

# Cartilage Lubrication in Osteoarthritis

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Contributor: Renjian Xie

The remarkable lubrication properties of normal articular cartilage play an essential role in daily life, providing almost frictionless movements of joints. Alterations of cartilage surface or degradation of biomacromolecules within synovial fluid increase the wear and tear of the cartilage and hence determining the onset of the most common joint disease, osteoarthritis (OA).

Keywords: articular cartilage ; osteoarthritis ; boundary lubrication ; chondrocytes

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## 1. Introduction

Articular cartilage is an avascular, aneural and alymphatic connective tissue (which determines its very poor self-recovery ability) lining the bone ends of diarthrodial joints <sup>[1]</sup>. Combined with excellent load-bearing capacities, this cushion of articular cartilage, especially the outer surface of cartilage, provides extremely low friction with a friction coefficient as low as  $10^{-3}$  under a wide range of physiological pressures (even up to 100 atm) to maintain daily movements during a person's lifetime <sup>[2][3][4]</sup>. Recently, researchers noticed that the increase of cartilage friction plays a determining role in initiating the most common degenerative joint disability disease, that is osteoarthritis (OA), which is mainly characterized by the progressive but irreversible degradation of articular cartilage <sup>[5][6][7][8][9]</sup>. Briefly, aging-related changes or lesions usually lead to the compromise of the outer surface of cartilage, which subsequently causes an increase of the friction coefficient. Chondrocytes, as the only cell type in cartilage, in return, up-regulate the secretion of the cartilage-degrading enzymes, such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) to degrade the type II collagen and aggrecan (the main components of cartilage matrix), respectively. Moreover, the cartilage degradation fragments are phagocytosed cells (such as macrophage and synovial fibroblasts) to inflame the synovium, promoting the production of MMPs and ADMATS to break down cartilage and deteriorate lubrication <sup>[10][11][12][13][14][15]</sup>. In this way, a positive feedback loop is formed due to the mutually reinforcing effect of increased friction and secretion of degradation enzymes, resulting in the progressive till total degradation of articular cartilage. Early, moderate, and late stages of OA can be classified mainly based on the degree of cartilage degradation. It is thought the breakdown of the type II collagen network initiates the point where the OA is considered irreversible <sup>[16][17]</sup>. Is it possible to modify and prevent the disease at its early stage especially considering the role of cartilage lubrication?

Among the population over 60 years old, 9.6% of men and 18.0% of women have OA symptoms, which made OA a serious global disease defined by the Osteoarthritis Research Society International in 2016 <sup>[18]</sup>. Cell-based therapies or cartilage tissue engineering for cartilage repair or regeneration have made significant advances recently <sup>[19][20]</sup>, such as the adhesive peptide-based 3D scaffolds for cell culture <sup>[21]</sup>, however, considerable efforts are still required for the tribological properties and durability of the neocartilage before clinical translation. Currently, the main nonsurgical options for OA treatment before the end of OA include using analgesics, anti-inflammatory drugs (such as acetaminophen), inhibitors (such as cyclooxygenase), or articular injection of hyaluronan and corticosteroids <sup>[22][23]</sup>. However, these nonsurgical options usually are highly controversial due to the nonuniversal effects when compared to that in state-of-the-art placebo-controlled <sup>[24][25]</sup>. Therefore, it is highly important to shed light on the remarkable lubrication of cartilage and the correlation between lubrication and cartilage regeneration, with the aim to improve the understanding of OA and encourage the development of approaches to alleviating and even treating it.

## 2. Articular Cartilage

A joint is a place where two or more bones meet, allowing the skeleton to move. Usually, joints differ in shape and structures according to the required movement and load, so we focus on discussing the diarthrosis knee joints. The knee joint consists of a joint capsule, ligaments, synovium, and the articular cartilage lining the ends of the opposing bones <sup>[1]</sup>. Synovial fluid within the capsule provides lubrication and nutrition, while the synovial membrane, a sac-like structure,

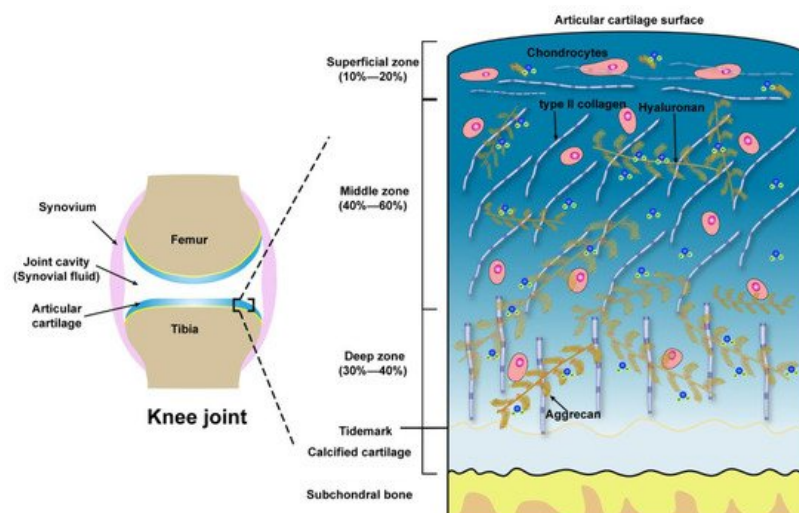
surrounds the joint cavity and synovial fluid [26]. In daily life, it's essential to maintain the normal structure of the synovial joint.

## 2.1. Structure and Components of Articular Cartilage

Articular cartilage (also referred to as hyaline cartilage) is a highly hydrated glassy connective tissue comprised of chondrocytes (the only cell type embedded within cartilage) and the extracellular matrix (ECM) which is secreted and maintained by chondrocytes [4][27]. The ECM is predominantly composed of type II collagen bundles, negatively charged proteoglycans, non-collagenous proteins, water, and ions (primarily  $\text{Na}^+$  and  $\text{Cl}^-$ ). 11 types of collagens could be found in articular cartilage. Among them, type II collagen, representing 90–95% of all collagens in ECM and accounting for 60% of the dry weight of articular cartilage, forms a crosslinked core network, to enable the cartilage tensile and shear strength [28][29].

The type II collagen fibril networks interweave with proteoglycans (such as aggrecans), the second most abundant macromolecules in articular cartilage, which contribute to the lubrication and load-bearing properties of cartilage due to their strong hydration [12]. Proteoglycans are proteins covalently attached to glycosaminoglycans (long repetitive dimers of hexosamine and uronic acid). The most prevalent and largest in size of proteoglycans in articular cartilage are aggrecans, representing a bottle-brush structure with a polypeptide as backbone and chondroitin sulfate and keratan sulfate as the side chains. Usually, there are over 100 chondroitin sulfate and 20–40 keratan sulfate chains in one aggrecan molecule [30][31]. Therefore, the aggrecans are highly sulfated and negatively charged conferred by the sulfate groups in their side chains. These negative charges attract large water molecules to further strengthen the cartilage matrix. Hyaluronic acid or hyaluronan (HA), the only non-sulfated glycosaminoglycan, is built by the repeated dimers of b-D-(1,4)-N-acetylglucosamine and b-D-(1–3) glucuronic acid with a molecular weight up to 6 MDa [32]. HA and aggrecan form an extensive aggregate, comprising of a central HA to which about 100 aggrecan molecules are non-covalently attached via the link protein, thereby stabilizing this aggregation [33]. These aggregates further bind to the type II collagen fibers and have been demonstrated to play a significant role in cartilage lubrication (will be discussed later).

Microscopically, three zones of the articular cartilage can be distinguished, that is the superficial zone (also referred to as the lamina splendens), the middle or transitional zone and the deep zone, as shown in **Figure 1**. These three zones of cartilage exhibit heterogeneity in the composition of ECM, which is reflected in the organization of collagen, size, phenotype, and metabolic activity of chondrocytes [34]. The superficial zone lies in the outer surface of articular cartilage, constitutes 10–20% of the full thickness of adult cartilage, characterized by two aspects, one is the type II collagen fibers, with a diameter of 30–35 nm, which are densely arranged and parallel to the articular surface, the other one is the long axis of flat and ellipsoidal chondrocytes parallel to the surface of the cartilage. Normally, the lubricating molecules are within the superficial zone. The middle zone is constituted of 40–60% of the thickness of total cartilage, the chondrocytes, exhibiting round or rectangular shape, are randomly distributed with their long axis perpendicular to the cartilage surface. The fibrils of type II collagen form an oblique transitional network and appear as arcades. The deep or radial zone constitutes the last 20–30% of the thickness of the cartilage. The shape of chondrocytes is round, the fibrils of type II collagen, with the largest diameter (40–80 nm), are perpendicular to the cartilage surface. The predominant biomechanical properties of the main three different zones of articular cartilage are summarized in **Table 1**.



**Figure 1.** Schematic illustration of the knee joint and the structure, compositions of articular cartilage from the surface to subchondral bone.

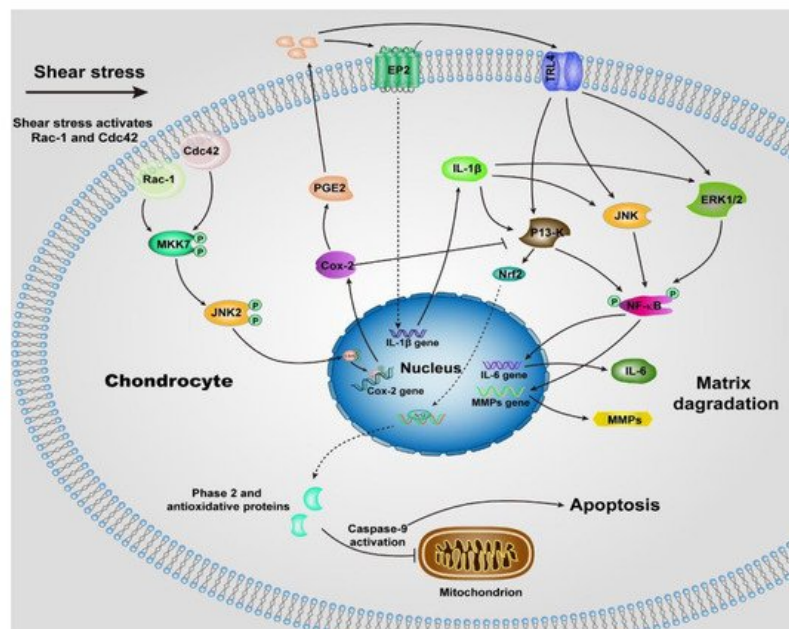
**Table 1.** The main biomechanical properties of the superficial zone, middle zone, and deep zone of articular cartilage.

Zones	Extracellular Molecules	Biomechanical Properties	References
<b>Superficial zone</b> (10 to 20%)	Outer of Surface Lubricin, HA, Phospholipids, COMP	Boundary lubrication, chondroprotection	[35][36][37]
	Below outer of Surface Type II collagen aggrecans, HA	Resist shear stress, bear ~20% load; Maintain tensile strength; As a barrier to fluid flow during loading; Subject to maximum strain; Contribute to elasticity and resiliency via interacting with collagen	[38][39][40]
<b>Middle zone</b> (40 to 60%)	Upper ~1/3rd Collagen type II, other collagens, aggrecans, HA	Transit shear and compression stresses; Exhibit high deformation during loading; Resist compression; Contribute to elasticity and resiliency to compression via interacting with collagen	[38][39][40][41]
	Lower ~2/3rd Thick collagen type II, other collagens, aggrecan, HA, GAGs	Compared with upper 1/3rd of the middle zone: Decrease tensile strength; Provide higher resistance to compression during loading	[42][43][44]
<b>Deep zone</b> (30 to 40%)	Thickest collagen type II, other collagens, aggrecans, HA, high GAGs	Relative to the middle zone: Further decreased tensile strength; Provide highest resistance to compression during loading	[42][43][44]

## 2.2. Mechanotransduction of Chondrocytes

Mechanotransduction refers to the process of sensing and converting mechanical signals into biochemical signals to regulate cellular activities [45]. Located on the joint surfaces, a range of static and dynamic stresses (standing, walking, and jogging) are applied on articular cartilage. It is well documented the metabolism of chondrocyte is strongly regulated by the normal stress (compression), static loads were shown to be detrimental to the anabolic processes (biosynthesis of type II collagen and proteoglycans) while oscillatory loads with moderate frequencies and amplitudes (compression strain under 20%) have been shown to effectively promote the matrix accumulation and decrease the secretion of TNF- $\alpha$  and IL-6, which contribute to the degradation of matrix [46][47][48][49].

Unlike normal stress, shear stress gives rise to the shear strain of the cartilage, and then be transmitted to the chondrocytes, especially those within the superficial zone. Many previous studies suggested the shear stress activates chondrocytes and up-regulates the proinflammatory cytokines (TNF- $\alpha$ , and the family of interleukins) and MMPs [48][50], which elicit the degradation of cartilage, most of the underlying signaling pathways remain unclear, but we can summarize some of them in **Figure 2** according to the previous reports [50][51][52][53][54][55][56]. The chondrocytes undergo a phenotypic switch to aberrantly express catabolic enzymes when the shear strain exceeds  $\approx 1\%$  estimated by Klein and Lin very recently under relative ideal circumstances considering the complexity of cartilage [57]. Moreover, the increased shear strain, or the shear stress or friction, induces chondrocyte apoptosis, which has been demonstrated by previous studies [58][59]. The mechanism regulating shear-mediated chondrocytes expression of IL-6 and MMPs and apoptosis is shown in **Figure 2**. The stimuli of high shear stress induce chondrocytes to express cyclooxygenase (Cox 2), which inhibits the activity of phosphatidylinositol 3-kinase (PI3-K), following decreases in antioxidant capacity to lead to chondrocyte apoptosis.



**Figure 2.** Schematic of shear-induced cartilage matrix degradation and apoptosis of chondrocytes. High shear stress activates the Rac-1/Cdc42, which then transactivates MKK7 to regulate JNK2 activation, and this, in turn, triggers c-Jun phosphorylation which induces the overexpression of Cox-2. Cox-2 suppresses the activity of P13-K, which represses Nrf-2 to decrease the antioxidant capacity to permit disruption of the integrity of mitochondrial, activation of caspase-9, and the apoptosis of chondrocytes. The expression of Cox-2 also triggers the expression of PGE2, as well as the concomitant downstream expression of receptor EP2, as a result, IL-1b is rapidly and sustainably synthesized. Moreover, up-regulation of TLR4 due to high shear stress activates ERK1/2, P13-K and JNK pathways, which is also activated by IL-1b, then regulates NF-kB-dependent IL-6 and MMP synthesis. Abbreviations: Cyclooxygenase-2 (Cox-2), mitogen-activated protein kinase 7 (MKK7), nuclear factor-kB (NF-kB), prostaglandin E2 (PGE2), Interleukin-1b (IL-1b), Interleukin-6 (IL-6), phosphatidylinositol 3-kinase (PI3-K), c-Jun N-terminal kinase 2 (JNK2), NF-E2 related factor 2 (Nrf2), matrix metalloproteinases (MMPs), toll-like receptor 4 (TLR4), extracellular signal-regulated kinase (ERK1/2).

Collectively, favoring cartilage longevity requires dynamic normal stress combined with quite low or even zero shear stress. To maximize the regeneration of cartilage, the main way is to decrease the shear strain arising from the shear stress by reducing the friction coefficient of cartilage. Therefore, a scenario in which treating or healing OA at its early stage by restoring the lubrication of OA-damaged cartilage can be imagined.

### 2.3. Lubrication Mechanism of Articular Cartilage

The friction coefficients of normal articular cartilage can be as low as  $\sim 0.002$ - $0.02$ <sup>[57]</sup>. The lubrication properties of articular cartilage have drawn attention since the 1930s and many theories have been proposed to claim the mechanisms behind the ultra-low friction of cartilage.

Recently, a new picture emerged where it is the synergy between the molecules in the synovial fluid that determines the lubrication of articular cartilage under severe joint loading<sup>[60][61]</sup>. Specifically, HA associates with aggrecan via the link protein to form a bottle-brush structure where HA serves as the backbone and aggrecan as the side chain. HA and lubricin also form a complex, which is physically trapped on the surface and contributes to effectively eliminate the wear damage of the cartilage. HA also shows a high affinity with phospholipids according to the previous report<sup>[62]</sup>. Thus, Klein et al. pointed to a scenario in which HA (alone cannot bind to cartilage surface) anchors at the outer surface of cartilage with the assistance of lubricin, then further complexes with the phospholipids to act as an effective boundary lubricant to enable the remarkable lubrication of articular cartilage at high pressure, via the hydration mechanism<sup>[63][64][65]</sup>. In this way, lubricin serves as a “carrier” between the HA, phospholipids, and the outer surface of the articular cartilage.

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