生命的化学, 2022, 42(3): 412-423 www.life.ac.cn doi: 10.13488/j.smhx.20210870

磷脂酰胆碱的生物学功能及其在心血管疾病中的作用

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摘要：磷脂酰胆碱(phosphatidylcholine，PC)作为真核细胞膜结构的主要成分，是哺乳动物细胞中含量最丰富的磷脂，占细胞总磷脂的45%~55%。由于PC脂肪酰基链的长度和饱和度可进行修饰重塑，因此PC分子具有很大的多样性。本文回顾了PC的合成、分解、生物学功能及其在心血管疾病中的作用，分析了PC作为膜组分构成细胞和细胞器膜，参与脂蛋白的组装和分泌，以及作为信号分子和炎性介质的前体分子发挥多种生物学功能，在动脉粥样硬化、高血压、冠心病、心力衰竭等多种心血管疾病的发生发展过程中具有重要作用。

关键词：磷脂酰胆碱；生物学功能；心血管疾病

Biological function of phosphatidylcholine and its role in cardiovascular diseases

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Abstract: Phosphatidylcholine (PC), as the main component of eukaryotic membrane structure, is the most abundant phospholipids in mammalian cells (45%~55% of the total phospholipids). Because the length and saturation of its fatty acyl chain can be modified and remodeled, PC molecules demonstrate great diversity. This paper reviewed the synthesis, decomposition, biological process of PCs and their roles in cardiovascular diseases. It is suggested that PCs not only constitute the cellular and organelle membrane as membrane components and participate in the assembly and secretion of lipoprotein, but also work as a precursor molecule of signal molecules and inflammatory mediators, so as to play an important role in the occurrence and development of atherosclerosis, hypertension, coronary heart disease, heart failure and other cardiovascular diseases.

Key Words: phosphatidylcholine; biological function; cardiovascular diseases

磷脂根据其骨架的不同分为甘油磷脂和鞘磷脂。甘油磷脂根据其取代基团的不同分为磷脂酰胆碱(phosphatidylcholine，PC)、磷脂酰乙醇胺(phosphatidylethanolamine，PE)、磷脂酰丝氨酸(phosphatidylserine，PS)、磷脂酰甘油(phosphatidylglycerol，PG)、磷脂酰肌醇(phosphatidylinositol，PI)、心磷脂(cardiolipin，CL)、缩醛磷脂(plasmalogen)、血小板活化因子(plateletactivating factor，PAF)等。

1847年，法国化学家Theodore Nicolas Gobley

收稿日期：2021-12-28

基金项目：国家自然科学基金项目(81874449)；国家自然科学基金项目(82174177)

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教授分离并鉴定了PC(也称为卵磷脂)的化学结构[1]。PC由甘油骨架和极性头部(磷酸基团)组成，甘油骨架上的两个-OH基与一系列包含不同长度和位置的双键脂肪酰基链结合，磷酸基团上的-H基被胆碱取代时，即为PC(PC分子结构通式见图1)。由于PC脂肪酰基链可经Lands循环进行重塑，即通过甘油磷脂的脱酰化和再酰化循环改变脂肪酰基链的组成，生成多种不对称的成熟PC分子，因此哺乳动物细胞中PC分子存在很大的多样性。PC作为真核细胞膜的主要成分，是哺乳动物细胞和细胞器中含量最丰富的磷脂，占细胞总磷脂的45%~55%。PC是目前已知的脂蛋白组装和分泌必需的唯一磷脂，是极低密度脂蛋白(very low density lipoprotein，VLDL)和低密度脂蛋白(low density lipoprotein，LDL)的主要磷脂成分[2]。PC作为甘油二酯(diglyceride，DAG)、鞘磷脂等信号分子的前体脂质[3]，是参与胆汁和肺表面活性物质二棕榈酰磷脂酰胆碱(dipalmitoyl phosphatidylcholine，DPPC)[4]形成的关键分子，具有重要的生理意义。本文综述了近年来国内外对PC的生物学功能及其在心血管疾病中作用的相关研究。

1 磷脂酰胆碱(PC)的生物合成

PC可通过三种途径合成：Kennedy途径(从头途径)、Lands循环和PEMT途径(仅限于肝细胞)(图2)。

1.1 Kennedy途径(CDP-胆碱途径)

内质网是PC合成的主要场所[5]，哺乳动物有核细胞中约70%的PC经此途径从头合成，该途径是20世纪50年代由Eugene Kennedy教授确立，因此通常被称为“Kennedy途径”[6]。胆碱通常来源于食物，也可由丝氨酸、甲硫氨酸合成。胆碱通过胆碱转运体进入细胞后，被细胞质中的胆碱激酶(choline kinase，CK)催化，由ATP提供磷酸，形成磷酸胆碱。其后，由ATP供能，以三磷酸胞苷(CTP)为底物，经由CTP：磷酸胆碱胞苷酰转移酶(CTP: phosphocholine cytidylyltransferase，CCT)催化，胆碱活化形成CDP-胆碱，该步骤是Kennedy途径合成PC的限速反应，CCT是Kennedy途径合成PC的限速酶[7]。最后，位于内质网膜外侧面的胆碱磷酸转移酶(CDP-choline: 1,2-diacylglycerol cholinephosphotransferase，CPT)催化CDP-胆碱与甘油二酯(DAG)缩合生成PC。Kennedy途径是调节磷脂和中性脂质平衡的重要生物学过程。

1.2 Lands循环

Lands循环是重要的磷脂重塑途径。PC首先通过Kennedy途径形成，其后通过Lands循环进行修饰重塑。在Lands循环中，磷脂酶A2(phospholipase

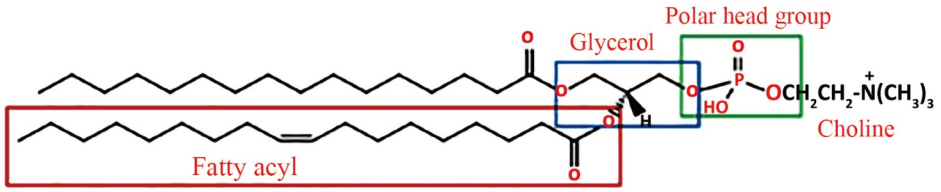

图1 磷脂酰胆碱(PC)的分子结构通式

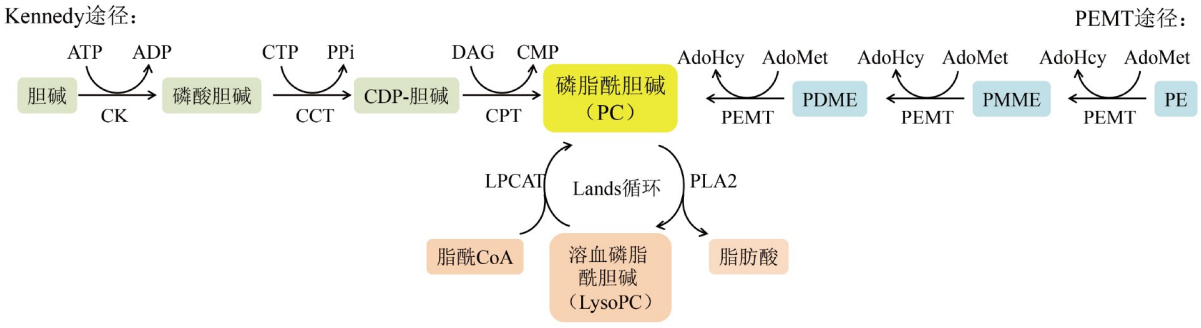

图2 磷脂酰胆碱(PC)的合成

A2，PLA2)去除PC的sn-2位置的脂肪酸，水解形成溶血磷脂酰胆碱(lysophosphatidylcholine，LysoPC)；或反向反应，通过溶血磷脂酰胆碱酰基转移酶(lysophosphatidylcholinyltransferase，LPCAT)在sn-2位置添加脂肪酸，产生PC。LPCAT是Lands循环中再酰化反应的关键酶，LPCAT通过修饰甘油磷脂sn-2位点的脂肪酰基碳链长度和饱和度形成不同种类的PC，改变表面曲度、影响表面/体积比来调节细胞内脂滴大小，在调节细胞脂质代谢和稳态中发挥重要作用[8]。

1.3 PEMT途径

PC也可以由S-腺苷甲硫氨酸(S-adenosylmethionine，AdoMet)提供甲基，磷脂酰乙醇胺N-甲基转移酶(phosphatidylethanolamine N-methyltransferase，PEMT)催化PE经连续甲基化转化为PC，占人PC合成总量的10%~15%。虽然PEMT途径仅存在于肝脏，但具有重要的生物学意义。PC/PE比值影响线粒体、内质网、脂滴等多个细胞器的结构和功能，影响线粒体能量的产生[9]，调节细胞内脂滴的大小和动力学改变，与代谢紊乱密切相关。

2 磷脂酰胆碱(PC)的分解

PC主要是通过磷脂酶D(phospholipase D，PLD)水解产生胆碱和磷脂酸(phosphatidylic acid，PA)，或通过磷脂酶A1(phospholipase A1，PLA1)和/或磷脂酶A2(phospholipase A2，PLA2)水解生成游离脂肪酸和甘油磷酸胆碱(图3)。其后甘油磷酸胆碱由磷酸二酯酶(phosphodiesterase，PDE)水解为3-磷酸甘油和胆碱。

3 磷脂酰胆碱(PC)的生物学功能

3.1 物理支持

PC最初被认为是一种细胞膜组分。PC通常自发形成一个平面双层结构，其中每个PC分子都以近圆柱形的几何结构脂质尾部彼此面对、极性头基与水相接触，组成生物膜的基本结构。不同类脂的存在和相对丰度，尤其是磷脂的脂肪酰基部分的链长和饱和度(双键或单键)差异决定了细胞膜的生物物理性质，包括其硬度、厚度、疏水性、流动性、曲率、子域结构和功能，并参与物质运输、信号转导等细胞过程。PC是肺泡表面活性物质的主要成分之一，肺表面活性物质通常由80%极性脂质(主要是DPPC)、10%中性脂质(胆固醇)和10%蛋白质组成[10]，以维持肺泡容积，增加肺的顺应性。由于PC是两亲性脂质，常用作口服给药制剂的赋形剂[11]。

PC在细胞膜上均匀分布，由于PC具有不饱和侧链的优势，内质网膜具有一定流体特征，其流动性是促进蛋白质进出内质网室所必需的[12]。PC耗竭可选择性地影响高度动态蛋白易位酶如线粒体内膜移位酶(mitochondrial import inner membrane translocase subunit Tim23，TIM23)复合物和线粒体外膜(mitochondrial sorting and assembly machinery，SAM)复合物的稳定性，损害蛋白质向线粒体内膜和线粒体基质的运输[13]。PC是染色质的次要成分之一，对细胞的存活至关重要，PC减少可能导致细胞增殖减弱[14]。PC参与细胞内脂滴形成和产脂基因表达，脂滴是细胞内中性脂质(甘油三酯和甾醇酯)的储存形式，表面由单层磷脂(主要是PC)包围。脂滴是高度动态的细胞器，在脂质

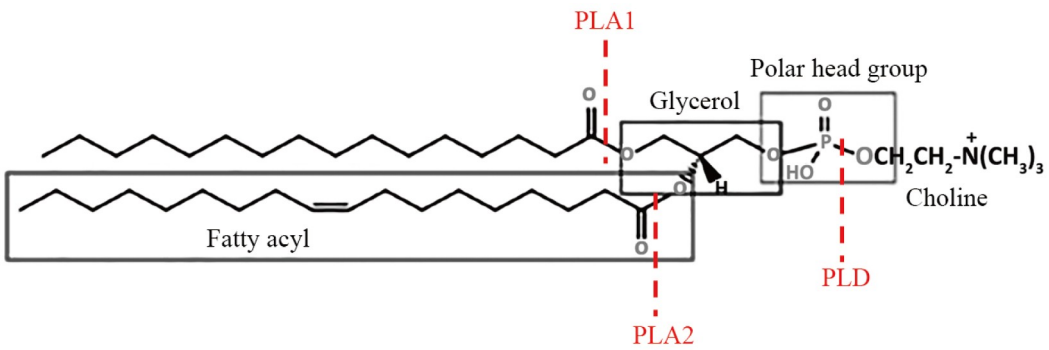

图3 磷脂酰胆碱(PC)的分解

摄取或释放时，其大小会迅速变化，其动力学要求脂滴表面结构的快速适应，以根据能量需求维持细胞内的脂质稳态[15]。

低PC水平可非特异性改变膜性质，上调脂肪生成和丝裂原激活蛋白激酶14(mitogen-activated protein kinase 14，MAPK14/PMK-1)依赖性先天免疫应答[16]。多种肿瘤细胞可上调LPCAT以促进PC合成和细胞内脂滴的积累，积累的脂滴可向周围细胞补充脂质、提供能量，并限制基因毒性应激、抑制Caspase级联激活和内质网应激，促进肿瘤的进展[17,18]。富含脂滴的肿瘤细胞可有效隔离活性氧或脂质过氧化物等损伤介质[19]，降低免疫原性细胞死亡、减少$CD8^+$ T细胞浸润，保护整个细胞群免受细胞毒性应激[20]。已有研究证实，PC与大肠癌、乳腺癌、胃癌、前列腺癌等多种肿瘤的进展、侵袭相关[21,22]。

上述研究结果表明，PC的生物学作用远不止对细胞结构的物理支持。

3.2 作为特定受体的配体直接发挥生物学功能

多个PC可直接激活过氧化物酶体增殖物激活受体(peroxisome proliferator activated receptor，PPAR)。1-棕榈酰-2-油酰-sn-甘油-3-磷酸胆碱(1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine，16:0/18:1 PC，POPC)是PPARα的特异性内源性配体，与PPARα结合后调控脂质代谢基因的表达，可竞争性抑制已知的PPARα激动剂与PPARα的结合，且特异性好，与PPARδ的相互作用较弱，不与PPARγ反应，当POPC减少时，PPARα活性降低[23,24]。二十二碳六烯酸磷脂酰胆碱(docosahexaenoic acid-phosphatidylcholine，DHA-PC)和二十碳五烯酸磷脂酰胆碱(eicosapentanoic acid-phosphatidylcholine，EPA-PC)可显著激活PPARγ，下调NF-κB通路，抑制Lewis肺癌小鼠的肿瘤生长和转移[25]。1-硬脂酰-2-柠檬酰-sn-甘油-3-磷酸胆碱(1-stearoyl-2-oleoyl-sn-glycero-3-phosphocholine，18:0/18:1 PC，SOPC)被鉴定为PPARδ的配体，参与日间肝脏对脂肪酸的摄取和肌肉中的β-氧化，SOPC可降低餐后的甘油三酯水平，并提高肌肉细胞中脂肪酸的利用[26]。

人肝受体同源物-1(liver receptor homologue-1，LRH-1)也称为NR5A2，是孤儿核受体家族成员之一，作为转录共激活因子调控胆汁酸的生物合成[27]。多个PC参与LRH-1的激活，促进脂肪的加工，减少肝脏脂肪变性的风险，双月桂酰磷脂酰胆碱(dilauroyl phosphatidylcholine，di-C12:0 PC，DLPC)是其中活性最强的激动剂，其活性约为二己基磷脂酰胆碱(dihexyl phosphatidylcholine，di-C10:0 PC)的两倍、二肉豆蔻酰磷脂酰胆碱(myristoyl phosphatidylcholine，di-14:0 PC，DMPC)的四倍[28]。DLPC可结合并进入肝细胞生物膜，增加膜的流动性和稳定性，修复受损的肝细胞膜及线粒体、内质网和高尔基体等细胞器膜，恢复膜功能，降低氧化应激、维持线粒体膜电位，减轻肝脏纤维化[29,30]。DLPC还可降低甾醇调节元件结合蛋白1(sterol regulatory element binding protein 1，SREBP1)的表达，参与甾醇生物合成，调节脂肪因子转录，提高胰岛素敏感性，维持葡萄糖稳态，改善胰岛素抵抗小鼠的肝脏脂肪变性[31]。

PC可抑制*CD14*基因表达和Toll样受体2(Toll like receptor 2，TLR2)依赖的单核细胞和树突状细胞(DC)活化，抑制动脉粥样硬化[32,33]。

3.3 作为多个信号分子和炎性介质的前体分子

DAG和PA是细胞内重要的第二信使，对维持细胞稳态至关重要。饱和PC是DAG和PA的主要前体分子，作为甘油二酯激酶δ(diacylglycerol kinase δ，DGKδ)的底物，参与DAG的生成和DAG磷酸化生成PA的过程，影响膜局部的物理结构，间接参与调节葡萄糖摄取和葡萄糖稳态，其中主要是含有棕榈酸(16:0)残基的DAG[34]。sn-1,2 DAG首先激活蛋白激酶C(protein kinase C，PKC)[35]，其后PKC与蛋白激酶D(protein kinase D，PKD)、Ras鸟苷酸释放蛋白(Ras guanylate releasing protein，RASGRP)、嵌合体(Rac GTPase激活蛋白家族)、Munc13家族(参与胞吐作用)和Ca^{2+}通道等多种蛋白质相互作用发挥生物学效应。PC通过激活细胞核内磷脂酰胆碱依赖性磷脂酶C(phosphatidylcholine-specific phospholipase C，PC-PLC)和DAG参与细胞增殖，DAG的增加也可以刺激PC的合成，PC合成的抑制是细胞凋亡的起始[36]。

PC是LysoPC的主要来源，PC和LysoPC通过Lands循环在调节细胞脂质代谢和稳态中发挥重要

作用。LysoPC可基于内皮细胞膜上的钠依赖性LPC转运体1(sodium-dependent LPC symporter 1/major facilitator superfamily domain containing 2A，MFSD2A)介导透过血脑屏障进入大脑，然后分解成多不饱和脂肪酸(polyunsaturated fatty acid，PUFA)，如ω-3多不饱和脂肪酸DHA(22:6)，实现长链脂肪酸向大脑的转运，实现脑内的细胞膜重塑、细胞信号传导等生物学功能[37]。血浆或脑脊液中的LysoPC/PC比值降低是阿尔茨海默病(Alzheimer's disease，AD)患者的重要代谢特征；但较高浓度的LysoPC可破坏线粒体完整性[38]并增强细胞中细胞色素C的易位[39]。LysoPC通过与其受体G蛋白偶联受体(G protein coupled receptor，G2A)结合后激活MAPK，包括ERK1/2、p38 MAPK、JNK和Toll样受体，诱导氧化应激、趋化因子表达和炎症反应[40]。LysoPC不仅是巨噬细胞向M1表型极化的强诱导剂，而且是氧化低密度脂蛋白(oxidized low density lipoprotein，Ox-LDL)皮质的主要组分和活性成分，在动脉粥样硬化冠状动脉斑块的起始、进展和斑块破裂中发挥重要作用[41]。LysoPC(P-17:0)和LysoPC(18:0)被鉴定为冠心病的生物标志物[42]。LysoPC(17:0)和LysoPC(18:2)被鉴定为心肌梗死的生物标志物[43]。肥胖人群循环LysoPC(16:0)、LysoPC(18:0)、LysoPC(18:1)、LysoPC(18:2)和LysoPC(20:4)水平显著增加，已知LysoPC棕榈酸酯(16:0)是人体血浆中含量最丰富的LysoPC，肥胖人群的血浆总LysoPC水平升高[44]。LysoPC越来越被认为是与心血管和神经退行性疾病正相关的关键标志物[45]。

PC是鞘磷脂(sphingomyelin，SM)合成的直接底物。在顺式高尔基体中，鞘磷脂合成酶1(sphingomyelin synthase 1，SMS1)催化PC将磷酸胆碱基团转移给神经酰胺，生成SM[46]。鞘磷脂以不同的囊泡运输到质膜，与胆固醇形成脂筏，参与肥胖、动脉粥样硬化、非酒精性脂肪肝、肿瘤的发生发展[47,48]。

PC分解释放的胆碱是神经递质乙酰胆碱的合成前体[49]，直接参与神经中枢胆碱能系统和外周胆碱能神经纤维的生理病理过程。脑内PC水平降低可能导致大脑突触减少，是AD早期记忆障碍的基础[50]。多个含乙醚基PC(PC ae C36.2、PC ae C40.3、PC ae C42.4和PC ae C44.4)与病理性脑脊液Aβ1-42相关，且在AD临床前阶段即有明显升高[51]。

在神经生长因子(nerve growth factor，NGF)刺激下，磷脂酶A1和酰基转移酶催化PC重塑产生1-油酰-2-棕榈酰-磷酸胆碱(1-oleoyl-2-palmitoyl-phosphatidylcholine，OPPC)，OPPC可吸引一部分膜蛋白，从而在突触前神经元质膜中形成一个新的膜室，促进神经元质膜的功能划分[52]。

PC还是花生四烯酸(arachidonic acid，AA)的主要前体分子[53]，AA作为第二信使，参与不同病理生理过程的信号传导。AA不仅能够激活NADPH氧化酶，诱导氧化应激[54]；还可以转化成前列腺素D2或前列腺素E2，形成具有抗炎特性的化合物；AA可激活PPARγ，参与能量代谢和脂肪细胞的分化[55]；或诱导星形胶质细胞血红素加氧酶-1(heme oxygenase-1，HO-1)的转录[56]。通过AA抑制膜对接，LysoPC阻止膜融合，二者协同抑制细胞的胞吐过程[57]。

3.4 参与脂蛋白分泌

PC是脂蛋白形成和稳定所必需的重要分子，ApoB表面60%~80%的磷脂是PC，与胆固醇一起形成脂质单层，包绕着由甘油三酯和甘油组成的中性脂质核心[58]。ATP结合盒转运蛋白A1(ATP binding cassette transporter A1，ABCA1)，基于ATP供能，促进细胞内胆固醇流出至ApoA-I，PC的数量和分子种类直接调节ABCA1的表达，影响ApoA-I依赖性PC和胆固醇外流和高密度脂蛋白(HDL)的形成。静脉注射PC可直接增加血浆HDL水平[59]。在装配和分泌VLDL及乳糜微粒时PC也是必需的，新生VLDL表面PC的减少可能增强分泌途径内VLDL的降解和清除，即PC生物合成决定了新生VLDL颗粒的数量[60]。当肝脏PC生物合成减少时，富含甘油三酯的脂蛋白的分泌受损，血浆VLDL和HDL水平降低。

PC对调节血脂水平、修复肝细胞具有重要的作用。肝脏分泌脂蛋白和胆汁等大量含有PC的分子，据计算，小鼠肝脏每天向胆汁中分泌相当于其整个PC池的PC。当胆碱供应轻度减少时，胆碱在肝脏中循环，并从肾、肺、肠重新分配到肝脏和大脑，以维持PC稳态[61]。但胆碱/蛋氨酸持续缺

乏、PC水平下降或PC/PE比值显著降低时，VLDL分泌减少，质膜的完整性难以维持，细胞因子等促炎分子外流而致肝细胞损伤，从而诱发脂肪性肝炎的发生发展[62,63]。肝脏PC数量减少，则VLDL分泌受损，甘油三酯在肝脏中积累，非酒精性脂肪肝的严重程度与肝脏PC/PE比率呈负相关[64]。PC合成酶PEMT或磷脂酰胆碱胞苷转移酶α(phosphatidylcholine cytidine transferase α，*CCTα*)基因敲除致PC合成受损，可导致小鼠甘油三酯分泌减少约50%，ApoB减少50%~70%。给*PEMT*基因敲除小鼠喂食胆碱缺乏饮食，使肝脏PC降低50%，则膜通透性增加，继而发生脂肪性肝炎和肝衰竭，并在5 d内致死[65]。但也有学者提出，PC直接参与肝脏甘油三酯合成，约65%的小鼠肝甘油三酯来源于PC，从循环HDL(约25%)和LDL(约50%)输送到肝脏的大量PC在肝细胞中转化为甘油三酯，脂蛋白相关PC升高可能促进肝脂肪变性的进展[66]。 PC的生物学功能总结见图4。

4 磷脂酰胆碱(PC)与心血管系统疾病

脂质对于心脏代谢至关重要，参与心肌细胞能量生成、发挥心脏功能。心脏脂质稳态的变化不仅是心脏功能的主要代谢特征，也可以代表炎症、虚弱等全身效应。

4.1 动脉粥样硬化

PC与动脉粥样硬化密切相关。据纳入1 081例人群的Meta分析显示，PC与内膜-中层厚度(IMT)呈负相关[67]。Hirose等[68]纳入96例女性的随机、双盲、安慰剂对照的研究发现，补充高剂量PC(1 200 mg/d)不仅能改善更年期妇女的疲劳感，还能降低舒张压和心-踝血管指数(cardio ankle vascular index，CAVI)。Zhao等[69]研究提出，抑制肝PEMT可降低PC和PC/PE比值，减少VLDL分泌、增加脂蛋白清除率，减轻动脉粥样硬化。Cole等[70]研究发现，抑制肝脏PC合成的PEMT途径，可缩小动脉粥样硬化斑块面积，抑制甘油三酯在心肌内的积累并改善心肌功能。Navder等[71]研究发现，二硫酰基磷脂酰胆碱(disulfide phosphatidylcholine，PPC)可防止LDL氧化，从而预防动脉粥样硬化。

由于PC在肠道微生物的作用下代谢产生三甲胺(trimethylamine，TMA)，三甲胺进一步氧化为氧化三甲胺(trimethylamine oxide，TMAO)，TMAO是明确的致动脉粥样硬化因子，因此，循环PC的水平被证实与动脉粥样硬化等心血管疾病呈正相关[72]。但Cho等[73]提出，食物中PC的不会引起TMAO升高。

4.2 心力衰竭

Wittenbecher等[74]纳入331例心衰和507名健康志愿者的研究发现，PC(32:0)与心衰风险高度相关。Marcinkiewicz-Siemion等[75]纳入36例患者的研究发现，慢性心衰患者血浆PC(34:4)和PC(36:5)水平降低。Cheng等[76]纳入515例不同阶段的心衰患者的研究证实，以血浆PC(C34:4)、组氨酸、苯丙氨酸和精胺组成代谢物组合具有与脑钠肽(brain natriuretic peptide，BNP)相似的诊断价值，且预后价值优于BNP。Mueller-Hennessen等[77]纳入526例

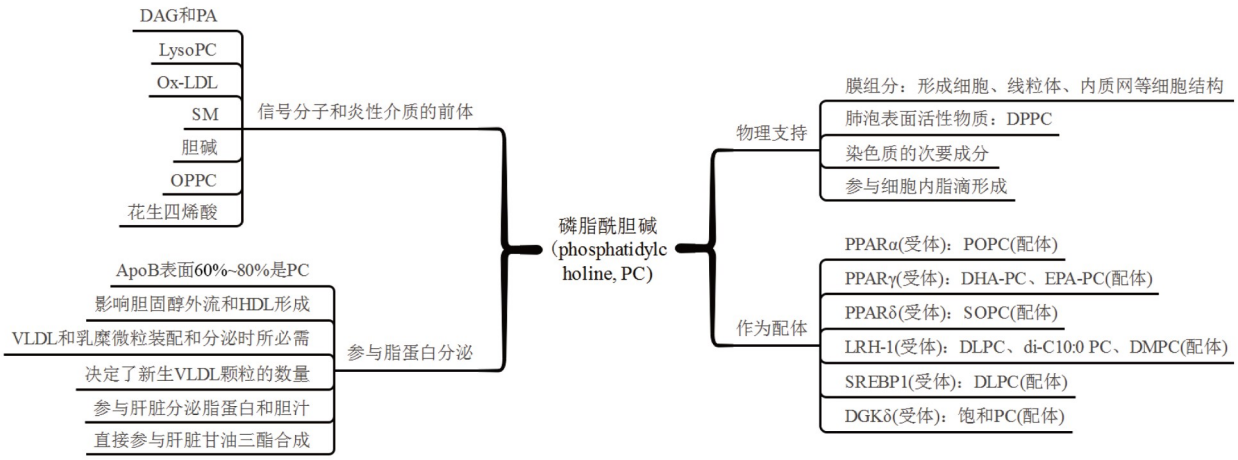

图4 磷脂酰胆碱(PC)的生物学功能

心衰患者和327名健康志愿者的研究发现，以PC(16:0/18:2)，TAG(18:1/18:0/18:0)和SM作为特征心脏脂质代谢物组合联合NT-proBNP可显著提高心衰的诊断性能，并能更准确地判断心衰早、中期心脏脂质稳态状况和心脏功能受损引起的末端器官的继发变化，更全面地表征心脏和心外表型。Yang等[78]发现PC(20:0/18:4)、PC(20:4/20:0)、PC40:4和PC(20:4/18:0)可用于心衰患者进行心脏再同步化治疗(CRT)应答的预测。Tang等[79]研究发现，心衰患者红细胞中的PC、PE和鞘磷脂水平均降低，而氧化胆固醇7-酮胆固醇(7-ketocholesterol，7KCh)、lysoPC、lysoPE和神经酰胺增加。这可能与心衰的病理进程密切相关。

4.3 冠状动脉粥样硬化性心脏病(冠心病)

据纳入1 571例女性的PREDIMED试验证实，独立于HDL和LDL，含有饱和脂肪酰(SFA)链和单不饱和脂肪酰(monounsaturated fatty acyl，MUFA)链的PC(羟基磷脂酰胆碱C34:2)与冠心病风险呈正相关[80]。Tang等[81]纳入4 007名冠心病患者在3年的随访中，经选择性冠状动脉造影等评价了膳食PC与心血管不良事件(死亡、心肌梗死、中风)之间的关系，证实膳食PC产生TMAO依赖于肠道微生物群的代谢，高TMAO水平与发生重大心血管不良事件的风险增加有关。Djekic等[82]纳入150例曾接受PCI治疗或最佳药物治疗的冠心病患者的研究证实，PC水平降低与Sullivan范围评分(SES，对冠心病的纵向范围进行分类)和狭窄病变总数呈正相关。Zhao等[83]评估了38例扩张型心肌病(dilated cardiomyopathy，DCM)、18例缺血性心肌病(ischemic cardiomyopathy，ICM)和20名健康志愿者发现，缺血性心肌病患者PC(18:0/18:3)水平显著高于DCM和健康人群。

4.4 高血压

高血压患者的血浆总PC水平升高[84]。氧化磷脂酰胆碱(oxidized phosphatidylcholine，OxPC)尤其是ω-醛OxPC和ω-羧基OxPC与高血压呈高度正相关[85]。欧洲前瞻性癌症和营养(EPIC)研究对随机抽取的135例非偶发性高血压和981例血压正常人群，随访9.9年，发现酰基-烷基-PC(C42:4)和酰基-烷基-PC(C44:3)与10年无高血压生存率高度相关，可用作预测未来10年的高血压风险标志物[86]。且高血压人群红细胞含有较高PC，高水平PC增加了红细胞膜脆性和流动性以及氧化应激和生理异常，可能与高血压的病理生理改变相关[87]。

4.5 心血管事件(CVD)

多个PC分子，尤其是血浆PC(36:5)水平升高被确定为与CVD风险呈显著正相关[88]。

纳入5 991例患者的PREDIMED队列研究证实，在非糖尿病人群中，PC(P-40:6)与心血管死亡风险高度正相关；含有PUFA的PC，特别是ω-6脂肪酰链PC(C20:4)，与CVD呈负相关[89-91]，并且在调整总胆固醇和HDL-c后，这种关联仍然存在。

据纳入3 316例患者的路德维希港风险和心血管健康(LURIC)试验研究发现，含有高度多不饱和脂肪酰的PC具有心血管保护作用；而循环PC与全因死亡率和心血管死亡率呈正相关；含有饱和脂肪酰链和单不饱和脂肪酰链的PC，尤其是二棕榈酰磷脂酰胆碱(PC32:0)与心因死亡率呈高度正相关[92]。

但据纳入18 076例CVD、5 343例心因性死亡和184 010名健康志愿者的随机效应Meta分析显示，偶发CVD与胆碱/甜菜碱摄入量无关，但CVD死亡率与PC呈正相关[93]，但此结果仍需进一步观察研究。

4.6 其他心血管相关危险因素

Lee等[94]研究显示，PC补给可减轻高脂饮食诱导的肥胖和肥胖相关并发症。Al-Sari等[95]研究显示，PC(35:4)与体重指数呈负相关，与HDL呈正相关。血浆中DHA-PC水平即PC(22:6)与人体脂肪库呈负相关，血浆中含高DHA-PC的人群具有更好的胰岛素敏感性，且与遗传效应无关。DHA PC(16:0/22:6)与皮下和腹腔脂肪量呈显著负相关，与胰岛素敏感性呈显著正相关。Gao等[96]的研究提出，DHA-PC可逆转高脂饮食引起的肥胖、胰岛素抵抗和高血糖，而大豆PC或鸡蛋PC不具有此作用。Bagheri等[97]纳入200例肥胖和100例健康志愿者的研究发现，二酰基磷脂酰胆碱(diacylphosphatidylcholine，PCaa)主要是PCaa(C32:1)、PCaa(C32:2)和PCaa(C38:3)与肥胖呈正相关，酰基烷基磷脂酰胆碱(PCae)主要是PCae(C34:3)、PCae(C38:4)和PCae(C40:6)与肥胖呈负相关。但Chen等[98]纳入1 243例亚裔美国人的研究证

实，PC(18:0/22:6)与代谢综合征呈显著正相关。Papandreou等[99,100]的前瞻性饱腹感创新(SANDIN)研究中，纳入162例减重8%的人群(BMI为27.0~35.0 kg/m^2)进行8周低热量饮食后，PC32:2、PC38:3、LPC14:0、LPC20:3和SM32:2显著降低并与总胆固醇和LDL水平降低相关，表明循环PC和SM可能通过调节总胆固醇和LDL来降低心血管风险。Noerman等[101]研究证实，血浆PC(P-18:0/22:6)和PC(P-18:0/20:4)升高与肥胖和白介素-1受体拮抗剂呈负相关。Fu等[102]研究发现，肥胖小鼠肝脏内质网的PC/PE比值明显高于较瘦小鼠内质网(1.97 *vs* 1.3)。Petkevicius等[103]研究发现，肥胖小鼠和人的脂肪组织巨噬细胞表现出PC从头合成速率增加，是导致白色脂肪组织炎症和胰岛素抵抗的重要诱因。

心肌缺血再灌注(I/R)期间，PC氧化生成具有生物活性的磷脂中间体，即OxPC。OxPC破坏线粒体能量生成和钙瞬变，诱发铁死亡，从而引起广泛的心肌细胞死亡，针对OxPC的干预措施有助于减轻缺血性心脏病患者I/R损伤期间的铁死亡及其相关的心肌细胞的收缩性及传导性改变[104]。

PCaa(C32:1、C36:1、C38:3和C40:5)是2型糖尿病的独立危险因素[105]。Yun等[106]研究发现，HbA1c正常人群的PC ae C36:1，PC aa C26:0，PC aa C34:2水平显著低于高HbA1c人群。Semba等[107]纳入472名平均年龄70.7岁的研究显示，PCaa(C34:4)、PCae(C32:1)、PCae(C32:2)、PCae(C34:2)、PCae(C34:3)和PCae(C36:3)与空腹血糖异常相关；PCae(C34:2)与2 h血糖降低相关；PCaa(C32:0)、PCae(C32:1、C32:2、C34:1、C34:2、C34:3、C36:2、C36:3、C40:5、C40:6、C42:3、C42:4和C42:5)与胰岛素抵抗相关。

Slade等[108]纳入980例志愿者的研究发现，在调整年龄、BMI、批次差异后，女性具有更高的PC、PE、PI、PG、SM、葡萄糖酰胺和神经酰胺水平，而男性具有更高的TG、DG、LPC、神经酰胺和胆固醇水平；与男性相比，女性的脂质水平与年龄增长关系更加密切，女性PC(p-36:1)、PC(o-36:2)水平随增龄下降，而男性保持不变；男性PC(o-42:3)水平随增龄升高，而女性下降；年龄与性别的交互作用在PC、SM和甘油三酯最为普遍。Xu等[109]纳入62例志愿者的安慰剂对照试验发现，鞘氨酸和PC20:5(5Z，8Z，11Z，14Z，17Z)/20:1(11z)与血清胆固醇水平呈正相关。

5 小结

磷脂酰胆碱不仅是细胞膜和细胞器膜的基本结构、胆汁和肺表面活性物质的主要成分，还是多个信号分子和炎性介质的前体分子，同时作为特定受体的配体参与信号转导，并且为脂蛋白的组装和分泌所必需，在调节细胞脂代谢和脂质稳态中发挥重要作用。多个PC参与动脉粥样硬化、高血压、冠心病、心力衰竭等心血管疾病的发生发展，尤其是循环PC水平与心血管事件具有明确的正相关。由于PC分子的多样性和复杂性，其生物学功能和临床价值亟待深入研究。

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