The Interface of Functional Biotribology and Regenerative Medicine in Synovial Joints

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ABSTRACT

Biotribology is the science of biological surfaces in sliding contact encompassing the concepts of friction, wear, and lubrication of interacting surfaces. This bioscience field has emerged from the classical field of tribology and is of paramount importance to the normal function of numerous tissues, including articular cartilage, blood vessels, heart, tendons, ligaments, and skin. Surprisingly, relatively little attention has been given to the restoration of surface characteristics in the fields of tissue engineering and regenerative medicine—the science of design and manufacture of new tissues for the functional restoration of impaired or diseased organs that depend on inductive signals, responding stem cells, and extracellular matrix scaffolding. Analogous to ancient civilizations (c. 3000 B.C.) that introduced wheeled vehicles, sledges for transporting heavy blocks, and lubricants, modern biotribologists must aim to restore surface characteristics to regenerated tissues and develop novel biomaterials with optimal tribological properties. The objective of this article is to highlight the significance of functional biotribology in the physiology of body surfaces and provide a comprehensive overview of unresolved issues and controversies as it relates to regenerative medicine. Specific attention is placed on the molecular basis of lubrication, mechanical and biochemical regulation of lubricating molecules, and the need to study wear processes in articular cartilage, especially in light of degenerative diseases, such as osteoarthritis. Surface engineering of replacement tissues exhibiting low friction and high wear resistance is examined using articular cartilage as an illustrative model system.

INTRODUCTION

Friction, wear, and lubrication are central phenomena that are ubiquitous in diverse biological surfaces and systems. High friction is desirable between the foot and the floor for walking, whereas low friction is necessary for effortless flow of arterial blood cells. Wear facilitates tooth cleaning during brushing in oral hygiene and dentistry, but may result in excruciating pain during joint movement following cartilage degradation in osteoarthritis. The effectiveness of lubrication in reducing friction and wear is demonstrated in the blinking function of the eye and conjugal functions of human reproduction. Surface contact at cellular and tissue levels (Fig. 1) is dynamic and influences integrated functions, including sensing, communication, growth, morphogenesis, remodeling, and apoptosis.1–4 Surface contacts are likely to be unnoticed until they break down or become impaired following damage or disease. For routine activities, this may mean slipping on an icy sidewalk during walking. For cells and tissues, the result may be more profound and detrimental—arteries accumulate fatty detritus, endobronchial airways inflame and constrict, and joints become painful and immobile.

Functional biotribology emphasizes surface characteristics and properties as a design endpoint for successful regeneration of tissues or biomaterials. The motivation for

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functional biotribology is practical and significant. It is expected that engineered tissues exhibiting suboptimal surface properties would result in poor function and decreased lifespan postimplantation in vivo. A fundamental design concept is to exploit lubricant substances that can reduce friction and wear of interacting surfaces. Thus, the focus of tissue engineering should not be simply on the bulk tissue but on the regeneration of specific biomolecules and cell types at surface tissue that can prolong the functional lifespan of the engineered construct.

The paradigm of regenerative medicine and tissue engineering is focused on the restoration of damaged tissues and organs through the use of morphogenetic signals, stem cells, and biomimetic materials. Knowledge of mechanical and biochemical signal transduction mechanisms is critical to optimizing biomolecular expression of key surface molecules. The main objective of this article is to relate concepts of basic mechanics, biochemistry, and molecular and cellular biology to biotribology of natural and tissue-engineered biomaterials, using the design of articular cartilage as a model system.

As living materials, bearings in the human body (e.g., articular cartilage and endothelium) facilitate constrained relative movement between two parts, and are far more complex than those found using traditional engineering materials, such as metals, plastics, and ceramics. Bearings of both engineering and living materials exploit the thickness and rheological behavior of the intervening viscous layer to produce low friction during relative surface movement. Lubrication of traditional engineering bearings can be achieved through the application of lubricious films consisting of natural (e.g., animal fats and mineral [petroleum] oils) or synthetic (e.g., hydrocarbons, esters, silicones, silanes, polyphenyl ethers, and perfluoropolyethers) substances that are often blended with special additives and can either physically adsorb at the surfaces (physisorption) or chemically react with the surfaces (chemisorption) to form and replenish low-friction, antwear thin films. Living bearings contain cells and thus exhibit regenerative potential and capacity to repair damaged tissue through biosynthesis and replenishment of proteins and other biomolecules that can act as natural lubricants. Mucin proteins (Fig. 2), in particular, have received considerable attention in recent years due to their role as biological lubricants in diverse tissues, such as saliva, glycocalyx, respiratory tract, and synovial fluid. These proteins form gel-like (monolayers adhering strongly to the underlying epithelium, hence imparting effective lubrication and, in turn, surface tissue protection against mechanical wear.

Why do human joints wear out during aging? Perhaps a more intriguing question is how do joints resist wear over a lifetime? Synovial (or freely movable) joints of the human body (e.g., knee, hip, and elbow) are complex living biological and mechanical systems consisting of articular cartilage, bone, menisci, ligaments, and synovium (Fig. 3) that allow for joint articulation and movement with minimal friction and wear. These joints are less constrained by ligamentous attachments compared to fibrous or cartilaginous joints, such as the skull and the spine.

Articular cartilage is the primary bearing biomaterial lining the bones of the joint through which contact forces are transmitted. The cartilage in the average young (25–34 years) human male and female undergoes approximately 5400 and 4700 loading cycles, respectively, during normal daily activities and more than 10^8 loading cycles over an 80-year lifespan. Even during simple daily activities, such as walking, cartilage sustains mechanical forces several times higher than the body weight. Peak joint forces range from...
1.2 to 7.2 times the body weight in the human knee\textsuperscript{14} (Fig. 4A) and from 2.5 to 5.8 times the body weight in the human hip joint.\textsuperscript{15} The macroscopic joint geometry and multiscale surface roughness produce nonuniform pressure distributions (determined from instrumented prostheses) with peak pressures approaching 18 MPa in the hip joint.\textsuperscript{15}

Articular cartilage is a highly organized structure. The tissue consists of cells, water, collagens, proteoglycans, and other matrix biomolecules. On a tissue and molecular scale, articular cartilage consists of surface, middle, and deep zones, each exhibiting unique cell architecture, biochemical composition, and mechanical properties\textsuperscript{16} (Fig. 3). The hydrated tissue is composed of biopolymers, such as type II collagen, aggrecan, chondroitin sulfate, keratan sulfate chains, and hyaluronan. The water and biopolymer contents vary with depth from the articular surface. Water accounts for more than 80\% of the wet tissue weight at the surface and 65\% in the deep zone. The collagen content (15–22\% of the wet tissue weight overall) is highest in the surface zone, while the proteoglycan content (4–7\% of the wet tissue weight overall) is lowest in the superficial zone and highest in the middle and deep zones. The viscoelastic properties of cartilage are attributed to the intrinsic properties of the macromolecules that form a solid porous matrix and the frictional drag of the interstitial fluid flow through this porous matrix.\textsuperscript{17–19} Material properties vary with tissue depth,
as demonstrated in studies of strain patterns generated during simple uniaxial and physiologically relevant compression loading.  

Arthritis is a type of rheumatic disease involving joint inflammation. Osteoarthritis, commonly thought of as a degenerative joint disease or the "wear and tear" of human joints, is the most common form of arthritis, affecting 12.1% of adults in the United States (about 20.7 million people), and is a leading cause of disability in America. In the most extreme cases, the cartilage may be worn off completely, resulting in bone-on-bone surface rubbing. Although the etiologies of this disease are largely unknown, it is likely that they involve multiple factors, including a biochemical imbalance between catabolic cytokines and anabolic morphogens and growth factors, mechanical injury or trauma, and progressive surface deterioration due to mechanical wear. Moreover, cartilage is recalcitrant to repair, partly due to the avascularity of the tissue, the high concentration of protease inhibitors, and, presumably, the presence of growth inhibitors.

FRICITION AND WEAR OF SYNOVIAL JOINTS

When two bodies in contact slide over each other, surface interaction occurs through isolated microscopic contacts, referred to as asperity contacts (Fig. 1), resulting in the development of a friction force and the removal of material by different wear processes occurring at the asperity scale. The friction force represents the resistance encountered when a body slides against another body, and arises in the direction directly opposite to the direction of motion. A basic mechanism of sliding friction is described by the physical and/or chemical interactions occurring between adhesive asperity contacts, which must be sheared off for relative movement to occur. The first friction law, attributed to both Amontons and Leonardo da Vinci,

\[ F = \mu W \]  

relates the friction force \( F \) to the external normal load \( W \) through the coefficient of friction \( \mu \). In articular cartilage, the average coefficient of friction may vary from 0.005 (Charnley) to 0.5 or even more (Pickard et al.), and shows a strong dependence on the testing conditions and the operating lubrication regime. Equation (1) indicates a direct proportionality between friction force and external normal load—that is, constant coefficient of friction. While this relationship is followed at the macroscale, a nonlinear relationship is often encountered at the microscale due to the increased importance of surface adhesion forces, such as van der Waals, capillary, and molecular forces, implying a dependence of the coefficient of friction on the applied normal load. This is due to the fact that adhesion forces represent an additional normal force at the microscale that can result in significantly higher friction when the external load is on the same order of magnitude as the adhesion forces. A time-dependent coefficient of friction response is commonly observed with cartilage surfaces sliding against different solid surfaces that has often been attributed to interstitial fluid pressurization of the hydrated tissue. Variations in the coefficient of friction have also been observed over a wide range of length scales and have been attributed to differences in the operating conditions (e.g., magnitude of contact stresses, sample hardness, elastic modulus, apparent contact area, and total sliding distance) encountered at different scales. Therefore, a mechanistic understanding of the origins of the friction force in a particular test configuration requires careful consideration of multiple contributing factors.

Comparatively, fewer studies have been devoted to examine the origins and evolution of cartilage wear. This is surprising in light of the prevalence of osteoarthritis, a degenerative joint disease of multifactorial causalities characterized by progressive cartilage tissue loss, believed to be partly due to different wear mechanisms. Wear occurs by mechanical and/or chemical processes that could be enhanced by frictional heating produced from surface rubbing. Wear mechanisms include adhesion, abrasion, fatigue, impact, cavitation, erosion, and corrosion. Understanding of the different wear mechanisms of articular cartilage in the context of degenerative diseases, such as osteoarthritis, and basic knowledge of their contributions to cartilage wear require further study. Adhesion, the most common type of wear, is characterized by the shearing of asperity contacts formed at the sliding interface of two nominally flat solid bodies, resulting in the formation of wear particles. The classical relationship of adhesive wear,

\[ V = k \frac{W_S}{H} \]  

is commonly used to relate the wear volume \( V \) to the wear coefficient \( k \), normal load \( W \), total sliding distance \( S \), and hardness \( H \) of the worn surface. Wear rates (defined as the thickness of the worn layer from the cartilage surface per cycle) for total hip arthroplasties have been reported to be on the order of \( 10^{-6} \) mm/cycle; however, wear rate estimates for natural cartilage have yet to be determined. Descriptive wear patterns in articular cartilage are limited to load-bearing joint regions. In an ovine meniscectomy model of osteoarthritis, early osteoarthritis was associated with a loss in immunostaining and mRNA levels of cellular proteoglycan 4 (PRG4), considered to be a boundary lubricant in articular joints. In a living tissue, cells within the material produce molecules (e.g., structural proteins or boundary lubricants) that can replenish worn tissue. The specific conditions regulating tribological homeostasis (i.e., a balance between wear and replenishment mechanisms) to maintain tissue function over time remain unknown. In view of the empirical descriptions of wear and associated lubrication regimes, fundamental studies in cartilage biotribology are of paramount importance to regenerative medicine.
Molecular Basis of Synovial Joint Lubrication

Lubricants generally reduce friction and wear of interacting surfaces. The main function of lubricants is to provide an easily sheared film between proximity surfaces in relative motion. Lubrication may be classified as fluid lubrication, when a thick film of fluid separates the surfaces, or boundary lubrication, when a molecularly thin (monolayer) film forms conformably on at least one of the sliding surfaces. Fluid lubrication may be further classified into three types: (i) hydrostatic lubrication, when a fluid film that separates the opposed surfaces is generated by external pressurization means (e.g., pump); (ii) hydrodynamic lubrication, when surface separation results from the formation of a thick fluid film due to the kinematics of the proximal surfaces, depending on the macroscopic bearing geometry (curvature effect), interfacial topography (roughness effect), normal load (pressure effect), relative speed (shear rate effect), and fluid film rheological properties (viscosity effect); and (iii) elastohydrodynamic lubrication, when the pressure in the self-generated hydrodynamic fluid film causes elastic deformation of the confining surfaces (i.e., the film thickness also depends on the elastic properties of the solid surfaces). The transition between lubrication regimes depends on the surface roughness and the film thickness, which is a function of the fluid viscosity, sliding speed, and applied normal load (or mean pressure)\(^3\) (Fig. 5A).

Human joints are complex bearings that operate effectively under both fluid film and boundary lubrication conditions.\(^3\) During normal activities, such as walking, joints may also function under so-called mixed lubrication conditions, implying the coexistence of fluid and boundary lubrication conditions at the contact interface.\(^10\) Hydrodynamic theory fails to predict an adequate film thickness for complete surface separation throughout a typical walking cycle (Fig. 4B). Therefore, it is likely that hydrostatic,\(^36\) elastohydrodynamic,\(^38\) and/or mixed lubrication conditions can be encountered during the swing phase (high velocity-to-load ratio), when the film thickness is greater than the average surface roughness of cartilage, whereas boundary lubrication conditions dominate during the stance phase between heel strike and toe off (low velocity-to-load ratio), when the film thickness is significantly less than the average surface roughness of cartilage.\(^6\) The wear coefficient in hydrodynamic lubrication may be 7 orders of magnitude less than that in boundary lubrication and 11 orders of magnitude less than that obtained with unlubricated surfaces\(^39\) (Fig. 5A). While fluid film effects in cartilage lubrication are critical to providing normal function of the joint, it is likely that in the absence of a continuous and self-replenishing boundary lubricant, joint degeneration will occur rapidly.\(^40\)

Hydrodynamic lubrication

Surface relative movement in the hydrodynamic lubrication regime is controlled by an interfacial fluid film of thickness much larger than the heights of the tallest asperities (Fig. 5B). Under these lubrication conditions, the normal load is transmitted through the pressurized fluid film, which exhibits a pressure-dependent shear resistance due to the exponential dependence of the fluid viscosity on pressure. Under isothermal conditions, the dependence of the

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FIG. 3. The synovial joint is a living bearing system that can be studied at different hierarchical levels, from the whole joint scale (bone shape; contact pressure) through the cellular scale (lubricant protein distributions; cellular biosynthesis) to the atomic scale (surface roughness; protein binding).
Fluid viscosity $\eta$ on pressure $p$ is given by a relationship of the form:

$$\eta = \eta_0 \exp(\alpha p)$$  \hspace{1cm} (3)

where $\eta_0$ is the ambient viscosity and $\alpha$ is the viscosity–pressure coefficient (expressed in units of m$^2$/N), an intrinsic rheological property of the fluid.\textsuperscript{41} The classical hydrodynamic lubrication mechanism involves wedge or entraining flow generated when two surfaces slide past each other. The narrowing wedge-shaped gap produces a hydrodynamic pressure in the fluid that tends to push the two surfaces apart.

A second classical mechanism, squeeze-film lubrication, occurs when the opposing surfaces approach each other at a relatively high speed, as in the case of dynamic contact loading, resulting in the pressurization of the fluid by the confining solid surfaces. The pressure distribution can be obtained by solving the Reynolds equation derived from the general Navier–Stokes equations of fluid flow. Hydrodynamic lubrication of human joints depends on the synovial fluid secreted from the synovium cells (synoviocytes). The synovium fluid is a dialysate of blood plasma that is devoid of clotting factors,
erythrocytes, and hemoglobin, and contains proteoglycans, glycoproteins (e.g., hyaluronate and lubricin), and phospholipids. A dependence of the apparent viscosity of synovial fluid on shear rate and concentration of hyaluronan has been observed in previous studies.

**Elastohydrodynamic lubrication**

In this type of lubrication, the bearing surfaces are separated by a highly pressurized fluid film that causes elastic deformation of the solid surfaces (Fig. 5B). Hence, the pressure and thickness of the hydrodynamic film depend on both the rheological properties of the fluid and the elastic deformation of the bearing surfaces. The high film pressure increases the fluid viscosity, producing a tendency for both the thickness and the shear resistance of the fluid film to increase due to the exponential dependence of viscosity on pressure (Eq. 3). The interdependence of local pressure, viscosity, surface deformation, and film thickness necessitates the implementation of a numerical iterative procedure to solve the Reynolds equation. It is likely that elastohydrodynamic lubrication is a significant mechanism in cartilage during normal activities, and is largely due to the multiphasic nature of the tissue.

**Boundary lubrication and mucins**

Surface relative movement in the boundary lubrication regime does not favor the formation of a fluid film of thickness much larger than the roughness of the counter-surfaces. Hence, the only barrier against direct solid-to-solid contact is an adsorbed molecular film that forms conformably with the surface topographies, preferably in a closed-pack arrangement that resembles a brush-like surface layer (Fig. 5B). In the absence of a strongly adsorbing, continuous, and self-replenishing boundary lubricant layer, intermittent asperity contact interactions promote rapid surface degradation by mechanical wear.

Mucins are a family of large and heavily glycosylated proteins (Fig. 2B). Glycosylation occurs as a posttranslational modification to the synthesized protein and provides hygroscopic characteristics. Mucin amino- and carboxyl-terminal regions are cysteine rich and likely involved in disulfide bonding, while the central region has multiple repeat residue sequences that are serine rich and threonine rich to allow glycosylation of primarily oxygen-linked oligosaccharides. Mucins can coat many surfaces in the human body, including teeth, respiratory and gastrointestinal tract, and reproductive organs, and are thought to act as boundary lubricants. Superficial zone protein (SZP) is a mucin domain-containing glycoprotein secreted from chondrocytes in the superficial layer of articular cartilage. This protein is homologous to lubricin and megakaryocyte stimulating factor (MSF) precursor and is encoded by the PRG4 gene. SZP is not retained in the matrix, but is mostly secreted into the synovial fluid or is bound to macromolecules in the lamina splendens and has also been localized in the lining joint cavities of the synovial membrane. In addition to its function as a boundary lubricant, SZP plays a role in the inhibition of integrative cartilage repair and synovial cell overgrowth. A mutation in the PRG4 gene has been linked to camptodactyly-arthritis-coxa vara-pericarditis (CACP) syndrome, an autosomal recessive disease characterized by synovial hyperplasia without evidence of inflammation, where the lack of the mucin protein apparently results in premature joint wear. It has also been reported that the SZP gene is alternatively expressed in the synovium of rheumatoid arthritis and osteoarthritis, implying a possible role in the pathogenesis of these diseases. Knockout mice lacking the SZP gene have demonstrated abnormal protein deposits on the cartilage surface, disappearance of the underlying superficial zone, synovial hyperplasia, and precocious failure of joint function.

The role of SZP in boundary lubrication is controversial. It has been suggested that surface-active phospholipid (SAPL) provides joint lubrication, as evidenced in part by the increased friction coefficient following phospholipase incubation. However, the role of phospholipids has been challenged, as it was later determined that commercial purified phospholipase contained trypsin-like activity. Digestion of bovine synovial fluid by phospholipase C in the presence of protease inhibitors did not affect negatively boundary lubricating efficacy compared to undigested control. Other authors reported that the removal of the superficial zone of bovine articular cartilage did not increase the friction coefficient of samples tested under reciprocating sliding motion to 2500 s. However, multiple factors were not controlled to specifically address the role of SZP in boundary lubrication, such as surface roughening due to microtoming that may influence the real area of contact and thus the friction coefficient. The boundary lubricant in synovial joints has been proposed as hyaluronan, SZP/lubricin/PRG4, SAPL, or a combination of these molecules. The synovial fluid constituents hyaluronan and PRG4 (either in physiologic or in pathophysiologic concentrations) contribute individually and concomitantly to boundary lubrication of articular cartilage.

**Mixed lubrication**

Mixed lubrication is characterized by the coexistence of interfacial regions operating under elastohydrodynamic and boundary lubrication conditions (Fig. 5B). This implies that multiple lubrication mechanisms can occur simultaneously in this transition lubrication regime. For instance, there may be interfacial regions where surface separation is only a few molecular layers as opposed to other regions where the surfaces may be separated by a micrometer-thick hydrodynamic film. Two mixed lubrication mechanisms have been proposed for articular cartilage—namely, “weeping” and “boosted” lubrication (Fig. 5C). In addition to asperity contact, fluid pressurization arises in weeping lubrication...
through exudation of fluid from the cartilage during compression, and exhibits hydrostatic lubrication characteristics. In contrast, asperity and fluid pressurization in the boosted lubrication mechanism forces fluid into the cartilage, leaving behind pools of concentrated lubricant. The nature of fluid flow (transport) through the tissue of cartilage under mixed lubrication conditions is a controversial subject. Another mechanism, termed interstitial fluid pressurization, is characterized by contact of the solid phase of cartilage (giving rise to friction at asperity contacts) and load support by the fluid phase (resulting in a small or perhaps negligible contribution to the friction force by viscous shear of the interstitial fluid and the synovial fluid). Surface asperity contact is inevitable in this mechanism, and thus the presence of surface lubricants (e.g., SZP) is important. The nonlinear nature of fluid depressurization under, for example, constant load causes a shift in the load support from the fluid to the solid phase over time. This time-dependent shift of the load can be observed in various normal physiologic activities, such as during a prolonged stance. In this case of increased load support by the solid phase, the presence of a boundary lubricant that influences surface contact of the solid phase becomes even more critical as time progresses. It is unclear to what extent interstitial fluid pressurization can be characterized as a mixed lubrication mechanism given the nature of solid contact and minimal fluid film thickness required for this mechanism to operate, and thus it may be more appropriately characterized as a mechanism operating in the boundary mode.

MECHANICAL REGULATION OF CARTILAGE LUBRICATION

Cells in the cartilage (chondrocytes) respond to mechanical signals and through unknown mechanisms convert mechanical input ultimately into protein expression of extracellular matrix molecules. For example, proteoglycan synthesis is sensitive to the frequency of dynamic compressive loading and could be synthesized during dynamic loading at 0.001 Hz, although synthesis may be reduced by as much as 50% from that of controls subjected to 1 MPa dynamic pressure of 1 Hz frequency. The expression of SZP in chondrocytes is sensitive to mechanical signals (Fig. 6). Studies have shown that while compressive loading can decrease SZP expression level, shear loading increases SZP expression. Shear loading may mediate SZP expression level through transforming growth factor (TGF-β) signaling pathways.

Mechanical regulation in boundary lubrication may involve a “sacrificial” layer mechanism characterized by the removal of the lubricant layer from the contacting surfaces to maintain a low friction coefficient, for example, through the formation of an easily sheared sacrificial layer, followed by the replenishment of the removed layer at the sliding interface. In this mechanism, the lubricating molecule has a strong affinity for surface attachment by physical adsorption. In the case of articular cartilage, SZP may bind to heparan sulfate or other binding partners only in the most superficial tissue layer (lamina splendens) to form a sacrificial layer. Interfacial friction (shear) forces may promote the removal of SZP, resulting in the increase of the friction coefficient and, in turn, accelerate tissue degradation at the cartilage surface. Recent findings indicate that shear force–induced biosynthesis of superficial zone chondrocytes may be instrumental in SZP replenishment at the articular surface.

BIOCHEMICAL REGULATION OF CARTILAGE LUBRICATION

Homeostasis of the major biomolecules (e.g., collagens and proteoglycans) for maintaining fluid film and boundary lubrication characteristics depends on various factors, including morphogens, growth factors, and cytokines (Fig. 6). Morphogenetic proteins and growth factors are molecules

FIG. 6. Mucins as a model boundary film for effective tissue lubrication. Regenerative medicine and tissue engineering strategies aimed at surface restoration of key design outcomes (e.g., surface mucin concentration) depend on several factors, including morphologic, mechanical, and other molecular signals. Color images available online at www.liebertonline.com/ten.
that specify cell identity during development.\textsuperscript{76} Bone morphogenetic proteins (BMPs) are a family of morphogens that promote new cartilage and bone growth.\textsuperscript{5,77} BMPs have chemotactic, mitogenic, and differentiation-inducing properties. The biological actions of BMPs are based on concentration-dependent thresholds. Articular cartilage contains endogenous morphogens, such as cartilage-derived morphogenetic protein (CDMP-1, a type of BMP). BMP-7, also called human osteogenic protein-1 (OP-1), plays an important role in human and bovine cartilage homeostasis and repair.\textsuperscript{78–80} Studies have shown that BMP-7 and other growth factors can synergistically promote increased survival and matrix synthesis by normal and osteoarthritic human articular chondrocytes.\textsuperscript{81–83} Other growth factors, such as TGF-\textbeta, basic fibroblast growth factor, insulin-like growth factor, and platelet-derived growth factor, have all been shown to be anabolic for cartilage and chondrocytes.\textsuperscript{84}

Morphogenetic proteins and growth factors bind to the receptors of the cell surface membrane to initiate signaling cascades. In the case of BMP-4, BMP-7, and CDMP-1, binding to the cell membrane occurs at BMP receptors IA and IB,\textsuperscript{84} which are membrane-bound serine/threonine kinases. The BMP type II receptors phosphorylate the BMP type I receptors, which, in turn, phosphorylate signal-transducing Smad proteins.\textsuperscript{85} The transcription of BMP-response genes, which are likely homeobox genes, is initiated by Smad 1 and Smad 4 proteins. Additionally, the antagonism of cartilage and BMP actions may be mediated by other binding proteins, such as noggin.\textsuperscript{86,87}

TGF-\textbeta is a potent regulator of SZP expression\textsuperscript{88,89} localized in the superficial zone of the tissue.\textsuperscript{90} SZP expression can either be up- or downregulated upon treatment with TGF-\textbeta1 and interleukin-1 (IL-1\alpha), respectively.\textsuperscript{52,90} Such inhibition may be mediated by proinflammatory cytokines, such as tumor necrosis factor-\textalpha (TNF-\textalpha) and IL-1\alpha, which promote cartilage matrix degradation in part by enhancing the expression of matrix metalloproteinases (MMPs).\textsuperscript{91} There is evidence that IL-1\alpha and TNF-\textalpha colocalize with MMPs in the superficial layer of arthritic cartilage, illustrating the key role of this layer in the pathogenesis of arthritic diseases.\textsuperscript{92}

RESURFACING AND REGENERATIVE MEDICINE

Functional biotribology refers to the restoration of the surface characteristics and properties. Through novel (simultaneous or sequential) combination of cells, acellular biomaterials, drugs, gene products, and genes, surfaces may be designed, specified, or fabricated as therapeutic agents.\textsuperscript{93} Particularly in cartilage, there has been limited success in the regeneration and repair of the tissue, with mixed reports of success\textsuperscript{94–96} and lack of characterization of the in vivo surface characteristics or properties.

Reconstitution of fluid film lubrication at the tissue surface requires scaffolding structures with optimal collagen and proteoglycan content, organization, and spatial heterogeneity that can produce tissue of appropriate elastic modulus, porosity, and permeability.\textsuperscript{97} Localization of cells and other matrix-bound factors and molecules is critical for long-term maintenance of the surface properties. Engineering of cartilage has produced tissues with increased coefficients of friction (up to 0.6 for engineered constructs vs. less than 0.2 for the equilibrium friction coefficient of native tissue) under mixed lubrication conditions. Although the engineered tissue design promoted fluid exudation from the constructs that affected significantly the frictional properties, the tissue was not effective in producing low friction coefficients similar to those of native cartilage.\textsuperscript{98}

Reconstitution of boundary lubrication at the tissue surface requires surface scaffolding with appropriate binding partners for biomolecules, such as proteoglycans. In addition, cellular localization is critical for maintaining the lubricant monolayer, especially in articular cartilage where a limited population of cells, particularly those in the tissue of load-bearing surface regions,\textsuperscript{74} are inductive to producing lubricating proteins. Initial efforts to restore the boundary lubricating ability of the superficial layer have involved stratified tissue constructs with specialized cell subpopulations specifically expressing SZP.\textsuperscript{99}

It is expected that engineered tissues exhibiting suboptimal surface properties would result in poor function and decreased lifespan postimplantation in vivo. The strategy for restoration of the surface characteristics, such as lubricant molecule concentrations, may require the optimal combination of morphologic, mechanical, and other inductive signals (Fig. 6). It is believed that replenishment and regeneration of boundary lubricants (e.g., SZP) can be achieved through optimal use of morphogens, such as TGF-\textbeta and BMPs, in concert with mechanical signals. In addition to inductive signals, such as morphogens and biomechanical factors, successful engineering of cartilage will likely be the result of a complex array of independent variables, including cell type,\textsuperscript{100} cell seeding density,\textsuperscript{101} extracellular matrix scaffolding and bioreactor design,\textsuperscript{102} and controlled enzymatic matrix degradation.\textsuperscript{103}

OUTLOOK

Recent progress in biotribology has yielded valuable insight into the complex nature of friction, wear, and lubrication mechanisms encountered at interfaces of living systems. The lack of basic knowledge of the dominant wear processes in biological tissues presents a major obstacle in treating diseases, such as osteoarthritis. However, contemporary surface analyses techniques, such as surface force microscopy, provide powerful tools for characterizing normal, diseased, and regenerated tissues. Biotribology provides a context and design paradigm for the functional restoration and regeneration of articular cartilage and a host of other tissues with optimal surface characteristics and properties.
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REFERENCES


32. Striebeck, R. Die wesentlichen eigenschaften der gleit- und rollenlager. Z Ver Dt Ing 46, 1341, 1902.


65. Mann, R.W. Letter to the editor commenting on “hydrostatic pressurization and depletion of trapped lubricant pool during creep and sliding contact of a rippled indenter against a biphasic articular cartilage layer.” J Biomech Eng 126, 538; author reply 539, 2004.

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