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脂蛋白相关磷脂酶 A2 及其与糖尿病视网膜病变相关性的进展

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[摘 要] 糖尿病视网膜病变(diabetic retinopathy，DR)是导致不可逆性眼盲的重要原因之一，DR发病与动脉粥样硬化密切相关，其治疗干预靶点成为当今研究的热点。脂蛋白相关磷脂酶A2(lipoprotein-associated phospholipase A2，Lp-PLA2)是一种新型炎症因子，与动脉粥样硬化及炎症反应等相关。了解Lp-PLA2与DR相关性研究现状可能为进一步研究DR治疗提供新的思路。

[关键词] 糖尿病视网膜病变；脂蛋白相关磷脂酶A2；动脉粥样硬化；血脂

Progress in lipoprotein-associated phospholipase A2 and its correlation with diabetic retinopathy

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Abstract Diabetic retinopathy (DR) is one of the important causes of irreversible blindness. DR is closely related to atherosclerosis, and its therapeutic intervention target has become a hot topic in current research. Lipoprotein-associated phospholipase A2 (Lp-PLA2), as a new inflammation factor, is related to atherosclerosis and inflammatory response. Understanding the current correlation of Lp-PLA2 and DR may provide a novel option in future treatment of DR.

Keywords diabetic retinopathy; lipoprotein-associated phospholipase A2; atherosclerosis; lipid

糖尿病视网膜病变(diabetic retinopathy，DR)是导致成人眼盲的主要原因。全球DR患病率约为34.6%，我国20%~40%的2型糖尿病(type 2 diabetes mellitus，T2DM)患者出现视网膜病变，其中约8%有严重视力丧失[1-2]。近年来许多研究[3-4]表明DR与糖尿病大血管病变有关系，与细胞因子介导的炎症反应及动脉粥样硬化(atherosclerosis，AS)密切相关。研究[5]发现颈动脉斑块是DR发生的危险因素。脂蛋白相关磷脂酶A2(lipoprotein-associated phospholipase A2，Lp-PLA2)是近年来发现的与动脉粥样硬化有关的一个独特的炎症因子，也是动脉粥样硬化事件发生的危险因子和预测因子[6-7]。目前关于Lp-PLA2与DR的研究日益增多，研究人员[8]发现Lp-PLA2在糖尿病患者体内增加，它可以促使血液中的脂肪新陈代谢从而导致血管内皮渗漏损伤，引起视网膜破坏，最终导致严重的视力丧失。

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1 Lp-PLA2 概述

1.1 Lp-PLA2 的生物学特征

Lp-PLA2是人类PLA2G7基因编码的磷脂酶超家族中的亚型之一，是由441个氨基酸残基构成的分子质量为45 kD的蛋白质，也是几种血小板活化因子乙酰基水解酶之一[9]。Lp-PLA2由T淋巴细胞、单核细胞衍生的巨噬细胞和肥大细胞以活性形式分泌。Lp-PLA2由于其促炎和促氧化作用已被证明在动脉粥样硬化的发展中起关键作用。人体内循环中的Lp-PLA2主要与脂蛋白颗粒结合，80%与低密度脂蛋白(low density lipoprotein，LDL)结合，水解氧化LDL上的磷脂酰胆碱，产生溶血磷脂酰胆碱和氧化的游离脂肪酸，它们都是促炎物质，有助于形成动脉粥样硬化斑块，并且LDL氧化过程在这一系列促炎症反应中更容易发生。少部分Lp-PLA2与剩余的与高密度脂蛋白(high density lipoprotein，HDL)结合，可以保护内皮免受氧化损伤，减少巨噬细胞的炎症反应，并介导胆固醇从巨噬细胞流出到HDL，发挥一定抗炎症作用[10]。尽管Lp-PLA2具有一定抗炎作用，但Lp-PLA2在新生动脉粥样硬化斑块中含量丰富，并参与动脉粥样硬化进展的多个阶段，主要具有明显的促炎和促氧化作用。

1.2 Lp-PLA2 的活性及影响因素

Lp-PLA2活性主要与LDL相关，与低密度脂蛋白胆固醇(low density lipoprotein cholesterol，LDL-C)正相关，与LDL-C结合的Lp-PLA2酶活性占90%~95%，与HDL负相关，在活性表达中仅占4.9%。其中与LDL-C所有亚型以及小颗粒高密度脂蛋白胆固醇(low density lipoprotein cholesterol，HDL-C)具有正相关性，而与大颗粒及中颗粒HDL-C具有负相关性[10-14]。Lp-PLA2活性还受遗传及外环境等多种因素影响，遗传因素包括基因型和基因多态性。Lp-PLA2浓度和活性水平与编码该蛋白的基因PLA2G7有关[15]。PLA2G7基因具有多态性，其中rs1805018(I198T)，rs1805017(r92h)和rs1051931(A379V)已在多个种族人群的报道，与Lp-PLA2活性和浓度水平呈显著的民族差异[16]。在中国进行的多省队列研究[17]首次发现rs13218408是影响Lp-PLA2活性与浓度水平的新的PLA2G7基因多态性位点。

有研究[18]表明T2DM患者Lp-PLA2活性显著升高，Lp-PLA2活性水平与血浆葡萄糖正相关。研究[19]表明如果血糖状态改善(通过糖化血红蛋白评估)，Lp-PLA2的活性降低。首先，T2DM糖代谢紊乱常同时伴随血脂异常，包括三酰甘油增加、HDL降低和小而密低密度脂蛋白(small-dense LDL，sdLDL)比例增加，sdLDL颗粒具有高度致动脉粥样硬化作用，这可能与Lp-PLA2活性增加有关。其次，糖尿病常伴随炎症活动增加，包括血管内皮氧化应激的增加、晚期糖化蛋白终产物增加和大量炎症因子的产生，这些共同导致血管内皮功能紊乱，可能与LP-PLA2活性增加有关。也有研究[20]表明Lp-PLA2活性水平与空腹血浆葡萄糖及糖化血红蛋白呈负相关。空腹高血糖与超常Lp-PLA2活性[定义为Lp-PLA2活性≥152 nmol/(min·mL)]呈负相关，当空腹血浆葡萄糖>7 mmol/L，超常Lp-PLA2活性降低50%[21]。多种药物影响Lp-PLA2活性，人与动物试验发现他汀类降脂药可降低Lp-PLA2活性[22-23]。有研究[24]表明：长期使用β受体阻滞剂治疗的患者斑块中Lp-PLA2及其酶产物溶血浓度显著较低，这可能与β受体阻滞剂减弱炎性细胞因子肿瘤坏死因子-α和白细胞介素1β的表达，而具有抗炎作用有关。有研究[25]发现阿司匹林、洋地黄类药物可轻度升高其活性。

2 Lp-PLA2 与血脂及动脉粥样硬化的关系

动脉粥样硬化是一种慢性炎症性疾病，众多炎症细胞参与其中[26]。Lp-PLA2是血脂代谢与炎症反应的交叉点，在动脉粥样硬化斑块形成及进展中发挥重要作用。临床数据[27]表明Lp-PLA2质量和活性升高与动脉粥样硬化进展有关。多项以人和动物试验[28-29]发现动脉粥样硬化与血浆中Lp-PLA2表达增加有关，Lp-PLA2加速了动脉粥样硬化进程。Lp-PLA2可以在动脉内膜中的LDL颗粒上水解氧化磷脂酰胆碱，这种生化反应产生溶血磷脂酰胆碱和氧化的游离脂肪酸，它们都是促炎性产物。Lp-PLA2通过产生促炎介质，参与血管平滑肌细胞的迁移、内皮功能障碍、黏附分子和细胞因子的表达，促进动脉粥样硬化及不稳定斑块的形成。溶血磷脂酰胆碱还能促内皮功能障碍使炎性细胞释放更多Lp-PLA2，形成恶性循环[30-31]。

动脉粥样硬化的主要原因是血脂异常，Lp-PLA2是动脉粥样硬化病变进展的关键酶。Lp-PLA2主要与LDL-C结合，活性与总胆固醇(total cholesterol，TC)、三酰甘油、载脂蛋白B及LDL-C水平呈明显正相关，尤其是与LDL-C水平相关性最强。汪晶等[32]在五指山小型猪模型中发现高脂饮食可诱发动脉粥样硬化。Lp-PLA2主要由动脉粥

样硬化斑块中巨噬细胞、淋巴细胞和泡沫细胞产生，是血管壁炎症的标志物。因此，Lp-PLA2介导了慢性炎症反应，并与脂质代谢共同作用导致动脉粥样硬化的发生。Lp-PLA2是血脂代谢与炎症反应的交叉点，多项研究[33-34]显示应用他汀类调节脂代谢药物可以降低血浆中Lp-PLA2活性。

3 血脂及动脉粥样硬化与 DR 的关系

尽管高血糖是DR的关键因素，但高脂血症在DR的发生发展中也起着重要作用[35-37]。T2DM常伴随着中度至重度高脂血症，其血脂异常的特征是三酰甘油和LDL-C水平升高和HDL-C水平降低[38]。这些患者患大血管和微血管并发症的风险大大增加，包括心血管事件和视网膜病变。血脂异常是DR的危险因素。有研究[39-40]报道高血脂可通过非酶促糖基化多元醇通路引起组织过氧化直接损伤微血管壁，同时导致视网膜屏障破坏和微血栓形成。Papavasileiou等[41]研究发现在非洲裔美国人的T2DM中，TC，LDL-C与视网膜硬渗出物及硬性渗出区面积相关，在调整其他DR风险因素，包括糖尿病病程、糖化血红蛋白、收缩压、降脂药使用情况后，发现若一名受试者的TC水平比他人低25 mg/dL，那么其视网膜硬性渗出的风险比他人低20%，结果表明血脂水平影响渗出物在视网膜内的形成和程度。在为期4年马德里糖尿病研究[42]发现当LDL-C >190 mg/dL，DR风险升高8倍。DR体外试验[35]表明脂毒性可以诱导增强葡萄糖水平从而引起线粒体损伤。1型糖尿病(type 1 diabetes mellitus，T1DM)和T2DM动物模型实验发现高血糖环境中高脂血症可加速线粒体损伤，导致毛细血管细胞细胞凋亡，促进DR的发展[43]。动脉粥样硬化可发生在全身各级别动脉，包括视网膜动脉，因此DR和动脉粥样硬化发生密切相关，并且推测DR微血管与大血管并发症具有类似的发展进程，都与动脉粥样硬化有关[44]。糖尿病患者不仅存在高血糖、高血脂，体内还存在高水平的炎症反应，脂代谢紊乱可以引起糖尿病患者血管炎症反应及炎性因子的释放[45]。DR和动脉粥样硬化可能具有相似的病理机制，脂质沉积引起动脉粥样硬化，进而阻塞视网膜血管，导致后者缺血缺氧；另外，在动脉粥样硬化形成过程中，一些细胞因子和炎性介质，导致血管通透性增加、血-视网膜屏障受损、小动脉壁增厚及血浆成分渗入引起管腔狭窄，视网膜血流受到影响，小动脉粥样硬化进展加快及形成微血栓，最终导致DR。

4 Lp-PLA2 与 DR

多项在T1DM和T2DM患者中进行的研究[46-48]中发现糖尿病血糖控制和持续时间是DR的危险因素，其他危险因素包括糖尿病发病年龄、男性、高血压、体重指数、血脂异常和吸烟。有研究[49]随访了亚洲青少年T1DM患者DR发生的相关危险因素，发现发生DR患者的LDL-C浓度显著高于未发生DR患者，血脂异常在DR发展中起一定作用。也有研究[50]表明血脂异常是DR发生的重要危险因素，与晚期DR进展有关，而与糖尿病类型无关。

Gong等[51]通过糖尿病大鼠动物实验表明：Lp-PLA2参与了视网膜周细胞和内皮的损伤和凋亡，在糖尿病大鼠视网膜微血管中Lp-PLA2蛋白水平明显升高。Staurenghi等[52]研究发现增殖型糖尿病性视网膜病的糖尿病患者血中Lp-PLA2水平升高。有研究[53]发现在高糖细胞培养以及糖尿病动物模型中，Lp-PLA2在内皮细胞和视网膜周细胞中表达增加。多项国内外研究[54-55]均表明DR患者血清Lp-PLA2水平升高，Lp-PLA2的增加与DR的严重程度平行。早期对DR进行临床干预，可以预防和延缓DR的进展，但DR早期症状隐匿、非特异性，故需更简单、有效的方法来发现DR的高危人群，以利于DR的筛选及治疗。Lp-PLA2在DR患者血清中水平升高已通过临床试验得到证实。Lp-PLA2是具有血管特异性的炎症标志物，很有可能成为DR潜在生物学标志，作为预测和评价指标。

Lp-PLA2作为动脉粥样硬化相对独立的危险因素，其活性与血脂密切相关，不仅参与了动脉粥样硬化的发展，并可能与二者共同参与DR发生发展。血脂水平升高，尤其是胆固醇和低密度脂蛋白，已被确定为DR的危险因素，并被认为与视网膜硬性渗出物的发展相关[49,56]。血脂异常在DR发生中起关键作用也引发了研究降脂药对DR的影响热潮。近年来，一些研究[57-61]表明糖尿病患者血脂的强化控制可以大大延缓DR的进展，并提示贝特类药物和他汀类药物(两种广泛使用的降脂药物)可减轻硬性渗出液和减少激光手术需求。

5 结语

DR是临床上糖尿病患者亟待解决的一大难题。早期诊断、及时干预DR的进展意义重大。Lp-PLA2在临床中是一项容易获得、检测方便且能被广泛使用的生化指标，其很有可能成为DR潜在生物学标志。但是Lp-PLA2的潜在作用及复杂的机制

仍未被完全发掘，降低其水平能否预防或延缓DR的进展，还需要多中心、大样本及前瞻性研究进一步验证。

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