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Mini review

The biology of Lubricin: Near frictionless joint motion

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ABSTRACT

Lubricin is a surface-active mucinous glycoprotein secreted in the synovial joint that plays an important role in cartilage integrity. In healthy joints, lubricin molecules coat the cartilage surface, providing boundary lubrication and preventing cell and protein adhesion. Arthropathy occurring in patients with joint trauma, inflammatory arthritis or genetically mediated lubricin deficiencies have insufficient lubricin to prevent damage to articular cartilage. Recent studies in lubricin null joints indicate that lubricin (Prg4) plays a role in preventing damage to the superficial zone and preservation of chondrocytes. Progress in the production of recombinant forms of lubricin and the successes of lubricin supplementation in small animal models identify rhPRG4 as a potential therapeutic for patients with transient lubricin deficiency in the setting of trauma or autoimmune arthritis.

Contents

1. Introduction

The inventor of the total hip joint prosthesis, Dr. John Charnley, was among the first of many investigators to appreciate that joints lubricated by synovial fluid have very low frictional properties (Charnley, 1959). Numerous mechanisms have been posited to explain how articulating cartilage surfaces under load, lubricated by synovial fluid, produce a coefficient of friction (μ) on the order of ~0.01 or less. Even our best manufactured bearing surfaces, for example Teflon, demonstrate significantly higher μ's (~0.04) and as Charnley discovered, Teflon does not handle load well. In fact, current arthroplasty devices replace the low friction articular surface with low wear but relatively higher friction bearings. Lubricating activity of synovial fluid was later studied outside of diarthrodial joints (McCutchen, 1962; Linn, 1968). Of note, synovial fluid lubricates in the absence of viscosity following digestion by hyaluronidase. The isolated lubricant, a ~227 kDa glycoprotein, was coined "lubricin" by David Swann (Swann et al., 1985). Later work confirmed many of the findings of Swann *et al.* and showed that lubricin was able to lubricate non cartilaginous surfaces as effectively as whole synovial fluid in the boundary mode (Jay, 1992). The goal of this review is to summarize advances in our

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understanding of mammalian joint lubrication systems and reflect on our new appreciation of relevant factors in joint motion, particularly how lubricin is a major contributor to joint longevity. Osteoarthritis is a remodeling "disease" process which, at its origin, may result from a tribologic pathophysiology type of disease process, resulting in *osteoarthrosis* from incipient friction induced biological damage (i.e. wear). The same joint trauma models which are used in understanding post-traumatic OA have also been utilized to understand lubricin metabolism. These studies suggest that osteoarthrosis in the peri-injury period following meniscus or anterior cruciate ligament trauma can be mitigated by the introduction of exogenous lubricin.

1.1. Joint mechanics

Diarthrodial joints exhibit complicated mechanics, characterized by high nominal contact pressures ~5 mPa (Hodge et al., 1986; Morrell et al., 2005), slow reciprocating speeds ~<1 mm/sec, and flattening of cartilage surface asperities under load. Cartilage compressibility and resultant extracellular fluid flows created by cartilage under pressure serve a major role in the ability of cartilage to work as a load-bearing material (Krishnan et al., 2004). Apposed and pressurized cartilage surfaces moving ~>1 mm/sec relative to one another are likely lubricated in a mixed mode fashion, relying on the contributions of both hydrodynamic and boundary lubrication (Fig. 1). Hydrodynamic lubrication takes advantage of uneven surfaces (before asperities have flattened) and the viscosity of synovial fluid provided by hyaluronic acid. The depressurization of cartilage requires more than several minutes (Krishnan et al., 2004) to reach a point of fluid desaturation at which time cartilage surfaces are fully engaged and effaced. This paradigm, under the mechanical constraints described above, requires an intervening coating of biomolecules to keep these surface asperities from adhering together — a boundary lubricant (Lee et al., 2013). Thus, the compliance of congruent cartilage surfaces, flattening of asperities, and very low speed of motion in joint kinematics are bearing parameters that dictate the need for boundary lubrication to prevent accumulated tissue damage with normal use (Coles et al., 2010a). In particular the knee joint, which can be characterized as a roller-slider bearing, displays a range of entraining velocities including near zero-sliding speed. The transition from boundary to hydrodynamic lubrication is described by the Stribeck diagram (Fig. 1)(Neu et al., 2008; Gleghorn et al., 2009). Nature has provided diathrodial joints with a delicate boundary lubricant — lubricin (PRG4) — which is released by the same bearing surfaces as well as the synovial tissue (Chan et al., 2012) and helps maintain very low friction as these surfaces reciprocate during motion.

1.2. Lubricin and superficial zone protein

In the pre-genomic era, lubricin was first dubbed "lubricating glycoprotein 1" by its discoverer David Swann (Swann et al., 1981). Lubricin was described as a ~227 kDa extensively O-linked glycoprotein, which when purified from synovial fluid digested by hyaluronidase, could reproduce the full friction reducing activity of synovial fluid (Swann et al., 1985). Molecular weight was described by sedimentation and light scattering analysis. Components on the surface of cartilage were also studied by investigators who were interested in the superficial layer of articular surfaces. Biochemical extraction of the superficial zone led to the purification of a 345-kDa protein with minimal glycosaminoglycan substitution, named superficial zone proteoglycan (SZP) (Schumacher et al., 1994). Others focused attention on a rare, Mendelian-inherited genetic arthropathy called camptodactyly-arthropathy-coxa vara-pericarditis (CACP) syndrome, which causes juvenile-onset, noninflammatory, precocious joint failure (Marcelino et al., 1999). These distinct and separate lines of investigation converged from the engineering, cartilage biology and musculoskeletal disease perspectives, resulted in similar conclusions: the secreted protein lubricin/SZP/CACP present in synovial fluid and the superficial zone of cartilage, plays an essential role in cartilage integrity and joint health (Flannery et al., 1999; Jay et al., 2000). Lubricin reduces friction in cartilage bearings in vitro (Swann et al., 1985; Gleghorn et al., 2009;

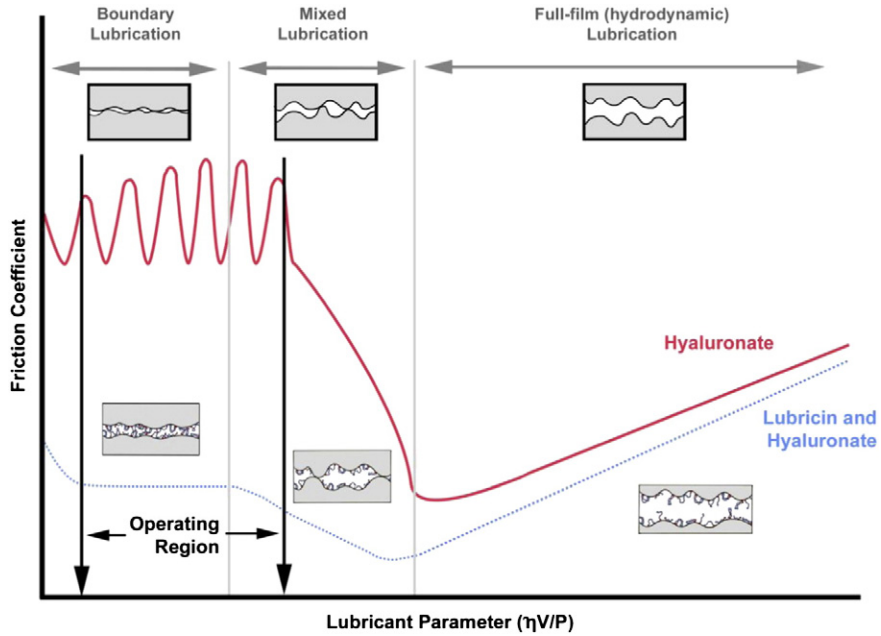

Fig. 1. Stribeck curve in synovial tribology. Boundary lubrication occurs in the presence of lubricin at very low sliding speeds when the lubricating film is the same thickness as the surface roughness manifested by flattened high points (asperities) on the apposing cartilage surfaces. In the absence of lubricin, adhesion occurs and friction is higher producing a stick-slip phenomenon. At higher entraining speeds, in the hydrodynamic regime, the intervening fluid adjoining the surface will move at the same speed as the joint surface during locomotion. The two cartilage surfaces move relative to each other and will be drag fluid into the interface. Synovial fluid (SF) that enters a converging gap in this manner will see a pressure increase as the gap converges, which creates hydrodynamic lift, and forces the surfaces apart like a wedge. Mixed lubrication occurs between boundary and hydrodynamic lubrication, as the name would suggest. The fluid film thickness is slightly greater than the surface roughness, so that there is very little asperity contact. The friction coefficient is the ratio of sliding to normal force, and the lubrication parameter is the product of SF viscosity (η) and entraining velocity (V), divided by the contact pressure (P).

Waller et al., 2013) and can also reduce friction between several rubbing synthetic surfaces including graphite (Jay et al., 2007a), latex (Jay et al., 2000), glass (Jay, 1992), mica (Zappone et al., 2007) and idealized surfaces (Chang et al., 2008). The gene responsible for lubricin expression was initially named megakaryocyte-stimulating factor (MSF), owing to the discovery that the 32-kDa amino terminal fragment of lubricin is able to stimulate megakaryocyte growth in vitro (Merberg et al., 1992). Lubricin/SZP is expressed by superficial zone chondrocytes at the cartilage surface (Flannery et al., 1999) and to a lesser extent by the intermediate zone chondrocytes (Schmidt et al., 2004). Lubricin is also expressed by synoviocytes (Jay et al., 2000).

Lubricin is highly conserved across species, in the case of mouse, rat, bovine and human lubricin displaying a capricious amount of serine (>5%) and threonine (>20%) residues, and reactivity to lectins such as peanut agglutinin which react with β(1,3)GalNAc-Gal. A central mucin domain is flanked by globular N- and C-termini which may be polyfunctional. Analysis of lubricin's amino acid sequence reveals it to be related to vitronectin. Both proteins contain a somatomedin B-like (SMB) domain and a hemopexin-like domain (Merberg et al., 1992) having greater than 40% sequence similarity in these regions. In the case of vitronectin, SMB and hemopexin-like domains, respectively, regulate the complement and coagulation systems (Zhou et al., 2003) and promote integrin-mediated cellular attachment to the extracellular matrix, involving the binding of heparin (Da Silva et al., 2003). The SMB domain in plasma vitronectin extends the lifetime of active plasminogen activator inhibitor-1, which controls hemostasis by inhibiting fibrinolysis (Gils and Declerck, 2004). Despite these essential biologic activities, vitronectin knockout mice have no obvious clinical phenotype (Zheng et al., 1995). Unlike vitronectin, lubricin contains a large, central, mucin like domain, characterized by the repeating motif (KEPAPTT), which is subject to extensive O-linked glycosylation (Jay et al., 2001).

One function in the N-terminus is to create a disulphide bond joining two lubricin monomers (Schmidt et al., 2009). Thus native lubricin exists as a monomer and dimer (Jay et al., 2010). The amino acid motif KEPAPTT in the mucin domain repeats degeneratively. The number of KEPA/EPTT repeats maybe proportional to the size of the mammal (Ikegawa et al., 2000). Lubricin physico-chemically adsorbs to surfaces as an end-grafted brush, which serves to coat and repel a like covered surface via steric repulsion. Cartilage surface interaction through either the N- or C-terminus, or both, occurs and results in a carpet-like covering of fully extended lubricin monomers/dimers and others that are folded in the mucin domain (Zappone et al., 2008) (Fig. 2). Since lubricin is 50% (w/w) glycosylated and removal of the penultimate galactose diminished lubricating ability in vitro (Jay et al., 2001), it is likely that hydration forces are also involved in the steric repulsion forces between adherent lubricin layers on apposed cartilage surfaces (Briscoe et al., 2006).

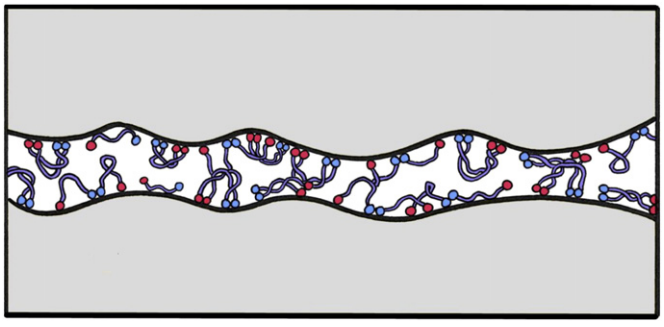

Fig. 2. Lubricin forms end-grafted brush structures on protected surfaces. (A) Lubricin is a semi-flexible extended rod type mucinous glycoprotein and exists as a monomer and dimer through disulphide bond linkage. Both the N (blue) and C-termini (red) appear capable of surface interaction which requires a hair pin turn in the intervening mucin domain. Physisorbed end-grafted molecules can assume a state where both termini interact with a surface or only the C-terminus. **(B)** As cartilage is compressed and asperities flatten the apposing carpets of end-grafted brushes interact and repel through steric repulsion.

The zonal stratification of lubricin expression is an interesting histological feature of cartilage. Lubricin is predominantly expressed by the superficial zone and the upper intermediate zone chondrocytes (Klein et al., 2003). Lubricin expression has also become a focus in the tissue engineering of articular cartilage intended for allograft transplantation (Klein et al., 2006). Lubricin is a useful indicator of zonal stratification, because greater amounts of lubricin secretion occur within the superficial layer of cartilage constructs as opposed to the intermediate and deeper layers. Whether this *in vitro* stratification will be functional *in vivo*, enabling lubrication under load, remains to be studied. Mechanotransduction experiments of chondrocytes in alginate culture show that lubricin expression is up regulated under tensile stress but not in pure compression (Grad et al., 2006; Nugent et al., 2006). Mice on a running wheel have also demonstrated Prg4 upregulation by the superficial zone chondrocytes (Ogawa et al., 2014). Tensile stresses are created by both loading and surface movement (Wong et al., 2008) and cyclic loading focuses tensile stresses within the superficial layers of the articular surface (Warner et al., 2004). The accumulation of lubricin is not uniform across the surface of articular cartilage. The anterior aspect of the femoral condyle has more extractable lubricin than posterior areas. Explants from different areas of the femoral condyle used in the measurement of cartilage friction confirm these observations (Neu et al., 2007).

The fact that lubricin lubricates a number of different synthetic surfaces supports the case that it is a highly surface-active mucinous glycoprotein. In vitro lubricating ability measured using a latex upon glass bearing showed a sigmoidal relationship with lubricin concentration (Jay, 1992). A high concentration lowered friction whereas a low concentration allowed higher friction. The same range of concentrations in a two phase mixture of saline and hexane respectively reduced and increased interfacial tension which supports its amphipathic behavior. Lubricin added to concentric disk and ring cartilage explants in vitro demonstrated reduced adhesive strength following six weeks of healing (Schaefer et al., 2004). This anti-adhesive quality has also been manifested in the ability of exogenous lubricin to interfere with tissue regeneration and healing response *in vivo*. Canine flexor tendons re-approximated with lubricin covering a simple anastomosis to restore normal gliding failed to heal adequately in some cases as evidenced by spontaneous rupture (Zhao et al., 2010). Only after late mobilization, and the insertion of mesenchymal stem cells, did the tendon anastomosis show a more typical healing response in the presence of chemically grafted hyaluronate and lubricin (Zhao et al., 2014) but this also served to prevent adhesions. The gross surface binding and growth-regulating properties of lubricin are also evident in the synoviocyte hyperplasia that occurs in patients with CACP (Marcelino et al., 1999). Further evidence for cellular growth inhibition may exist in patients with aseptic prosthetic loosening, which has been correlated to MSF/lubricin up-regulation of between 20-and 300-fold across six individuals (Morawietz et al., 2003).

1.3. Lubricin in the lamina splendens

Lubricin occupies the uppermost superficial layer of the cartilage ultra structure referred to as the lamin*a* splendens. The lamina splendens contains hyaluronate, fibronectin (Zea-Aragon et al., 2004), and lipid (Sarma et al., 2001), possibly existing as a bilayer (Guerra et al., 1996). Lubricin is also present as it is easily immuno-detected on the surface of articular cartilage (Schumacher et al., 1999). The pressurized cartilage surface imaged by confocal laser microscopy revealed a reversible fringe pattern consistent with liquid crystal formation (Kobayashi and Oka, 2003). This phenomenon could be a result of confined lubricin monomers/dimers and structuring of water (Briscoe et al., 2006). The lamina splendens is easily removed with proteolytic digestion (Teeple et al., 2007) but is resistant to complete digestion

with hyaluronidase and chondroitinase ABC (Kumar et al., 2001). Following its removal, a fibrous structure was observed under scanning electron microscopy that is likely the underlying collagen network of the superficial zone. The ankle joint contains a greater density of superficial zone chondrocytes than the knee, which has been implicated as a reason why primary osteoarthritis (OA) is more common in the knee (Schumacher et al., 2002).

1.4. Role of hyaluronate

Hyaluronate by itself does not appear to have boundary lubricating properties when studied in vitro (Jay et al., 1992; Waller et al., 2012). However, nanotribologic evidence with the surface force apparatus suggests that chemical binding of hyaluronate to a bearing surface is necessary to initiate a reduction in friction (Tadmor et al., 2003) and wear reduction (Lee et al., 2014). This is an important observation because the hyaluronate interaction enables lubricin to lubricate under higher contact pressures in vitro (Jay et al., 1992; Das et al., 2013). Synovial hyaluronate levels were found to vary among patients undergoing revision arthroplasty (Mazzucco et al., 2004). Lubricin together with hyaluronate appear to lower COF synergistically on both cartilage (Schmidt et al., 2007) and idealized model surfaces (Chang et al., 2008; Das et al., 2013; Lee et al., 2014). High molecular weight hyaluronate is more effective in its interaction with lubricin in both reducing friction (Kwiecinski et al., 2011) and wear (Greene et al., 2011) particularly if the hyaluronate is tethered to cartilage. Hyaluronate is also decorated with inter-alpha-trypsin inhibitor (ITI) which is a potent serine protease inhibitor (Yingsung et al., 2003). The proximity of ITI to lubricin leads one to speculate if preservation of joint surface lubricating ability is a target since a number of catabolic enzymes observed to digest lubricin (Elsaid et al., 2005; Elsaid et al., 2007) can be inhibited by ITI.

1.5. Lipids in articular surfacing

Lipids have been proposed to have boundary lubricating properties (Hills, 2002). Evidence supporting this derives from the loss of lubricating ability after digestion of synovial fluid with phospholipase. However, low-level proteolytic enzyme contamination of phospholipase is responsible for this result, because digestion of synovial fluid in the presence of proteolytic inhibitors prevented an increase in friction in a latex-glass bearing system (Jay and Cha, 1999). Lipid does not appear to further reduce the synergistic reduction in friction by lubricin and hyaluronate (Schmidt et al., 2007). The composition of lipid in the superficial layer of cartilage is 41% phosphatidylcholine, 27% phosphatidylethanolamine, and 32% sphingomyelin (Sarma et al., 2001). However, these values may be affected by a contribution from the synovium following needle aspiration or excision during synovial fluid collection. This potential confounder has not been controlled. Lipid exists in synovial fluid in the form of oligolamellae (Schwarz and Hills, 1996) but it is unclear how these structures would interact with the surface of articular cartilage. A combination of dipalmitoyl phosphatidylcholine liposomes and hyaluronic acid, delivered in vivo in a rabbit model, was shown to reduce the coefficient of friction of the articular surface in injured rabbit stifle joints oscillating under load ex vivo (Kawano et al., 2003). These rabbits had undergone anterior and posterior cruciate ligament transection. The group treated with both the hyaluronate and liposomes histologically showed the least damage to the articular surface. Understanding the chemical composition of the surface of articular cartilage will be crucial in efforts to completely understand boundary lubrication. Lubricin's interaction with hydrophobic surfaces such as latex and idealized hydrophobic surfaces (Chang et al., 2009) is an important but non-specific feature that appears to emulate this aspect of biologic activity in vivo. The surface of cartilage also displays hydrophobic character (Chappuis et al., 1983). The interaction of lubricin with polymerized collagen type II is stronger than amorphous collagen and suggests that a chemical interaction between lubricin and collagen type II is not responsible for its ability to coat articular cartilage (Chang et al., 2014).

2. Lubricin in preventing PTOA

Three different laboratories have re-introduced native or recombinant human lubricin into rat joints post-traumatically and demonstrated disease-modifying effect in animal models of post-traumatic arthritis. Rats that underwent a medial meniscectomy (Flannery et al., 2009) or ACL transection (Jay et al., 2010; Elsaid et al., 2012) have been so treated with either repeated intra-articular (IA) dosing or in a single dose-escalated strategy (Jay et al., 2012). In these studies, chondroprotective effect was demonstrated by improved histology, cartilage thickness or preservation of glycosaminoglycans compared to non-treated controls. Two studies showed a reduction in urine levels of CTX-II (Elsaid et al., 2012; Jay et al., 2012). Another study in post-ACL transected rat knee joints showed an improvement in the radiographic outcome following supplementation with lubricin (Teeple et al., 2011). Chondroprotective results were more evident in rats that underwent forced exercise while rats that did not receive lubricin showed comparatively greater damage (Elsaid et al., 2012). The practice of lubricin supplementation has been dubbed *tribosupplementation* and was noted to also decrease the number of apoptotic chondrocytes (Elsaid et al., 2012) and increase native lubricin expression compared to non-treated controls. The inflammation associated with meniscectomy and ACL transection is thought to down regulate PRG4 expression which was observed in chondrocyte culture and in cartilage explants in vitro in the presence of IL-1 (Jones and Flannery, 2007; DuRaine et al., 2009).

The *in vivo* half-life of a radio labeled recombinant, truncated lubricin with a shortened mucin domain (LUB:1) was found to be 6.7 hours in a medial menisectomized rat (Vugmeyster et al., 2012). However, this value must be reconciled with the fact that the radioactivity was still present on the articular surface up to 28 days following IA injection. The half-life of the LUB:1 is triphasic with α, β and γ phases. The calculation is weighted primarily by the former while the γ phase is significantly longer and may explain why radio labeled LUB:1 continues to be detectable well past the reported 6.7 hour time point.

Over expression of *Prg4* has also been reported in mice following medial meniscal destabilization and in an aging mouse model (Ruan et al., 2013). An adenoviral vector which successfully achieved over expression was noted to be highly chondroprotective in this mouse model as indicated by the maintenance of cartilage thickness measured by micro CT and OARSI histological grading. These investigators concluded that anabolic pharmacogenetic targets, like lubricin, should be targeted to prevent post-traumatic OA in lieu of catabolic enzyme targets.

2.1. Lubricin in established arthritic diseases

Synovial fluid from patients with OA has near normal lubricating ability in a latex upon glass bearing system (Jay et al., 2004). However, lubricin/SZP was found to be ineffective in reducing friction in arthritic articular cartilage (Neu et al., 2010). Therefore, lubricin levels in synovial fluid may not always reflect the protein's function at the cartilage surface. However, significantly reduced lubricin levels have been observed in synovial fluid from patients with ACL injuries (Elsaid et al., 2008) as well as diminished lubricating ability in synovial fluid aspirates in patients with traumatic synovitis (Jay et al., 2004). Similarly, the reduced lubricin concentration and lubricating ability in synovial fluid aspirates from patients with established OA can be normalized with supplemental lubricin (Ludwig et al., 2012). In these instances, enzyme-mediated proteolytic destruction of lubricin in synovial fluid maybe mirroring comparable destruction at the cartilage surface (Teeple et al., 2008). Since injury (Anderson et al., 2011) and occupation (Lohmander et al., 2004; Fleming et al., 2005) continue to be identified as factors in the pathogenesis of OA and may involve transient

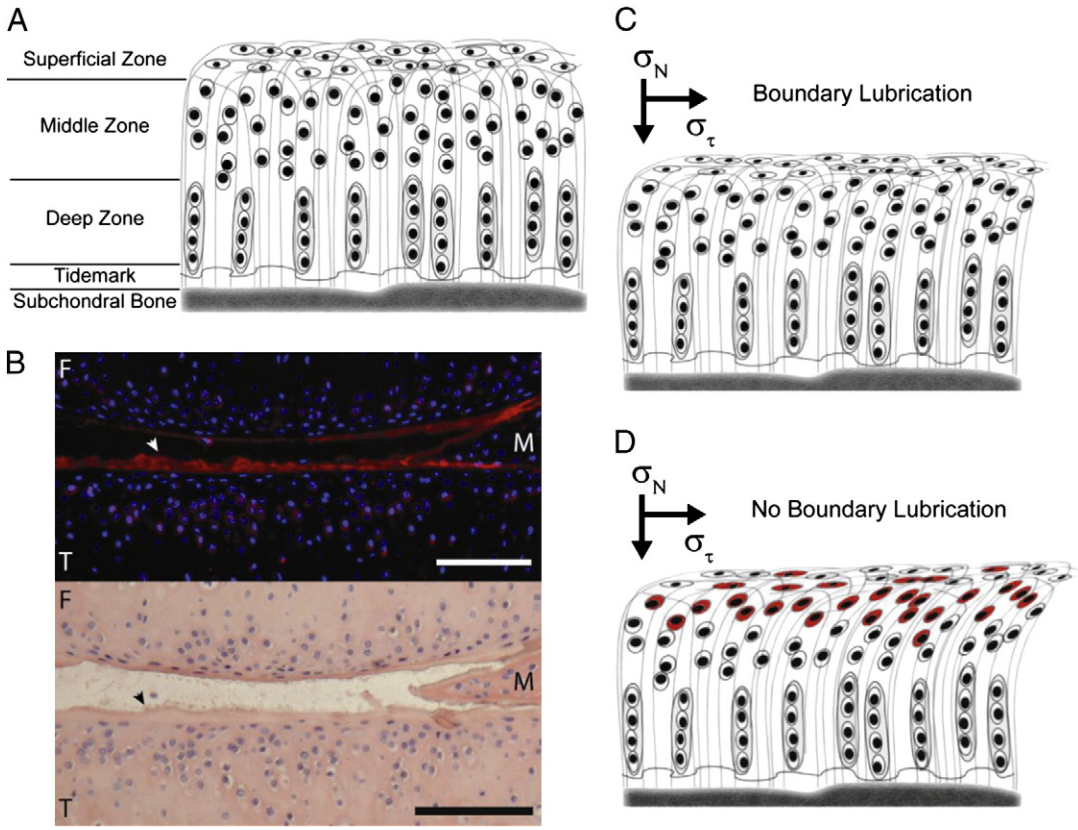

Fig. 3. Schematic of collagen and cellular structure in cartilage and response to load (σ_N) and shear (σ_τ). (A) Collagen bundles extend radially from the deep zone, resisting axial stress, bend through the middle and upper middle zones to become parallel to the cartilage surface in the superficial zone, where they resist shear stress. Superficial zone chondrocytes are flattened; whereas, middle zone and deep zone chondrocytes are rounded, with deep zone chondrocytes forming columns within lacunae. **(B) *Prg4*$^{-/-}$ mouse knee at 8 weeks of age. (top)** Staining for active caspase-3 (red) indicates apoptotic chondrocytes. Cell nuclei are indicated by DAPI (blue). Many apoptotic cells reside in the middle zone located below the flattened superficial zone chondrocytes. Red fluorescence on the surface of both the femoral condyle (F) and tibial plateau (T) indicates protein deposition (white arrowhead). **(bottom)** Corresponding section stained with H&E. Cartilage fibrillation and protein deposition (black arrowhead) are common in lubricin null joints. Damage to the meniscus (M) and cellular cloning is also evident. Scale bars indicate 100 μm. **(C)** Schematic showing cartilage response to axial and shear forces in the presence of boundary lubrication. Forces are supported by the collagen structure throughout the cartilage, which accommodate typical axial and shear cartilage loads. **(D)** In the absence of boundary lubrication, such as in the case of *Prg4*$^{-/-}$ mice, elevated shear forces due to increased friction deform the cartilage surface, causing the highest deformation in the rounded cells located below the flattened superficial zone chondrocytes. In response deformed cells undergo apoptosis (red).

mechanical overload and inflammation, we speculate that transient deficiency of lubricin in synovial fluid and at the lamina splendens, may initiate the early process of cartilage damage (i.e., osteoarthrosis) that will ultimately evolve into OA. If this is the case, then studying traumatic or inflammatory-induced fragmentation of this protein and consequent neoepitope formation may offer a unique biomarker opportunity with which to follow joint disease onset and progression. In addition, the inflammasome may alter the glycosylations on lubricin which may adversely affect lubricating activity (Estrella et al., 2010).

2.2. Camptodactyly-arthropathy-coxa vara- pericarditis syndrome (CACP)

The essential role of lubricin in maintaining joint integrity was demonstrated by the identification of disease causing truncating mutations in patients with the autosomal recessive disorder CACP (Albuhairan and Al-Mayouf, 2013). These mutations result in lack of protein expression or function (Marcelino et al., 1999). Individuals with CACP have normal-appearing joints at birth, but with advancing age develop early joint failure associated with non-inflammatory synoviocyte hyperplasia and subintimal fibrosis of the synovial capsule (Bahabri et al., 1998). These patients frequently require joint replacement surgery by the third decade. The clinical syndrome of CACP was recapitulated in a lubricin null mouse which early in postnatal development displays loss of superficial zone chondrocytes, invasion of articular cartilage by synoviocytes (Rhee et al., 2005) and an elevated whole joint coefficient of friction upon positioning the joint as the fulcrum of a pendulum (Jay et al., 2007a; Drewniak et al., 2012). Loss of cartilage stiffness and staining for glycosaminoglycan may also be an outcome of lubricin deficiency (Coles et al., 2010b). Aspirates of synovial fluid from six patients with CACP demonstrated loss of fluid elastic modulus (Jay et al., 2007b) and no ability to lower the coefficient of friction in a latex and glass bearing which would typically be well lubricated by normal synovial fluid (Jay et al., 2007a). Perhaps most importantly, the cartilage in non-weight bearing newborn lubricin null mice appears normal. By two weeks of age, the knee cartilage from these animals show significant disruption of tangentially oriented surface collagen type 2, suggesting accumulating surface damage as soon as the lubricin null animals begin to weight bear on their extremities. Lubricin null mice display active caspase-3 localized to chondrocytes just beneath the articular surface, suggesting that the non-lubricated surface is mechanically overloaded (Waller et al., 2013). Restoring lubricin expression early is a critical determinant in joint preservation (Waller et al., 2014).

2.3. Chondroprotection definition

The presence of synovial fluid with an adequate level of lubricin will prevent adhesion of cartilage surface asperities and damage to tangentially oriented collage type II. This has been observed experimentally in both in vitro (Buckley et al., 2008) and in vivo conditions (Jay et al., 2007a; Waller et al., 2013). Elevated surface shear stress is generated by a stick-slip phenomenon caused by these adhesions (Lee et al.,

2013) (Fig. 1). These stresses also cause a rise in subsurface strain (Wong et al., 2009) which appears to initiate chondrocyte apoptosis (Waller et al., 2013). Apoptosis is most pronounced in chondrocytes which are located where the tangential and radial collagen fibrils intersect (Fig. 3) where strain is maximized. Chondrocyte apoptosis has also been implicated in cartilage degradation (D'Lima et al., 2001), and its association with elevated friction due to lubricin deficiency may be medically important. Furthermore, fragmented collagen type II may go on to initiate complement fixation and innate inflammation (Wang et al., 2011).

3. Conclusion

Lubricin is a highly conserved, mucinous glycoprotein serving a primary function as an articular boundary lubricant necessary for maintaining mammalian joint health. Reduction of friction between pressurized and rubbing articular surfaces has been studied ex vivo and in vitro with both non biologic and cartilaginous surfaces, arriving at similar conclusions. The recent works using recombinant forms of lubricin (Flannery et al., 2009; Jay et al., 2010) have focused attention on what intra-articular lubricin administration might do to mitigate established arthritic disease or to prevent its emergence if identified early enough. Ongoing investigations seek to: 1) characterize joints that display osteoarthrosis (Radin et al., 1991) which may benefit by tribosupplementation prior to the hallmarks of OA (Loeser et al., 2012), 2) create a reliable platform of PRG4 expression, and 3) explore biocompatible polymers that mimic the friction-reducing activity of lubricin (Wathier et al., 2013). Renewed interest in joint surface tribology and the role of frictional damage in OA pathophysiology will result in translatable technologies deserving of clinical trial.

Acknowledgements

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