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Phosphatidylcholine and Follistatin Revisited: Unveiling New Indications for These Panaceas in Human Health and Disease

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ABSTRACT

Phosphatidylcholine and follistatin, with their versatile and wide-ranging medical applications, have intrigued for more than 20 years [3]. They account for more than 50% of the total phospholipids in human cell membranes and up to 95% of the total choline pool in most tissues, playing a significant role in the structure and function of these membranes. Phosphatidylcholine, for instance, has made an impact as a lipid-lowering drug [1]. This drug has also effectively detected certain cancers, treated ulcerative colitis recalcitrant to empirical therapy, and steered osteoclast and osteoblast cells to prevent osteopenia and osteoporosis [2,3,8]. PC also aids in diagnosing and monitoring the treatment progress of Multiple sclerosis and sculpting the body via local subcutaneous lipolysis [10]. Follistatin, on the other hand, is a celebrated muscle builder and sexual libido enhancement and prevents bone and cartilage degeneration [16,17]. Its primary role is antagonising and neutralising the activity of transforming growth factor β (TGF-β) superfamily members [13]. Follistatin administration foils muscle diseases such as sarcopenia, and local subcutaneous follistatin injections decrease body weight and eliminate visceral fat [15,18]. Interestingly, natural plasma follistatin levels are elevated years before the onset of type 2 diabetes [13]. Follistatin maintains vascular health and offers a new treatment option for keloids [20,23]..

Keywords
Phosphatidylcholine, Follistatin, Hyperlipidemia, Muscle building.

Phosphatidylcholine

Introduction

Phosphatidylcholine is a naturally occurring glycerolphospholipid composed of a glycerol backbone with two fatty acids, a phosphate group and a choline headgroup component [1,2]. Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) account for more than 50% of the total phospholipids in human cell membranes and play significant roles in the structure and function of these membranes [3]. PC is synthesised by an amino alcohol phosphotransferase reaction, utilising *sn*-1,2-diacylglycerol and cytidine diphosphate (CDP)-choline [3]. This is the last step in the Kennedy pathway, a crucial process in PC synthesis that accounts for up to 95% of the total choline pool in most tissues. PC can also be assembled via the phosphatidylethanolamine N-methyltransferase pathway [3].

PC has 4 essential functions:

1. Emulsifying fat (dietary fat digestion) [1].
2. Cholesterol metabolism [1]
3. Cell membrane (component) [1]
4. Hepatic secretion of very low-density lipoprotein (VLDL) secretion [3]

Choline is a quaternary amine and is an essential nutrient for mammals. Choline is recycled in the liver and redistributed from the kidney, lung, and intestine. The controlled breakdown of choline phospholipids can regenerate choline and choline metabolites. The main pathway for PC-mediated hydrolysis occurs via phospholipase D, which produces choline and phosphatidic acid, and phospholipases A1 and A2, which generate free fatty acids and glycerol-phosphocholine [3]. PC has been indicated

for treating hyperlipidaemia, atherosclerotic disorders, diabetic angiopathies, angina pectoris, post-myocardial infarction, hypertension of sclerotic origin, and thromboembolism pre- and postoperatively [1].

Neuronal cell death is the essence of neurodegenerative diseases and injury, a leading cause of mortality, responsible for almost 9 million deaths per year [4]. The potential of increasing PC's choline component to escalate neuronal cell growth and differentiation offers a ray of hope, confirming PC's role as a potential neurotherapeutic target [1,4]. This promising potential of PC in treating neurodegenerative diseases should instil hope and optimism in the audience. Restoring choline levels improves cognition in certain brain disorders and gives PC an anti-Alzheimer's effect [1,5].

PC's ability to regulate lipid and cholesterol metabolism is a reassuring prospect in liver disease research. PC positively affects cholesterol levels, alcohol-induced mitochondrial injury, alcohol-induced hepatocyte apoptosis, and liver fibrosis, instilling confidence in its potential therapeutic applications [4].

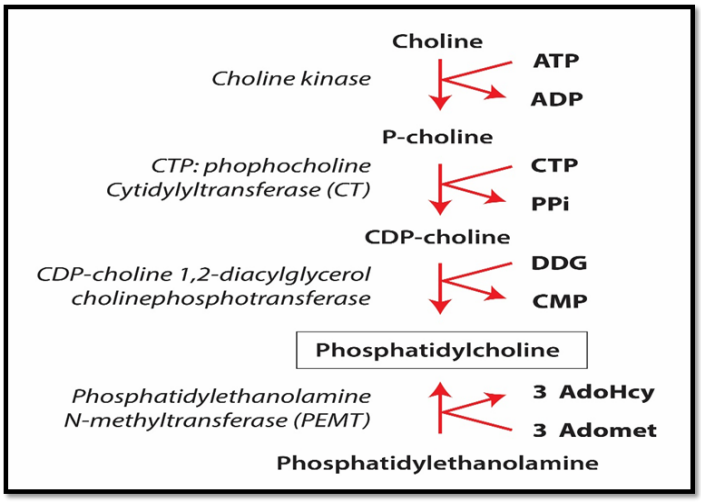

Figure 1: The two pathways are responsible for PC biosynthesis in the liver, the choline pathway and the phosphatidylethanolamine N-methyltransferase pathway.

New Indications

PC metabolism is altered in certain cancers. Elevated phosphocholine levels in cancer are ascribed to growth factor-activated Ras and phosphatidylinositol 3-kinase (PL3K) signalling cascades that surge choline kinase (CK) levels in the Kennedy pathway. CKs are activated in malignant cells of the lung, colon, breast, prostate, cervix, and ovarian tumours. CKs are potential prognostic markers for cancer progression and molecular targets for chemotherapeutic agents [3]. Certain choline metabolites and enzymes relevant to phospholipid homeostasis are biomarkers to monitor tumour progression and treatment response. They display breakdown resistance to anticancer chemotherapy. PC also possess antitumorigenic properties. Breast cancer disease progression is influenced by aberrant signal transduction in cell proliferation. The phospholipase-C (PLC) family, particularly phosphatidylinositol-specific phospholipase-C (PI-PLCs), mediates signal transduction by regulating several key membrane oncogenic receptor proteins, such as phospholipase-C-γ1 (PLC-γ1) regulates epidermal growth factor receptor (EGFR) activities, and phospholipase-C-δ4 (PLC-δ4) enhances the expression of human epidermal growth factor receptor-2 (HER2) and EGFR in Michigan Cancer Foundation-7 (MCF-7) breast cancer cells [4].

PC plays a major role in HDL metabolism in the liver. PC is bound to apolipoprotein (apo)A-1 by the transporter ATP-binding cassette transporter A1 (ABCA1) during HDL genesis. The HDL-PLC is then channelled into bile secretion, preventing bile stone formation. Furthermore, high levels of PC in plasma augment cholesterol efflux, lecithin: cholesterol acyltransferase (LCAT) activity, and the selective uptake of HDL-cholesteryl esters. This inverse relationship between HDL-cholesterol concentration and cardiovascular disease (CVD) highlights the reverberations of PC in promoting cardiovascular health [6,7]. Conversely, the kidney regulates the excretion and reabsorption of inorganic electrolytes and water to control blood volume, mineral content levels, and pH^4. The accumulation of advanced glycation end products (AGEs) fosters acute liver and kidney injury by ischemia and toxicity [5]. PC ameliorates the level of AGEs-induced MAPK signalling like transcription factor p-NF-kB, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), Phospho-p38 MAPK (p-p38 MAPK), phospho-ERK (p-ERK), and phosphor-JN (p-JN). The disintegration of AGEs by PC correlates with improved cell viability in damaged hepatic and renal cells [5].

Stremmel et al. reported that a delayed released oral PC preparation (rPC) is effective in replenishing the lack of PC in the rectal mucus of patients with ulcerative colitis (UC) [5]. In a double-blind, randomised, placebo-controlled trial, where 60 subjects were treated for 3 months, 90% of subjects on the rPC reached clinical remission or showed more than 50% improvement in disease activity and endoscopic activity index. PC ensured the functional reestablishment of the mucosal barrier, alleviating the inflammatory response in the rectal mucus. PC is an effective therapy for the recalcitrant disease patient population of steroid-refractory UC. The lack of PC in the colonic mucus is of critical pathogenetic relevance in the new concept of PC as an alternative therapy for UC, especially for steroid-refractory UC cases [8].

Maggiori et al. first used PC injections for the aesthetic treatment of xanthelasmas [1]. Later, PC injection indications expanded to include subcutaneous injections for infraorbital fat pads and localised subcutaneous lipolysis. Hasengschwandtner et al. noted that in their treatment for subcutaneous fat lipolysis, diluted PC combined with vitamin B-complex demonstrated an average circumference reduction of 3.7 cm on the upper belly, 3.9 cm on the lower belly, 1.9 cm on the hips, and 1.6 cm on the upper arm within 2 treatments in 441 subjects [1]. Palmer et al. confirmed in their clinical trial involving 172 doctors administering 10581 subcutaneous PC injections to treat localised subcutaneous fat reduction that 73.8% of patients were either "very satisfied" or "satisfied" with treatment, and the treatment is associated with minimal risks [9].

Osteoporosis, a disease characterised by reduced bone density and an increased fracture risk, is intricately linked to lipid metabolism [2]. Elevated phospholipid levels, notably PC, can significantly impact bone remodelling processes by swaying the activity of osteoblasts and osteoclasts via modulating the signalling pathways related to inflammation and bone cell activity, conditioning bone density and strength.

Ye et al. demonstrated that Natural Killer (NK) cells marked CD16(+), CD56(+) and CD3(−) are essential for immune defence and are linked to the innate and adaptive immune systems. CD16(+) and CD56(+) NK cells are associated with bone health. Their authority ranges from regulating osteoclasts and osteoblasts activity to secreting factors that alter bone density. PC regulates CD16(+) and CD56(+) NK cell's activation and proliferation; hence, it is correlated with osteoporosis, implying that elevated PC levels, through the physiological functions of CD16(+) and CD56(+) NK cells, diminish the risk of osteoporosis. TNF accumulation is an inflammatory response that directly impacts bone metabolism and activates cytokines and mediators, creating a proinflammatory environment that escalates bone loss. TNF promotes the expression of receptor activator of nuclear factor kappa-B ligand (RANKL), which triggers osteoclast synthesis, leading to increased bone resorption, a critical factor in the development of osteoporosis. It also inhibits osteoblast formation, reducing bone matrix production and mineralisation, thereby exacerbating osteoporosis. PC's ability to downregulate TNF further reduces the risk of osteoporosis [2].

Multiple sclerosis (MS) is a demyelinating neurodegenerative disease that generally affects young people [10]. The diagnosis of MS lies in the detection of oligoclonal IgG bands in the cerebrospinal fluid obtained via lumbar puncture. Developing antibodies towards lipids is the primary pathologic of MS. Sánchez-Vera et al. developed a highly sensitive ELISA test to detect PC using IgM (IgMPC) from serum samples of MS patients. The test is based on the principle that myelin has abundant lipids, cholesterol, PC, sphingomyelin, cerebrosides, and sulfatide.

Almost 90% of MS patients in the early stages of the disease, clinically isolated syndrome (CIS) or relapsing-remitting MS exhibited positive IgMPC in their serum. The assay's sensitivity is equivalent to the oligoclonal IgG bands detecting test, the gold standard for diagnosing MS. The detection of serum IgMPC enables a rapid diagnosis of MS and, thus, early treatment. The serum IgMPC levels test is also quantitative, allowing the assessment of the response to treatment [10].

The progressive deterioration of cellular and organismal functions characterises ageing. One of the prominent hallmarks of ageing is Mitochondrial dysfunction. Mitochondrial dysfunction induces cellular deterioration and blunts the efficacy of anti-ageing interventions that rely on metabolic plasticity in the elderly [11]. Shiino et al. proved from biochemical analyses that PC inhibition resulted in mitochondrial fragmentation [12]. PC inhibition disrupts the transport of PE from the mitochondria to the endoplasmic reticulum, leading to mitochondrial destruction. Declining PC levels are a known conserved driver and marker of natural mitochondrial ageing. Poliezhaieva et al. discovered that S-adenosylmethionine synthase (SAMS-1) safeguards longevity in the context of mitochondrial impairment [11]. This gene gets progressively inactivated during ageing, disrupting the mitochondrial network integrity and triggering a mitochondrial unfolded protein response. SAMS-1 influences mitochondria through their role in the synthesis of PC. PC supplementation halts mitochondrial-influenced ageing and restores metabolic resilience [11].

Follistatin

Introduction

Follistatin (FST) is a single-chain glycoprotein whose primary role is antagonising and neutralising the activity of transforming growth factor β (TGF-β) superfamily members, which includes activin A and B, myostatin or Growth and Differentiation Factors (GDFs), and bone morphogenetic proteins (BMPs) [13,14]. Activin A increases the production of the inflammatory mediators and regulators of fibroblasts [15]. Activin and myostatin negatively influence the size of muscle fibres and glucose metabolism. BMPs primarily stimulate cells from the soft and hard tissues to become bone. In some cases, cartilage-forming cells modulate different aspects of adipocyte differentiation, including adipose tissue [15]. FST's name arose from the glycoprotein's ability to suppress the follicle-stimulating hormone (FSH) [14]. FST-related proteins such as FST-like-3 (FSTL3) share similar properties [13]. FST is secreted mainly from the liver; the glucagon-to-insulin ratio regulates its expression and secretion, where glucagon enhances and insulin reduces FST release. The gene encoding FST is located on chromosome 5q11.2. FST possesses a TGF-β binding receptor site where all TGF-β members are immediately bound and neutralised [13,14]. These substances bind to serine/threonine kinase receptors and Smads transcription factors to transmit their signal into the nucleus and change the transcription of targeted genes. TGF-β family members bind to type I & type II receptors on the cell wall via phosphorylation [14].

The type I receptor then phosphorylates Smad molecules, eventually forming complexes with Smad4 [15]. This complex translocates to the nucleus to activate gene transcription. FST prevents this reaction by binding to the TGF-β superfamily members, neutralising them in the extracellular space. FST translocates directly into the nucleus, downregulating rRNA synthesis and ribosome biogenesis to maintain cellular energy homeostasis [15]. FST has a well-established role in skeletal muscle development and sexual libido enhancement and prevents bone and cartilage degeneration [16,17].

New Indications

All organisms undergo environmental stresses, including oxidative stress, nutritional deficiency, hypoxia, etc. [15]. In response to stressors, these cells undergo molecular changes to adapt against unfavourable environmental conditions. Stress-responsive proteins are expressed during a cellular stress response to help

cells survive. FST is a stress-responsive protein that purveys protection against various stresses, including oxidative stress and glucose deprivation. FST down-regulates NOX2 protein levels, attenuating the production of reactive oxygenated species (ROS), which hedges vascular endothelial integrity from oxidative stress. As a myostatin inhibitor, FST inhibits ROS production in muscles, thwarting muscle wasting and fending off sarcopenia in older people. FSTs' role in foiling cellular stress is a pre-emptive strike on disease inception and progression. Its administration improves symptoms of muscle diseases such as sarcopenia and Duchenne muscular dystrophy (DMD), inflammatory diseases such as endotoxemia and cigarette smoke-induced inflammation, and attenuates myocardial, renal and hepatic ischemia-reperfusion injury (IRI) [15].

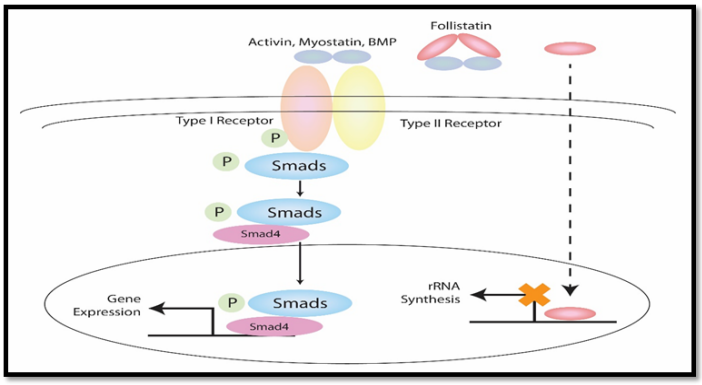

Figure 2: The mechanisms of action of FST.

Type 2 diabetes (T2D) is triggered by insulin resistance, firstly leading to enhanced demand for insulin in peripheral tissues and relative deficiency of this hormone [3]. Still, later, it ushers the functional failure of pancreatic β-cells and absolute insulin deficiency [14]. Hansen et al. showed that plasma FST level is slightly elevated in people with T2D compared to healthy subjects, and it correlates positively with fasting glucose levels. FST creates better glucose tolerance and heightens insulin glucose uptake. FST levels are raised in increased energy demand conditions, and Vamvini et al. demonstrated that plasma FST amplified 3-4-fold during prolonged fasting. Wu et al. confirmed that naturally elevated circulating FST increases the risk of T2D by inducing adipose tissue insulin resistance. Plasma FST levels are elevated many years before the onset of T2D [14].

Obesity is a metabolic disorder described as the excessive accumulation and distribution of body fat, which is detrimental to health [13]. FST trims obesity by promoting FFA breakdown and energy expenditure. This process is called “the browning of adipose tissue”, and it involves converting white adipose tissue (WAT), responsible for energy storage, into beige/brown adipose tissue (BAT), which is linked to axing body weight and regulating glucose levels via the action of mitochondrial uncoupling protein-1 (UCP-1) and impeding TGF-β’s signalling pathway [13,16]. The inhibition of the pp38 member of the mitogen-activated protein kinases/ Extracellular signal-regulated kinase1/2 (MAPK)/ pERK1/2 pathway in 3T3-L1 cells fetters the upregulation of the FST-induced UCP1 protein, inducing WAT browning [18]. This phenomenon can be detected by measuring fibronectin type III domain 5 (Fndc5) levels, the irisin precursor secreted in muscle and WAT. FST induces browning of WAT through the AMP-activated protein kinase/ Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (AMPK-PGC1α-Fndc5) pathway. Clinicians have now moved on to intraperitoneal FST injections to decrease body weight and eliminate visceral fat [18].

FSTL1 levels can independently predict major adverse cardiac or cerebrovascular events (MACCE). FSTL1 is a highly expressed cardiokine released upon cardiac injury, where it predicts poor outcome. Elevated plasma and serum FSTL1 levels were observed in patients with acute coronary syndrome (ACS) and in patients with acute Kawasaki disease, which is a primary cause of acquired coronary artery aneurysms (CAA) in childhood, indicating that elevated levels of FSTL1 is a prognostic biomarker indicating a higher risk of cardiovascular death. The FSTL1 levels in plasma were found to be high before elective percutaneous coronary intervention (PCI). FSTL1 reduces the incidence of cardiovascular disease (CVD) by quelling inflammation and proinflammatory cytokines. The FSTL1 activation of AMPK fends off ischemic injury by squelching apoptosis and its inflammatory response. FSTL1 also instigates Janus kinase (JAK/STAT3) and NFκB signalling via toll-like receptor-4 (TLR4) and TGF1-SMAD2/3 signalling. FST, in the form of FSTL1, plays a protective role by boosting cardiovascular function, promoting angiogenesis and repair during cardiac injury, and shielding inflammation and fibrosis via TGFs. Cardiac fibroblasts or cardiomyocytes deficient in FSTL1 increase the risk of heart failure by twofold. Cardiomyocyte-specific deletion of FSTL1 exacerbates cardiac hypertrophy, fibrosis, ventricular performance, and myocardial capillary density 4 weeks post-transverse aortic constriction (TAC). The therapeutic administration of recombinant FSTL1 to ventricular cardiomyocytes prompts resistance to pressure overload myocardial hypertrophy. Patients with dilated cardiomyopathy with higher myocardial levels of FSTL1 exhibited significantly better recovery with improved ejection fraction. Shimano et al. noted that cardiomyocyte-specific FSTL1 activates AMPK and reduces nitric oxide synthase-3 (NOS3) phosphorylation and natriuretic peptide A (NPPA) and NPPB gene expression, which are molecular markers of cardiac, confirming that FSTL1 reduces cardiac hypertrophy [19].

FSTL1 forestalls apoptosis via:

1) AMPK-acetyl-CoA carboxylase alpha (ACACA) signalling [19]
2) DIP2A-phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)-AKT axis
3) Mitogen-activated protein kinase 1/2 (MEK1/2)-ERK pathway [19]
4) Inhibition of pro-apoptotic BMP4 [19]

Besides the heart, Cardiomyocyte-specific FSTL1 deficiency also exacerbates kidney injury after subtotal nephrectomy, affirming that FSTL1 released from the heart is essential in protecting the

kidney from damage. Endothelial dysfunction is an initiating factor in the development of hypertension and related complications [20]. FSTL1 elevates endothelial cell function and vivifies revascularisation in response to ischemic insults. Liu et al. found that FSTL1 treatment reversed impaired endothelium-dependent relaxation (EDR) in the mesenteric arteries and lowered blood pressure. The FSTL1 administration decreased AMP-activated protein kinase (AMPK) phosphorylation, elevated endoplasmic reticulum (ER) stress markers, increased reactive oxygen species (ROS), and halted nitric oxide (NO) production. These findings prove that FSTL1 prevents endothelial dysfunction, thus regulating blood pressure [20].

Inflammation plays a key role in wound healing [21]. FST regulates keratinocyte proliferation in the epidermis and skin wounds [22]. Keratinocyte-derived FST protects epidermal cells from activin-induced stromal cell activation, which leads to excessive fibrosis and scar tissue. FST also curbs delayed hair follicle cycling due to the downregulation of BMP-2 expression in the skin. FST promotes wound healing by accelerating keratinocyte proliferation and reepithelialisation during the first days after injury. Downregulating myostatin assists wound healing by reducing scarring, decreasing inflammatory response and altering fat distribution [21,22]. Ham et al. conducted a clinical trial investigating a novel keloid treatment using FST, based on the theory that keloids are benign tumours caused by abnormal wound healing driven by increased expression of cytokines, including activin A [23]. Activin A (INHBA) and the connective tissue growth factor (CTGF) gene expression are significantly upregulated in keloid fibroblasts, as is the activin A protein expression. A single treatment of FST over 5 days significantly barricades Activator protein 1 inhibitor (SR11302), INHBA, CTGF and various matrix-related genes in keloid fibroblasts. FST-bound activin A, clogging the reactive pathway, suppresses CTGF expression and validates its utilisation as a novel therapeutic drug for keloids and perhaps other fibrotic diseases [23].

Conclusion

PC and FST are drugs that have been on the market for 20 years. They have been given a new lease on life with new therapeutic uses. The latest information on phospholipid metabolism and the advancement of lipidomics has fuelled a resurgence in interest in PC [3]. PC is a prominent drug essential in cell physiology, regulation, and maturation of numerous cellular processes. PC has found new uses in cancer and multiple sclerosis biomarkers, ulcerative colitis therapy, fat elimination and osteoporosis prevention. FST is a renowned drug in the field of muscle-building and fat reduction. FST is now used for body sculpting, T2D and CVD monitoring and wound healing.

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