Critical review

The role of lubricin in normal and pathological joint tissue: a contemporary review

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Abstract

Introduction

The aim of this article was to critically review the literature about lubricin and its involvement in normal and pathological joint tissue. In particular, our research focused on new therapeutic approaches for the treatment of osteoarthritis related to lubricin.

We reviewed the literature regarding lubricin expression. We examined the current literature by searching on PubMed and Scopus using appropriate keywords related to lubricin and joint tissue. Main research articles were then selected for review.

Discussion

Cartilage is the tissue that covers the ends of the bones where the bones meet to form a joint. The cartilage allows the bones to glide over one another with limited friction and wear. It contains proteoglycans such as aggrecan and lubricating fluid-containing glycosaminoglycans such as hyaluronic acid. Osteoarthritis is the most common form of arthritis, a degenerative joint disease that mostly affects the cartilage. Lubricin, also commonly referred to as the superficial zone protein, is a glycoprotein specifically synthesised by chondrocytes located at the surface of articular cartilage. It has been shown that lubricin is critical to normal joint function, providing boundary lubrication of congruent articular surfaces under conditions of high contact pressure and near-zero sliding speed. Recent studies have demonstrated that administration of recombinant lubricin in the joint cavity would be effective in the prevention of cartilage degeneration in animal osteoarthritis models. It is a promising treatment for cartilage diseases, but further studies are necessary to shed light on its therapeutic value.

Conclusion

This critical review reported recent findings about the possible distribution of lubricin in some normal and pathological tissues and further provided new insights for future approaches in the treatment of osteoarthritis.

Introduction

Lubricin, also commonly referred to as the superficial zone protein, was originally isolated and purified from the culture media of explants derived from the superficial zone of bovine articular cartilage[1]. It is a large, multifaceted, water-soluble glycoprotein encoded by the proteoglycan 4 (PRG4) gene. This protein has a molecular mass of approximately 227.5 kDa, consists of approximately equal proportions of proteins and glycosaminoglycans and contains multiple protein domains that likely contribute to its diverse biological properties. Lubricin is known to be involved in the joint lubrication system. This system consists of three parts: lubricin, surface active-phopholipids and hyaluronic acid (HA). Lubricin's 1404 amino acid sequence contains somatomedin B and hemopexin-like domains that have been suggested to regulate the complement and coagulation systems, mediate extracellular matrix attachment and promote cell attachment and proliferation[2]. Purified hemopexin interacts with HA, suggesting that the haemopexin-like domain could also mediate lubricin binding to HA present at or near the articular surface[3]. In addition, lubricin attachment to the articular surface may be maintained by disulphide bond formation via the unmatched cysteine residue near the C-terminus[4].

Lubricin was originally identified as a lubricating glycoprotein present in the synovial fluid (SF), specifically synthesised and expressed by articular chondrocytes of the superficial zone. It is recognised to have a major protective role in preventing cartilage wear, synovial cell adhesion and proliferation and reducing the coefficient of friction of the articular cartilage surface[1,5,6].

Electron microscope measurements show that the lubricin molecule is a partially extended, flexible
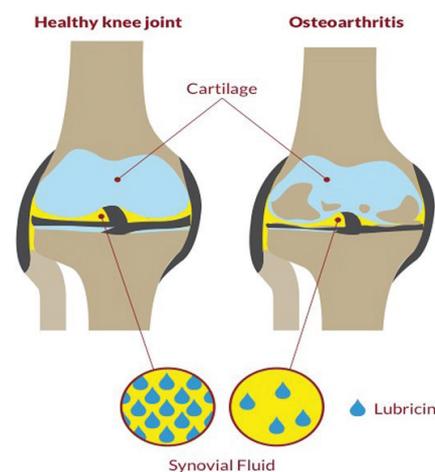
Figure 1: Diagram of the presence of lubricin in the SF of the healthy knee joint and OA knee joint.

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rod and, in solution, occupies a smaller spatial domain than would be expected from structural predictions. This characteristic feature of the lubricin molecule may aid the molecule's boundary-lubricating ability. Depletion of the lubricin function has also been associated with camptodactyly-arthropathy-coxavara-pericarditis syndrome, an arthritis-like autosomal recessive disorder[5].

Lubricin biosynthesis and biodistribution are mostly regulated by cytokines and growth factors. Exposure of synoviocytes, chondrocytes and cartilage explants to proinflammatory cytokines such as interleukin-1 and tumour necrosis factor-alpha, results in a marked reduction in the expression and/or abundance of secreted lubricin, with corresponding alterations in the amounts of cartilage-associated lubricin. Conversely, exposure to transforming growth factor-beta significantly upregulates lubricin synthesis, secretion and cartilage boundary association[7]. Many studies have investigated the various roles of lubricin, including lubrication and cytoprotection. Lubricin plays an important role in articular joint physiology, and the loss of accumulation of lubricin may be a factor in the pathology of osteoarthritis (OA) (Figure 1). Therefore, a recent study[8] demonstrated that recombinant lubricin has a role in chondroprotection in an animal OA model which suggested the potential use of recombinant lubricin molecules in new approaches for the treatment of OA and associated cartilage alterations. This critical review focuses on lubricin, emphasising its role in different normal and pathological tissues, its current use and its promising future in various therapeutic strategies.

Discussion

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Animal care was in accordance with the institution guidelines.

Lubricin distribution in some normal joint tissues

Lubricin has previously been shown to be a proteoglycan specifically synthesised and expressed by articular chondrocytes of the superficial layer[9]. It contributes to the boundary lubrication properties, facilitating low friction levels at the interfacing surfaces of articular cartilage[10].

It is secreted predominantly by superficial zone chondrocytes while cells from the middle and deep zone synthesise very low amounts of this protein[9]. During normal joint articulation, expres-sion of lubricin plays a crucial role in both preventing cell attachment to the articular surface as well as maintaining lubrication properties at the cartilage-SF interface[8]. Loss of lubricin influences the functional properties of synovial joints and could have a role in the pathogenesis of cartilage degeneration[11]. Some authors have demonstrated that lubricin provides essential chondroprotective properties to articular cartilage and can interact with HA in the SF to enhance its chondroprotec-tive properties via the dissipation of shear-induced energy[12]. Other studies found that it appeared to have a detrimental effect in damaged joints by coating the surfaces of damaged cartilage and inhibiting integrative repair of articular cartilage lacera-tions[13].

Other studies showed that lubricin is visualised at the surface of fibrocartilaginous regions of the tendon[14] and in sections of bovine calf meniscus[15]. In the latter, it was detected in two regions including surfaces of the meniscus, and within and near cells along the radial fibres and circumferential fibres. Lubricin is also present in the infrapatellar fat pad (IFP) of the knee and is synthesised and secreted by the IFP stromal cells into the SF and therefore contributes in maintaining healthy joint function and homeostasis[16]. Moreover, recent studies have demonstrated that lubricin is present in many joint tissues (Table 1), e.g. in the anterior cruciate ligament (ACL), in the knee lateral collateral ligament[17], in the human temporomandibular joint (TMJ) disc[18] and in the bilaminar zone of the TMJ[19], without any degenerative changes. Lubricin contributes to the lubrication in tendons and ligaments where it facilitates the relative movement of collagen bundles. It is present in several locations of the TMJ disc, being significantly more expressed at disc surfaces than in the central part[18].

Lubricin may also have a role in the normal disc posterior attachment physiology through the prevention of cellular adhesion as well as providing lubrication during normal bilaminar zone function[19]. The distribution of lubricin varies in different tissue types, and this variation in splicing and physical distribution suggested that the variants of lubricin might play different roles in different locations.

Lubricin distribution in some pathological joint tissues

Authors demonstrated that the PRG4 gene is expressed differently in the synovium of rheumatoid arthritis (RA) and OA, which implies its possible role in the pathogenesis of these diseases[20]. Lubricin was also studied in the TMJ disc with internal derangement[21]. Our group[22] studied the application of orthodontic forces to the teeth, showing a transduction of mechanical forces to the cells of the periodontal ligament (PDL), which triggers several biological reactions causing the synthesis of prostaglandins, cytokines and growth factors.

Furthermore, almost all PDL cells in the adjacent tooth cementum and alveolar bone were more heavily immuno-labeled by the lubricin antibody, contrary to those located in the central portion of the PDL. Therefore, lubricin expression seems related to PDL remodelling and tooth displacement following the application of an orthodontic force, and it appears that lubricin may play an important role during tooth movement. Acute joint trauma and altered biomechanics negatively affect the frictional properties of the articular surface and result in cartilage degeneration. Studies of animal models and human samples have consistently shown significant changes in both the structure and metabolism of joint cartilage matrix after joint injury. SF lubricin concentrations were also measured after knee damage and were significantly reduced at the early stage following ACL injury when compared with those in the contralateral joint. Furthermore, within 12 months, concentration in the injured knee approached that of the contralateral knee and did not change with time[12]. Therefore, the decrease in SF lubricin concentrations following ACL injury may place the joint at an increased risk of wear-induced damage as a consequence of lack of boundary lubrication, potentially leading to secondary OA. In a rabbit knee injury model, Elsaid and coworkers[23] found that the articular cartilage degradation was associated with the loss of the boundary-lubricating ability of SF, while the lubricin concentrations in the SF were markedly decreased after injury. Damage to the meniscus or ligaments sustained during traumatic joint injury causes instability, subjecting articular cartilage to abnormal biomechanical effort, resulting in release of inflammation mediators[24].

The early post-injury events are held to be crucial, especially with relation to the risk of developing post-traumatic OA. In this regard, we studied the expression of lubricin, both *in vivo* and *in vitro*, in intact menisci and in menisci from patients with recent knee joint injury, using different techniques. Very strong lubricin expression was observed in intact menisci; in contrast, weak expression was seen in injured menisci. These data provide information concerning the immediate *in vivo* response to injury of the human knee menisci by documenting early changes in the boundary lubricating ability of the SF and articular cartilage integrity[25]. Other authors suggested that acquired lubricin degradation occurring in inflammatory joint disease predisposed the cartilage to damage[26]. Lubricin was also expressed in the cartilaginous deposits and osteoarthritic cartilage in patients with advanced OA[27].

The above findings indicated that lubricin is involved in joint disease and may play a beneficial role against the degradation of articular cartilage.

Lubricin and new therapeutic approaches for the treatment of OA

OA is classically defined as a progressive and degenerative, rather than an inflammatory, disease and is characterised by deterioration of the joints, including loss of articular cartilage and subchondral bone, as well as osteophyte formation[28]. OA affects about 8 million people in the United Kingdom and nearly 27 million people in the United States. It is one of the most common joint diseases and is associated with a substantial negative impact on the patient's quality of life as well as on healthcare costs[29]. It also influences disability in middle-aged and older people, especially in developing countries. However, the effectiveness of OA prevention in clinical practice is limited. Therefore, there is a great interest in finding novel potential biotherapeutic approaches for the treatment of OA. Lubricin is a chondro-protective glycoprotein which acts as a vital counteragent against aberrant protein and/or cellular adhesion, infiltration and over-proliferation, and serves as a critical boundary lubricant between opposing cartilage surfaces. This protein is less expressed with aging and during OA; moreover, the lubricin gene is differently expressed in the synovium of RA and OA, implying a possible role in the pathogenesis of these diseases. HA and lubricin are two major joint lubricants and effective 'boundary lubricants' that exhibit low friction and protect surfaces from wear[30]. The lubrication system, as a whole, requires both HA and lubricin to function optimally. Besides their role in lubrication, both lubricin and HA have additional functions in the joint, for e.g. lubricin regulates synovial cell adhesion and proliferation. Future studies will need to define, in more detail, the lubricin splice forms, its receptors and its activities in cells involved in OA. Authors reported that intra-articular injection of recombinant lubricin protected against cartilage degradation in a rat model of OA induced by meniscectomy and medial collateral ligament transaction[7]. Lubricin also protected against glycosaminoglycan depletion, collagen degradation and loss of cells in the cartilage superficial zone[31]. Teeple et al.[32] used an OA model in rats to test lubricin purified from the human SF and also compared it to and combined it with HA. These results confirmed the protective effect of lubricin, and the therapeutic benefit was enhanced by the addition of exogenous HA that alone did not have protective effects[32]. These studies shed new light on the role of joint lubricants as potential OA therapies and present a promising opportunity for lubricants as therapeutic targets in post-traumatic arthritis, which is associated with an acute deficiency of lubricants. For a better understanding of the potential of lubricin, we studied its expression in different cases. In our recent study[33], we evaluated lubricin expression in chondrocytes from the articular cartilage of the knee, from patients with OA, and compared them to

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Table 1. Distribution of lubricin in the joint cavity. ACL, anterior cruciate ligament; IFP, infrapatellar fat pad; LCL, lateral collateral ligament; PDL, periodontal ligament; SF, synovial fluid.

Joint cavity	Cell types	Reference
Synovial fluid (SF)	None	Swann et al. [10] Elsaid et al. [12]
Articular cartilage	Articular chondrocytes	Schumacher et al. [6, 9] Jones et al. [4]
Synovium	Synoviocytes	Flannery et al. [8]
Synovium	Synovial fibroblasts	Jay et al. [1]
Meniscus	Meniscus cells	Musumeci et al. [25] Young et al. [11] Schumacher et al. [15]
Tendon	Tenocytes	Rees et al. [14]
Infrapatellar fat pad (IFP)	IFP stromal cells	Lee et al. [16]
Anterior cruciate ligament (ACL)/Lateral collateral ligament (LCL)	ACL/LCL cells	Sun et al. [17]
Human temporomandibular joint disc	Fibrochondrocytes	Leonardi et al. [18, 19, 21]
Periodontal ligament (PDL)	PDL cells	Leonardi et al. [22]

normal cartilage. Chondrocytes were investigated both *in vivo*, on paraffin sections and *in vitro,* after encapsulation in hydrogel poly (ethylene glycol) diacrylate (PEGDA). In this study, for the first time, we showed that lubricin is down regulated in OA cartilage explants and cell cultures from knee joints. More interestingly, we demonstrated that OA chondrocytes encapsulated in PEGDA scaffolding are able to restore lubricin biosynthesis. In fact, after four weeks of culture of OA chondrocytes encapsulated in PEGDA hydrogel, lubricin expression nearly reached the level of the control scaffold. This increased expression of lubricin in OA chondrocytes may, somehow, be related to the absence of cytokines, which seem to influence lubricin biosynthesis. A deregulation of lubricin metabolism, under the influence of elevated cytokine concentrations in diseased or damaged joints, might thereby lead to lubrication deficiencies and loss of function. In another study[34]

we focussed on the isolation, cultivation and characterisation of human mesenchymal stem cells (MSCs) from adipose tissue. We also focused our study on the differentiation of MSCs into chondrocytes through the NH-ChondroDiff medium. The main aim was to investigate some markers of biomechanical quality of the cartilage, such as lubricin, and collagen type I and type II. Little is known, in fact, about the ability of chondrocytes from human MSCs of adipose tissue to generate lubricin. Adipose tissue is an alternative source for the isolation of multipotent MSCs, which allows them to be obtained by a less invasive method and in larger quantities than from other sources. These cells were isolated from cosmetic liposuctions in large numbers and easily grew under standard tissue culture conditions. The results showed that chondrocytes from the MSCs of adipose tissue, grown in nodules in a three-dimensional culture, were able to express lubricin, collagen type I and

type II, which was indicative of hyaline cartilage formation. Our results suggest that chondrocyte nodules producing lubricin could be a novel biotherapeutical approach for the treatment of cartilage abnormalities. The possibility of applying autologous cell transplantation in conjunction with chondrocyte nodules from adipose tissue producing lubricin, for repairing cartilage lesions in patients with OA, could be of great interest. Lubricin could reduce the progression of articular diseases and prevent the process of OA. In our recent study[35], we investigated the effects of procedures or drugs affecting bone metabolism on articular cartilage in rats with prednisolone-induced osteoporosis. We evaluated the outcomes of physical activity by treadmill and vibration platform training on the articular cartilage and its lubricin and caspase-3 expression. The effects of drug therapy with glucocorticoids decrease the expression of lubricin and increase the expression of caspase-3 in the rats, while after physical activity the values return to normal, equipared to the control group. The study confirms the beneficial effect of physical activity by mechanical stimulation on the articular cartilage that releases lubricin, which is capable of inhibiting caspase-3 activity and preventing chondrocyte death. We can assume that the physiological balance between lubricin and caspase-3 could maintain the integrity of the cartilage.

Conclusion

Lubricin is present in the SF and on the superficial layer of the articular cartilage and therefore plays an important role in joint lubrication and synovial homeostasis. The expression of lubricin has also been localised in joint cavity, and in other organs: lung, liver, heart, bone, muscle and skin. Many studies have investigated the role of lubricin in joint diseases, mainly OA, to prevent cartilage wear and synovial cell

adhesion and proliferation. Moreover, several recent studies have found that treatment with recombinant lubricin could protect articular cartilage and prevent the process of OA in an animal model. This suggests that lubricin is important for physiological cartilage preservation and may have important implications for treating or preventing joint disease in the future. Further longer-term *in vitro*, *in vivo* and clinical studies are needed to understand the exact mechanism of synthesis and the regulatory role of lubricin in articular cartilage. This would provide new insights into the occurrence and progression of OA. It may represent the biological basis for future attempts in medical therapy to preserve the tissue function and prevent further cartilage damage.

Acknowledgements

Abbreviations list

ACL, anterior cruciate ligament; HA, hyaluronic acid; IFP, infrapatellar fat pad; MSC, mesenchymal stem cell; OA, osteoarthritis; PDL, periodontal ligament; PEGDA, poly (ethylene glycol) diacrylate; PRG4, proteoglycan 4; SF, synovial fluid; TMJ, temporomandibular joint.

References

1. Jay GD, Tantravahi U, Britt DE, Barrach HJ, Cha CJ. Homology of lubricin and superficial zone protein (SZP): products of megakaryocyte stimulating factor (MSF) gene expression by human synovial fibroblasts and articular chondrocytes localized to chromosome 1q25. J Orthop Res. 2001 Jul;19(4):677–87.

2. Deng G, Curriden SA, Hu G, Czekay RP, Loskutoff DJ. Plasminogen activator inhibitor-1 regulates cell adhesion by binding to the somatomedin B domain of vitronectin. J Cell Physiol. 2001 Oct;189(1):23–33.

3. Nugent-Derfus GE, Chan AH, Schumacher BL, Sah RL. PRG4 exchange between the articular cartilage surface and synovial fluid. J Orthop Res. 2007 Oct;25(10):1269–76.

4. Jones AR, Gleghorn JP, Hughes CE, Fitz LJ, Zollner R, Wainwright SD, et al. Binding and localization of recombinant lubricin to articular cartilage surfaces. J Orthop Res. 2007 Mar;25(3):283–92.

5. Rhee DK, Marcelino J, Baker M, Gong Y, Smits P, Lefebvre V, et al. The secreted glycoprotein lubricin protects cartilage surfaces and inhibits synovial cell overgrowth. J Clin Invest. 2005 Mar;115(3):622–31.

6. Schumacher BL, Block JA, Schmid TM, Aydelotte MB, Kuettner KE. A novel proteoglycan synthesized and secreted by chondrocytes of the superficial zone of articular cartilage. Arch Biochem Biophys. 1994 May;311(1):144–52.

7. Jones AR, Flannery CR. Bioregulation of lubricin expression by growth factors and cytokines. Eur Cell Mater. 2007 Mar;13:40–5.

8. Flannery CR, Zollner R, Corcoran C, Jones AR, Root A, Rivera-Bermúdez MA, et al. Prevention of cartilage degeneration in a rat model of osteoarthritis by intraarticular treatment with recombinant lubricin. Arthritis Rheum. 2009 Mar;60(3):840–7.

9. Schumacher BL, Hughes CE, Kuettner KE, Caterson B, Aydelotte MB. Immunodetection and partial cDNA sequence of the proteoglycan, superficial zone protein, synthesized by cells lining synovial joints. J Orthop Res. 1999 Jan;17(1):110–20.

10. Swann DA, Silver FH, Slayter HS, Stafford W, Shore E. The molecular structure and lubricating activity of lubricin isolated from bovine and human synovial fluids. Biochem J. 1985 Jan;225(1): 195–201.

11. Young AA, McLennan S, Smith MM, Smith SM, Cake MA, Read RA, et al. Proteoglycan 4 downregulation in a sheep meniscectomy model of early osteoarthritis. Arthritis Res Ther. 2006;8(2):R41.

12. Elsaid KA, Fleming BC, Oksendahl HL, Machan JT, Fadale PD, Hulstyn MJ, et al. Decreased lubricin concentrations and markers of joint inflammation in the synovial fluid of patients with anterior cruciate ligament injury. Arthritis Rheum. 2008 Jun;58(6):1707–15.

13. Englert C, McGowan KB, Klein TJ, Giurea A, Schumacher BL, Sah RL. Inhibition of integrative cartilage repair by proteoglycan 4 in synovial fluid. Arthritis Rheum. 2005 Apr;52(4):1091–9.

14. Rees SG, Davies JR, Tudor D, Flannery CR, Hughes CE, Dent CM, et al. Immunolocalisation and expression of proteoglycan 4 (cartilage superficial zone proteoglycan) in tendon. Matrix Biol. 2002 Nov;21(7):593–602.

15. Schumacher BL, Schmidt TA, Voegtline MS, Chen AC, Sah RL. Proteoglycan 4 (PRG4) synthesis and immunolocalization in bovine meniscus. J Orthop Res. 2005 May;23(3):562–8.

16. Lee SY, Nakagawa T, Reddi AH. Induction of chondrogenesis and expression of superficial zone protein (SZP)/lubricin by mesenchymal progenitors in the infrapatellar fat pad of the knee joint treated with TGF-beta1 and BMP-7. Biochem Biophys Res Commun. 2008 Nov;376(1):148–53.

17. Sun Y, Berger EJ, Zhao C, An KN, Amadio PC, Jay G. Mapping lubricin in canine musculoskeletal tissues. Connect Tissue Res. 2006;47(4):215–21.

18. Leonardi R, Musumeci G, Sicurezza E, Loreto C. Lubricin in human temporomandibular joint disc: an immunohistochemical study. Arch Oral Biol. 2012 Jun;57(6):614–9.

19. Leonardi R, Rusu MC, Loreto F, Loreto C, Musumeci G. Immunolocalization and expression of lubricin in the bilaminar zone of the human temporomandibular joint disc. Acta Histochem. 2012 Jan;114(1):1–5.

20. Justen HP, Grunewald E, Totzke G, Gouni-Berthold I, Sachinidis A, Wessinghage D, et al. Differential gene expression in synovium of rheumatoid arthritis and osteoarthritis. Mol Cell Biol Res Commun. 2000 Mar;3(3):165–172.

21. Leonardi R, Almeida LE, Loreto C. Lubricin immunohistochemical expression in human temporomandibular joint disc with internal derangement. J Oral Pathol Med. 2011 Aug;40(7):587–92.

22. Leonardi R, Loreto C, Talic N, Caltabiano R, Musumeci G. Immunolocalization of lubricin in the rat periodontal ligament during experimental tooth movement. Acta Histochem. 2012 Nov;114(7):700–4.

23. Elsaid KA, Jay GD, Warman ML, Rhee DK, Chichester CO. Association of articular cartilage degradation and loss

of boundary-lubricating ability of synovial fluid following injury and inflammatory arthritis. Arthritis Rheum. 2005 Jun;52(6):1746–55.

24. Guilak F, Fermor B, Keefe FJ, Kraus VB, Olson SA, Pisetsky DS, et al. The role of biomechanics and inflammation in cartilage injury and repair. Clin Orthop Relat Res. 2004 Jun;423:17–26.

25. Musumeci G, Loreto C, Carnazza ML, Cardile V, Leonardi R. Acute injury affects lubricin expression in knee menisci: An immunohistochemical study. Ann Anat. 2013 Mar;195(2):151–8.

26. Jay GD, Torres JR, Rhee DK, Helminen HJ, Hytinnen MM, Cha CJ, et al. Association between friction and wear in diarthrodial joints lacking lubricin. Arthritis Rheum. 2007 Nov;56(11):3662–9.

27. Zhang D, Johnson LJ, Hsu HP, Spector M. Cartilaginous deposits in subchondral bone in regions of exposed bone in osteoarthritis of the human knee: histomorphometric study of PRG4 distribution in osteoarthritic cartilage. J Orthop Res. 2007 Jul;25(7):873–83.

28. Musumeci G, Loreto C, Carnazza ML, Martinez G. Characterization of apoptosis in articular cartilage derived from the knee joints of patients with osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2011 Feb;19(2):307–13.

29. Musumeci G, Loreto C, Carnazza ML, Strehin I, Elisseeff J. OA cartilage derived chondrocytes encapsulated in poly(ethylene glycol) diacrylate (PEGDA) for the evaluation of cartilage restoration and apoptosis in an in vitro model. Histol Histopathol. 2011 Oct;26(10):1265–78.

30. Hui AY, McCarty WJ, Masuda K, Firestein GS, Sah RL. A systems biology approach to synovial joint lubrication in health, injury, and disease. Wiley Interdiscip Rev Syst Biol Med. 2012 Jan–Feb;4(1):15–37.

31. Jay GD, Fleming BC, Watkins BA, McHugh KA, Anderson SC, Zhang LX, et al. Prevention of cartilage degeneration and restoration of chondroprotection by lubricin tribosupplementation in the rat following anterior cruciate ligament transection. Arthritis Rheum. 2010 Aug;62(8):2382–91.

32. Teeple E, Elsaid KA, Jay GD, Zhang L, Badger GJ, Akelman M, et al. Effects of supplemental intra-articular lubricin and hyaluronic acid on the progression of posttraumatic arthritis in the anterior cruciate ligament-deficient rat knee. Am J Sports Med. 2011 Jan;39(1):164–72.

33. Musumeci G, Loreto C, Carnazza ML, Coppolino F, Cardile V, Leonardi R. Lubricin is expressed in chondrocytes derived from osteoarthritic cartilage encapsulated in poly (ethylene glycol) diacrylate scaffold. Eur J Histochem. 2011;55(3):e31.

34. Musumeci G, Lo Furno D, Loreto C, Giuffrida R, Caggia S, Leonardi R, et al. Mesenchymal stem cells from adipose tissue which have been differentiated into chondrocytes in three-dimensional culture express lubricin. Exp Biol Med (Maywood). 2011 Nov;236(11):1333–41.

35. Musumeci G, Loreto C, Leonardi R, Castorina S, Giunta S, Carnazza ML, et al. The effects of physical activity on apoptosis and lubricin expression in articular cartilage in rats with glucocorticoid-induced osteoporosis. J Bone Miner Metab. 2012 Dec.