MINNEAPOLIS • MAY 20-24, 2018

Control ID: 2847482

Boundary lubrication and antiphospholipid syndrome (APS) in natural joints

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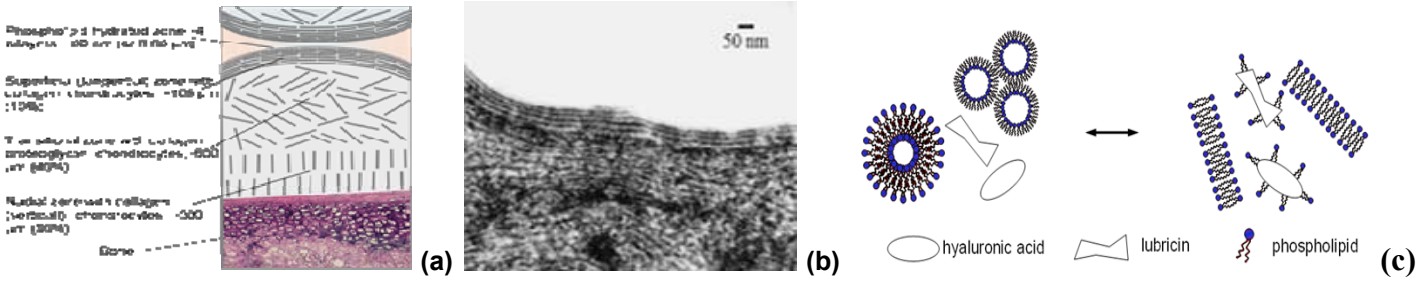
Introduction

Phospholipids (PLs) form an important class of biological molecules that play both structural and functional roles in the human body. The most important function of phospholipids is to form the phospholipid bilayer of the plasma membrane. Bilayers of phospholipids on the surface of articular cartilage (AC) contribute to boundary lubrication as the main lubricant (membrane of PLs) with support provided by synovial fluid (SF) macromolecules (Fig.1) [1].



(a) **(b)** **(c)**

Fig.1. **(a)** Schematic view of the three zones is identified with the phospholipids solid bilayers adsorbed at the surface. **(b**) An electron microscopy image of the articular cartilage surface of a human knee demonstrating the oligolamellar lining consisting of phospholipid bilayers. The bar represents 50 nm [2]. **(c)** Equilibrium in synovial fluid between phospholipids (liposomes and inverted hexagonal phases) and macromolecules of hyaluronan and lubricin, and lamellar phase formation under load in articular cartilage.

The three main components of SF: lubricin, hyaluronan, and phospholipids in the form of liposomes and lamellar phases are likely to possess the boundary-lubricating ability. Synovial fluid macromolecules, lubricin, and hyaluronan interact with phospholipids to form stable complexes (see Fig.1c). During joint inflammation, PLs bilayers are degraded and the content of phospholipids in synovial (SF) is increased 2 to 3 times above the normal range [3, 4]. This study was undertaken to learn whether or not the surface active phospholipid loses its ability of self-organization and lubrication in diseased joints. In this study, we tried to identify bilayers of PLs deactivation (surface of AC) as well as deactivation of phospholipid in the synovial fluid (SF) from samples either with active rheumatoid arthritis (RA) or with early or late stages of osteoarthritis (OA). Our hypothesis that β2-Glycoprotein I, (β2-GPI) (MW of 50 kDa) circulates in the body and autoimmune disease transforms β2-GPI in antibody [5, 6]. β2-GPI participates in the antiphospholipid antibody syndrome (APS) through binding of β2-GPI to the anionic charged phospholipid (-PO4-) group.

Results and Discussion

A joint disease named osteoarthritis (OA) or degenerative arthritis *is* caused by the damage the cartilage surface tissue in the joint *to* cause pain and stiffness. Rheumatoid arthritis (RA) is an autoimmune disease with signs and symptoms that include joint swelling, pain, prolonged morning joint stiffness, fatigue, muscle atrophy, and joint erosions [7, 8], with bilaterally symmetrical joint damage [9]. Compared to synovial fluid from controls, SF from patients with early eOA and those with late lOA had higher levels of most PLs species (2 to 3 times) above the normal range (see Fig. 2a and 2b). Data extracted from [3, 4].

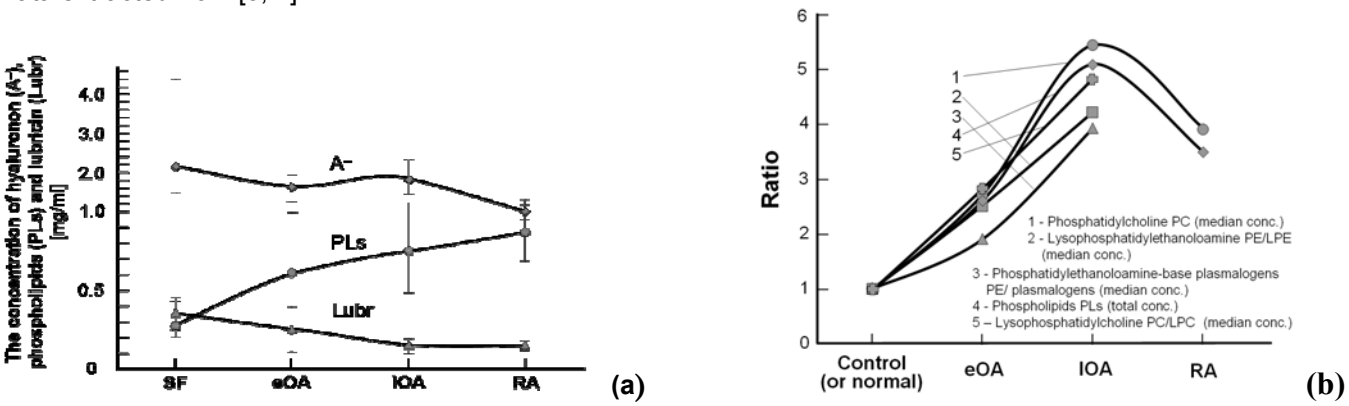


Fig.2 (a). The *levels* of hyaluronan (A-), phospholipids (PLs) and lubricin (Lubr) in human synovial fluid (SF) in patients with healthy joints control (SF) and joint diseases with early osteoarthritis (eOA), late osteoarthritis (lOA) and rheumatoid arthritis (RA) were 2 to 3 times higher above the normal range. **(b).** Ratios of some phospholipid classes in human synovial fluid from controls/or normal samples, patients with early eOA, patients with late lOA, and patients with RA. The ratio (curve 1) of phosphatidylcholine PC/LPC (median conc.), (2) lysophosphatidylethanolamine PE/LPE (median conc.), (3) phosphatidylethanolamine-base plasmalogens PE/plasmalogens (median conc.), (4) phospholipids PLs (total conc.), and (5) lysophosphatidylcholine PC/LPC (median conc.).

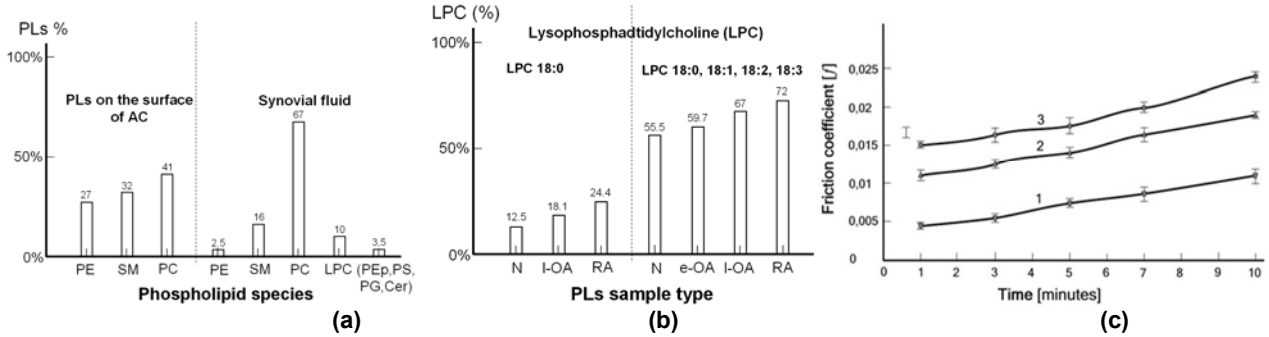


Fig.3. **(a)** The surface active PLs (SAPL) on the surface of AC and in synovial fluid. (**b**) The major lysophosphatidylcholines in SF. (**c**) Friction coefficient *vs.* time for the (cartilage/cartilage) pair, (curve 1) normal one and (curve 2) with early osteoarthritis and (curve 3) late osteoarthritis.

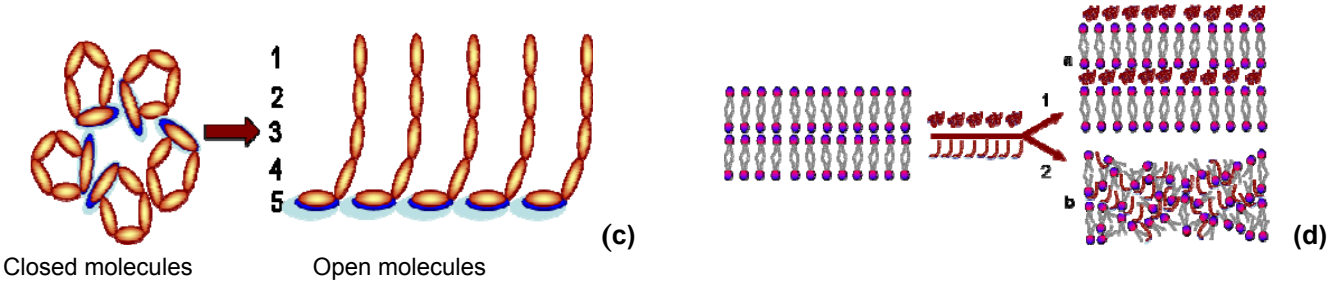


Fig.4 (c). Conversion of β_2-Glycoprotein I, β_2-GPI of the circular conformation (closed molecules) into an open hockey-stick-like conformation, each molecule has five domains (1-5). **(d).** Bilayers of phospholipids in the environment vicinity of plasma β_2-Glycoprotein I (β_2-GP I), (1a) the closed circular conformation of plasma β_2 - GP I as it circulates in plasma in a healthy joint, and (2b) the open hockey stick-like conformation in APS syndrome and β_2-GP I is binding to negatively charged phospholipids. The autoantibodies will bind and stabilize β_2-GP I in its hockey-stick-like conformation.

The phospholipid-binding site in domain 5 of β_2-GP I (Fig. 4c) contains 326 positively charged amino acids group ($-NH_3^+$). In plasma, it occurs as a closed circular protein in which domain 1 interacts with domain 5. At a pH around 7 amino acids (arginine, lysine and tryptophan) are positively charged ($-NH_3^+$): an acid-base interaction occurs between the protonated amino acid group ($-NH_3^+$) and the phosphate ($-PO_4^-$) membrane group: (β_2-GPI-NH_3^+) + (PLs–PO_4^-) → ($-NH_3^+$ $PO_4^{-=}$) interaction and electrostatic attractions is strong enough to destroy the PLs bilayer on cartilage surface and deactivate all phospholipids in SF (Fig. 4d).

Conclusion. Enzymatically activated of β_2-Glycoprotein I, β_2-GPI, during joint inflammation and OA, undergo transformation into antibody conformation. We tried to recognize the resulting antiphospholipid antibody syndrome (ASP) as one being responsible for dysfunction of cartilage surface in the process of lubrication.

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Acknowledgments

We gratefully acknowledge the financial supports from the Tribochemistry Consulting (Grant no. 03. 2016) and University of Economy (Grant 01. 2018)

Keywords: Applied tribology, Boundary lubrication, Surface modification, Amphoteric AC; Friction coefficient, Deactivation of SAPL; β_2-Glycoprotein I (β_2-GP I) as deactivator