia Morphologica*, 72(3), 181–187.
- Nallamshetty, S., Chan, S. Y., & Loscalzo, J. (2013). Hypoxia: A master regulator of microRNA biogenesis and activity. *Journal of Free Radicals in Biology & Medicine*, 64, 20–30.
- Ng, C. T., Biniecka, M., Kennedy, A., McCormick, J., Fitzgerald, O., Bresnihan, B. ... Veale, D. J. (2010). Synovial tissue hypoxia and inflammation in vivo. *Annals of the Rheumatic Diseases*, 69, 1389–1395.
- Nunomura, A., Moreira, P. I., Castellani, R. J., Lee, A.-G., Zhu, X., Smith, M. A., & Perry, G. (2012). Oxidative damage to RNA in aging and neurodegenerative disorders. *Neurotoxicity Research*, 22, 23–48.
- Papathanasiou, I., Malizos, K., & Tsezou, A. (2012). BMP-2-induced Wnt/ β -catenin signaling pathways activation through enhanced low-density-lipoprotein receptor-related 5 catabolic activity contributes to hypertrophy in osteoarthritic chondrocytes. *Arthritis Research & Therapy*, 14, R82. Retrieve from. <http://arthritis-research.com/content/14/2/R82>
- Pattappa, G., Johnstone, B., Zellner, J., Docheva, D., & Angele, P. (2019). The importance of physioxia in mesenchymal stem cell chondrogenesis and the mechanisms controlling its response. *International Journal of Molecular Sciences*, 20, 484. <https://doi.org/10.3390/ijms20030484>
- Peterson, K. J., Dietrich, M. R., & McPeck, M. A. (2009). MicroRNAs and metazoan macroevolution: Insights into canalization, complexity, and the Cambrian explosion. *BioEssays*, 31(7), 736–747.
- Philbey, A. W., Lawrie, A. M., Alleson, C. J., & Taylor, D. J. (2006). Lower urinary tract obstruction in a Mediterranean tortoise (*Testudo graeca*) with coxofemoral arthritis. *The Veterinary Record*, 159, 492–495.
- Plavicki, J. S., Baker, T. R., Burns, F. R., Xiong, K. M., Gooding, A. J., Hofsteen, P., ... Heideman, W. (2014). Construction and characterization of a SOX9b transgenic reporter line. *The International Journal of Developmental Biology*, 58(9), 693–699.
- Portal-Nunez, S., Esbrit, P., Alcaraz, M. J., & Longo, R. (2016). Oxidative stress, autophagy, epigenetic changes and regulation by miRNAs as potential therapeutic targets in osteoarthritis. *Biochemical Pharmacology*, 108, 1–10.
- Posadas, D. M., & Carthew, R. W. (2014). MicroRNAs and their roles in developmental canalization. *Current Opinion in Genetics & Development*, 27, 1–6. <https://doi.org/10.1016/j.gde.2014.03.005>
- Prum, R. O. (2017). *The evolution of beauty* (pp. 41–42). New York, NY: Doubleday.
- Ramage, L., Nuki, G., & Salter, D. M. (2009). Signaling cascades in mechanotransduction: Cell-matrix interactions and mechanical loading. *Scandinavian Journal of Medicine & Science in Sports*, 19, 457–469.
- Repe, S., Datta, H. K., & Gautvik, K. M. (2017). Omics analysis of human bone to identify genes and molecular networks regulating skeletal remodeling in health and disease. *Bone*, 101, 88–95.
- Roberts, S., Colombier, P., Sowman, A., Mennen, C., Roling, J. H. D., Guicheux, J., & Edwards, J. R. (2016). Aging in the musculoskeletal system. *Acta Orthopaedica*, 87(eSuppl 363), 15–25.
- Rossi, R. O. D., Costa, J. J. N., Silva, A. W. B., Saraiva, M. V. A., Vanden Hurk, R., & Silva, J. R. V. (2015). The bone morphogenetic protein system and regulation of ovarian follicular development in mammals. *Zygote*, 24, 1–17.
- Rothschild, B. M., & Panza, R. K. (2007). Lack of bone stiffness/strength contribution to osteoarthritis—Evidence for primary role of cartilage damage. *Rheumatology*, 46, 246–249.
- Row, R. H., Pegg, A., Kinney, B. A., Farr, G. H., Maves, L., Lowell, S., ... Martin, B. L. (2018). BMP and FGF signaling interact to pattern mesoderm by controlling basic helix-loop-helix transcription factor activity. *eLife*, 7, e31018.
- Sassi, N., Laadhan, L., Allouche, M., Aschek, A., Kallel-Sellami, M., Makni, S., & Sellami, S. (2014). WNT signaling and chondrocytes: From cell fate determination to osteoarthritis pathophysiology. *Journal of Receptor and Signal Transduction Research*, 34(2), 73–80.
- Saudek, D. M., & Kay, J. (2003). Advanced glycation endproducts and osteoarthritis. *Current Rheumatology Reports*, 5(1), 33–40.
- Scanzello, C. R., & Goldring, S. R. (2012). The role of synovitis in osteoarthritis pathogenesis. *Bone*, 51, 249–257.
- Schroder, A., Naget, U., Muschter, D., Grassel, S., Proff, P., & Kirschneck, C. (2019). Impact of mechanical load on the expression profile of synovial fibroblasts from patients with and without osteoarthritis. *International Journal of Molecular Sciences*, 20, 585. <https://doi.org/10.3390/ijms20030585>
- Sempere, L., Cole, C. N., McPeck, M. A., & Peterson, K. J. (2006). The phylogenetic distribution of metazoan microRNA: Insights into evolution, complexity and constraint. *Journal of Experimental Zoology. Part A, Comparative Experimental Biology*, 306B, 575–588.
- Sen, C. K., & Ghatak, S. (2015). MiRNA control of tissue repair and regeneration. *The American Journal of Pathology*, 185(10), 2629–2640.
- Sharma, A. R., Jagga, S., Lee, S.-S., & Nam, J.-S. (2013). Interplay between cartilage and subchondral bone contributes to pathogenesis of osteoarthritis. *International Journal of Molecular Sciences*, 14, 19805–19830.
- Shen, J., Wang, C., Li, D., Xu, T., Myers, J., Ashton, J. M., ... O'Keefe, R. J. (2017). DNA methylation 3b regulates articular cartilage homeostasis by altering metabolism. *JCI Insight*, 2(12), e93612. doi.org/10.1172/jci.insight.93612
- Shi, S., Wang, C., Acton, A. J., Eckert, G. J., & Trippel, S. B. (2015). Role of Sox-9 in growth factor regulation of articular chondrocytes. *Journal of Cellular Biochemistry*, 116(7), 1391–1400.
- Shimizu, S., Moore, R. K., Otsuka, F., & Erikson, G. F. (2004). The bone morphogenetic protein system in mammalian reproduction. *Endocrine Reviews*, 25(1), 72–101.
- Smith, K. K. (2001). Heterochrony revisited: The evolution of developmental sequences. *Biological Journal of the Linnean Society*, 73, 169–186.

- Steinberg, J., Brooks, R. A., Southam, L., Bhatnagar, S., Roumeliotis, T. I., Hatzikotoulas, K., ... Zeggini, E. (2018). Widespread epigenomic, transcriptomic and proteomic differences between hip osteophytic and articular chondrocytes in osteoarthritis. *Rheumatology*, 57, 1481–1489.
- Stender, M. E., Carpenter, R. D., Regueiro, R. A., & Ferguson, V. L. (2016). An evolutionary model of osteoarthritis including articular cartilage damage and bone remodeling in a computational study. *Journal of Biomechanics*, 49, 3502–3508.
- Tsang, J., Zhu, J., & van Oudenaarden, A. (2007). MicroRNA-mediated feedback and feedforward loops are recurrent network motifs in mammals. *Molecular Cell*, 26, 753–767.
- Tuddenham, L., Wheeler, G., Ntounia-Fousara, S., Waters, J., Hajihosseini, M. K., Clark, I., & Dalmay, T. (2006). The cartilage specific miRNA-140 targets histone deacetylase 4 in mouse cells. *FEBS Letters*, 580, 4214–4217.
- Van den Bosch, M. H. (2019). Inflammation in osteoarthritis: Is it time to dampen the alarm(in) in this debilitating disease? *Clinical and Experimental Immunology*, 195(2), 153–166.
- Van der Kraan, P. M., Davison, E. N. B., & van den Berg, W. B. (2010). Bone morphogenetic proteins and articular cartilage: To serve and protect or a wolf in sheep's clothing. *Osteoarthritis Cartilage*, 18(6), 735–741.
- Van der Kraan, P. M., & van den Berg, W. B. (2007). Osteophytes: Relevance and biology. *Osteoarthritis Cartilage*, 15, 237–244.
- Van der Kraan, P. M., & van den Berg, W. B. (2008). Osteoarthritis in the context of ageing and evolution—Loss of chondrocyte differentiation block during ageing. *Ageing Research Reviews*, 7, 106–113.
- Van Meurs, J. B. J., Boer, C. G., Lopez-Delgado, L., & Riancho, J. A. (2019). Role of epigenetics in bone and cartilage disease. *Journal of Bone and Mineral Research*, 34(2), 215–230.
- Vrtacnik, P., Mare, J., & Ostanek, B. (2014). Epigenetic mechanisms in bone. *Clinical Chemistry and Laboratory Medicine*, 52(5), 589–608.
- Wang, J.-X., Gao, J., Ding, S.-L., Gong, Y., Zhou, Z., & Li, P.-F. (2015). Oxidative modification of miR-184 enables it to target Bcl-xl and Bcl-w. *Molecular Cell*, 59, 50–61.
- Wang, T., & He, C. (2018). Pro-inflammatory cytokines: The link between obesity and osteoarthritis. *Cytokine and Growth Factor Reviews*, 44, 38–50.
- Warner, S. C., & Valdes, A. M. (2016). The genetics of osteoarthritis: A review. *Journal of Functional Morphology and Kinesiology*, 1, 140–153.
- Williams, E. L., Edwards, C. J., Cooper, C., & Oreffo, R. O. C. (2013). The osteoarthritis niche and modulation of skeletal stem cell function for regenerative medicine. *Journal of Tissue Engineering and Regenerative Medicine*, 7, 589–608.
- Wolfe, T. C., Stringer, E., Krauss, S., & Trout, T. (2015). Phytotherapy as an adjunctive treatment for severe osteoarthritis in a 20-year old Komodo dragon (*Varanus komodoensis*). *Journal of Zoo and Wildlife Medicine*, 46(1), 164–166.
- Wu, C.-I., Shen, Y., & Tang, T. (2009). Evolution under canalization and the dual roles of microRNAs—A hypothesis. *Genome Research*, 19, 734–743.
- Wu, Q., Zhang, Z.-M., Zhu, S.-Y., Liao, C. R., Pan, Y., Zeng, J.-H., ... Chen, J. T. (2016). Advanced oxidation protein products induce chondrocyte apoptosis via receptors for advanced glycation endproducts-mediated, redox-independent intrinsic apoptosis pathway. *Apoptosis*, 21, 36–50.
- Xu, W., Gao, P., Zhang, Y., Piao, L., & Dong, D. (2019). microRNA-138 induces cell survival and reduces WNT/ β -Catenin signaling of osteoarthritic chondrocytes through FKK2. *IUBMB Life*, 71, 1355–1366. <https://doi.org/10.1002/iub.2050>
- Yokoyama, S., Hashimoto, M., Shimizu, H., Ueno-Kudoh, H., Uchibe, K., Kimura, I., & Asahara, H. (2008). Dynamic gene expression of Lin-28 during embryological development in mouse and chicken. *Gene Expression Patterns*, 8, 155–160.
- Young, R. L., & Badyaev, A. V. (2007). Evolution of ontogeny: Linking epigenetic remodeling and genetic adaptation in skeletal structures. *Integrative and Comparative Biology*, 47(2), 234–244.
- Yu, C., Chen, W.-P., & Wang, X.-H. (2011). MicroRNA in osteoarthritis. *The Journal of International Medical Research*, 39, 1–9.
- Zancan, I., Bellesso, S., Costa, R., Salvalaio, M., Stroppiano, M., Hammond, C., ... Moro, E. (2015). Glucocerebrosidase deficiency in zebrafish affects primary bone ossification through increased oxidative stress and reduced Wnt/ β -catenin signaling. *Human Molecular Genetics*, 24(5), 1280–1299.
- Zhang, M., Lygrisse, K., & Wang, J. (2017). Role of microRNA in osteoarthritis. *J Arthritis*, 6(2), 1–12. <https://doi.org/10.4127/2167-7921.1000239>
- Zhang, M., Thelena, J., Lagrisse, K. A., & Weng, J. (2019). Epigenetic mechanisms underlying the aging of articular cartilage and osteoarthritis. *Gerontology*, 65, 387–396. <https://doi.org/10.1159/000496688>
- Zhang, R., Ma, J., & Yao, J. (2013). Molecular mechanism of the cartilage-specific microRNA-140 in osteoarthritis. *Inflammation Research*, 62, 871–877.
- Zhao, G.-Q., Liaw, L., & Hogan, B. L. M. (1998). Bone morphogenetic protein 8a plays a role in the maintenance of spermatogenesis and the integrity of the epididymis. *Development*, 125, 1103–1112.
- Zhao, X., Xu, D., Li, Y., Zhang, J., Liu, T., Ji, Y., ... Xie, X. (2013). MicroRNA regulates bone metabolism. *Journal of Bone and Mineral Metabolism*, 32(3), 221–231. <https://doi.org/10.1007/s00774-013-0537-3>
- Zhou, Y., Wang, T., Hamilton, J. L., & Chen, D. (2017). Wnt/ β -catenin signaling in osteoarthritis and in other forms of arthritis. *Current Rheumatology Reports*, 19(9), 53. <https://doi.org/10.1007/s11026-017-0679-2>
- Ziskoven, C., Jager, M., Zilkens, C., Bloch, W., Brixius, K., & Krauspe, R. (2010). Oxidative stress in secondary osteoarthritis: From cartilage destruction to clinical presentation? *Orthopaedic Review*, 2, e23. <https://doi.org/10.4081/ot2010.e23>
- Zmasek, C. M., & Godzik, A. (2013). Evolution of the animal apoptosis network. *Cold Spring Harbor Perspectives in Biology*, 5, a008649.

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