# 浅谈LXA4在局部组织中的抗炎作用

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**摘要** 脂氧素A4(lipoxin A4, LXA4)作为一种新兴的内源性花生四烯酸, 经脂加氧合酶途径代谢形成一种有效抗炎物质, 能够促进炎症的消退, 在炎症过程中作为内生的“制动信号”。它通过促进白色脂肪组织炎症消退, 对肥胖以及相关疾病起治疗作用。将LXA4固定在生物制剂上, 送达到治疗部位, 能够促进局部炎症消散和牙周损伤修复。作为LXA4的受体激动剂BML-111, 同样具备促炎症消退作用。该文就LXA4及其受体激动剂在局部组织中的抗炎作用机制作简要综述。

**关键词** LXA4; 炎症; 消散; 受体激动剂

## The Anti-inflammatory Effect of LXA4 in Local Tissues

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**Abstract** LXA4 (lipoxin A4), an emerging endogenous arachidonic acid, is metabolized by the lipoxygenase pathway to form an effective anti-inflammatory substance that promotes the regression of inflammation and acts as a endogenous “brake signal” during inflammatory process. It promotes the treatment of obesity and related diseases by promoting the regression of inflammation of white adipose tissue. Fixing LXA4 on the biological agent and delivering it to the treatment site can promote local inflammation dissipation and periodontal damage repair. As a receptor agonist of LXA4, BML-111 also has a pro-inflammatory remission effect. This article briefly reviews the anti-inflammatory mechanism of LXA4 and its receptor agonists in local tissues.

**Keywords** LXA4; inflammation; dissipate; receptor agonists

脂加氧酶(lipoxygenase)催化花生四烯酸, 通过跨细胞途径合成脂氧素(lipoxins, LXs)。 LXs根据分子中羟基位置和构象的不同可分为LXA4、LXB4、15-epi-LXA4 和15-epi-LXB4。其主要合成途径3条[1]: 5-脂加氧酶(15-lipoxygenase, 5-LO)催化花生四烯酸合成白三烯, 再由12-脂加氧酶(12-lipoxygenase, 12-LO)催化生成LXA4和LXB4; 或者15-脂加氧酶(15-lipoxygenase, 15-LO)催化花生四烯酸生成中间产物后, 再由中性粒细胞(polymorphonuclear, PMN)的5-LO催化生成LXA4和LXB4; 或者经阿司匹林(acetylsalicylic acid, ASA)诱发形成, ASA阻断COX-2合成前列腺素, 催化ASA成为15R-HERE再被5-LO催化合成15-epi-LXA4和15-epi-LXB4。脂氧素极不稳定, 半衰期很短, 容易降解[2]。其中, 脂氧素受体激动剂5(*S*),6(*R*),7-三羟基

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庚酸甲酯[5(*S*),6(*R*),7-trihydroxyheptanoic acid methylester, BML-111], 其具有较好的稳定性被广泛用于科学研究[2]。天然的LXs在体内迅速被灭活, 并合成稳定类似物LXA4。LXA4作为抗炎类花生酸, 有较强的生物利用度和效能[3]。

LXA4是一种独特的花生酸类脂氧合酶衍生物, 其促炎症消退疗效在多种细胞试验和临床试验中被充分证实[4]。LXA4是具有强力消炎和促分解活性的ω-6-PUFA衍生(omega-6-PUFA-derived)的脂质介质[5], 属于涉及炎症分解阶段的第一类脂质介质, 是从内源性花生四烯酸源通过连续脂肪氧化酶Lipoxygenase(LOX)LOX-LOX相互作用的多细胞途径产生的三羟基–二十碳四烯酸[6-7] 。

在急性炎症分解阶段, 研究人员已经鉴定了从膜磷脂衍生的多不饱和脂肪酸内源性产生的一类新型抗炎和促分解脂质介质。这些分子被称为专门的促炎症消散介质, 不仅作为炎症反应的“停止信号”, 而且也是及时解决炎症的有利因素[8]。利用LXA4途径促进炎症消散可能代表一种新型的炎症治疗选择。

炎症是一种清除病理性病原和恢复体内平衡的损伤的先天性生理性宿主反应。生物合成的内源性脂质介质高度调节炎症反应的消退。而且, 炎症的自限性表明, 生物体存在内源性抗炎机制。在广泛的临床前期疾病模型中, 这些内源性脂质介质显示出有效的促进炎症反应消退及组织愈合的特性[9], 开辟了许多基于炎症的人类疾病治疗的新前景[10]。阿司匹林在细胞相互作用过程中所产生的脂质介质就是脂氧素, 是花生四烯酸经脂加氧合酶途径代谢所形成的一种有效抗炎物质。

本文对近年来研究LXA4及其受体激动剂BML-111在局部组织中的抗炎作用进行综述, 为挖掘LXA4替代治疗提供新的思路。

## 1 LXA4的促炎症消散作用

### 1.1 LXA4与炎症性肥胖

脂肪组织分为白色脂肪组织(white adipose tissue, WAT)和棕色脂肪组织(brown adipose tissue, BAT)2种类型[11]。WAT脂肪细胞主要包含甘油三酯(triglycerides, TAG)和胆固醇酯组成的特征性单一脂质液滴的有核细胞, 其占据了大部分细胞, 并且从细胞质的边缘移位到周边[7,11]。最近的研究表明, 肥胖WAT中的“轻度”炎症[4], 除了巨噬细胞, 其他免疫细胞如淋巴细胞也参与WAT炎症[12]。

研究发现, 在进行减肥手术的肥胖个体的大网膜WAT中PGE 2(prostaglandin E2)在脂肪组织重塑、炎症、适应性发热和脂肪分解中的发挥调节作用[5]。在进行减肥手术的肥胖患者的大网膜WAT中LXA4的水平不平衡[5,13]。有趣的是, 降低的血清LXA4水平和增加的腹部内脏脂肪面积是代谢综合征风险的独立预测因子[14]。此外, ω-6环氧化物和ω-3环氧化物也在肥胖小鼠中过量表达[15-16]。有研究表明, 小鼠和人类WAT都具有产生LXA4的能力, 类花生酸如白三烯B4(leukotriene B4, LTB4)和LXA4在肥胖中可能起关键作用。虽然LTB4参与脂肪组织炎症和胰岛素抵抗, 但LXA4可能发挥抗炎作用[8], 减轻肝脂肪变性[13]。这2种脂质介质来源于相同的途径, 其中涉及花生四烯酸5-脂氧合酶(arachidonate 5-lipoxygenase, ALOX5)及其伴侣花生四烯酸5-脂氧合酶激活蛋白(arachidonate 5-lipoxygenase-activating protein, ALOX5AP), 它们具有良好的促炎症消散作用[17]。研究发现, 肥胖个体白色脂肪组织中存在的持续炎症状态不利于炎症消散, 此外还提示, 促分解脂质介质可作为预防肥胖相关代谢并发症新疗法的切入点[7]。

ALOX5和ALOX5AP的表达在肥胖和具有胰岛素抵抗的人和啮齿动物中增加[18]。研究发现, 在脂肪组织中过表达*ALOX5AP*的转基因小鼠LXA4水平更高, 而非LTB4水平较高, 其部分是由于WAT的褐变[13,17]。小鼠中ALOX5AP的过度表达导致LXA4的产生增加, 而不是LTB4增加, 与WAT和BAT中的发热活化引起的能量消耗相关联[17]。此外, LXA4保护转基因小鼠免受饮食诱导的肥胖和胰岛素抵抗[8]。实验表明, 肥胖个体的脂肪组织中的持续性炎症可能是该组织的促炎症消散能力减弱的结果[9]。肥胖脂肪组织中LXA4水平降低导致脂肪组织促炎症消散的能力减弱, 致使促炎症介质和促分解介质水平之间的不平衡, 这可能是导致WAT慢性炎症的原因[12]。

由于LXA4是通过促炎症脂质介质的生物合成机制产生的, 所以促进促炎症消散介质生成是有利于LXA4合成的[8]。提高脂肪组织中LXA4浓度可以抑制WAT慢性炎症进展[13]。这些数据说明, LXA4可能在开发肥胖和相关疾病治疗策略方面具有潜力。

### 1.2 LXA4与自身免疫性疾病

肾炎是由免疫介导、炎症介质(如补体、细胞

因子、活性氧等)参与, 导致肾组织发生炎性改变, 从而引起肾功能减退的一种肾脏疾病。研究表明, 慢性肾脏疾病患者循环血液中LXA4含量与炎症密切相关, 而且糖尿病肾病患者体内LXA4含量比非糖尿病肾病患者更低, 提高LXA4血液含量能够起到较好的抗炎作用[19]。同样有研究表明, LXA4通过调节炎症因子的表达, 对缺血性急性肾损伤中发挥一定疗效[20]。增加11% LXA4含量, 能够提高慢性肾脏疾病患者的健康指数10%[21]。

人群中关节炎的病因复杂, 与自身免疫反应、感染、代谢紊乱、创伤、退行性病变等因素有关。而骨关节炎是最常见的人类风湿性疾病和长期残疾的主要原因[22]。15-脂加氧酶(15-lipoxygenase, 15-LO)催化生成LXA4。15-脂加氧酶在关节炎动物模型中的含量偏低[23]。在家兔模型中过表达的15-脂加氧酶能够降低骨的丢失、减轻炎症反应引起的牙周组织损伤。研究者发现, LXA4能够减轻卡拉胶引起的关节炎[24]。也有研究表明, LXA4抑制炎症在骨关节炎的发展, 并降低骨成分的丢失[25]。应用LXA4受体激动剂治疗, 能降低关节炎裸鼠的死亡率[26]。有研究表明, 激活LXA4的合成途径, 提高LXA4含量对骨性关节炎的治疗具有一定的保护作用[27]。

### 1.3 LXA4与其他炎症疾病

炎症反应与急性肝损伤具有密切关系。有研究证实, 脂氧素及其类似物能够减轻药物诱导的急性肝损伤, 其机制可能与调节炎症因子的表达有关[28-30]。LXA4通过降低气道阻力, 促进炎症的消退, 从而抑制肺炎的进展[31-32]。研究表明, LXA4能够降低TNF-α、IL-1β、ROS在急性肺损伤中的肺组织含量, 并提高IL-10含量。这些效应与抑制NF-κB炎症转录信号通路有直接关系[33]。此外, LXA4不仅够改善肠道炎症[34], 还能降低急性胰腺炎的损伤[35]。

## 2 LXA4的生物制剂

研究证明, LXA4具有促进人牙周膜干细胞(human periodontal ligament stem cells, hPDLSCs)的增殖, 迁移和伤口愈合的特性[36]。有研究者尝试将LXA4纳入高度多孔的聚合物电纺丝膜, 并确定这些膜是可以将生物活性的LXA4递送到应用部位[9]。LXA4可通过调节人牙周膜干细胞的功能来促进牙周病患者牙周组织修复。研究者使用静电技术将LXA4嵌入由聚氧化乙烯(polyethylene oxide, PEO)[37-38]和聚消旋聚乳酸(poly dl lactic acid, PDLLA)制成的生物膜[9], 利用扫描电子显微镜和差示扫描热法观察该膜, 发现其与人牙周膜干细胞有极好的相容性[25-26]。LXA4能够附着于该生物膜上, 虽然水性缓冲介质能够洗脱生物膜上LXA4总量的15%~20%, 但是洗脱下来的LXA4完全保留其激活人牙周膜干细胞的增殖能力[9]。LXA4可防止牙周炎实验模型中的组织损伤, 而且PEO/PDLLA生物膜可以装载抗炎LXA4, 并且这些含药的生物膜保留原有的药理活性[9]。此外, LXA4通过促进常规牙周成纤维细胞和牙周韧带干细胞的增殖和迁移, 促进牙周伤口的愈合。尽管没有研究LXA4与PEO/PDLLA膜之间的化学/物理相互作用, 也没有研究LXA4在水性介质中如何释放, 但是能够确定的是, LXA4的释放对促进局部炎症消散和牙周损伤修复至关重要[36]。

研究证实, PEO/PDLLA生物膜能够承载并递送LXA4, 并保留其生物活性能够减轻牙周炎局部炎症反映并且促进组织修复。除了牙科医学, 在手术伤口或烧伤的愈合中, 这种新型制剂炎症病灶的组织修复过程中也是极有前景的[9]。

## 3 LXA4的受体激动剂BML-111

BML-111属于G-蛋白偶联的lipoxin受体激动剂, 被称为甲酰肽受体2(formyl peptide receptor 2, FPR-2), 相比于LXA4而言, 不易被降解, 稳定性更好。NF-κB/p65的激活增加许多促炎细胞因子的表达[41]。参与促炎性细胞因子、黏附因子和趋化因子基因编码的调节。研究表明, BML-111抑制NF-κB p65易位入细胞核[42]。

在大鼠盲肠结扎和穿刺引起的急性肝功能障碍中, BML-111均发挥抗炎和促炎症消散作用, 此效应与调控NF-κB信号转导抑制促炎性细胞因子的产生和中性粒细胞的聚集有关[41]。研究表明, BML-111可能通过调控NF-κB信号转导来发挥抗炎作用[43]。此外, BML-111可以有效抑制NF-κB的活化, 具有抗炎活性[44]。LXA4及其类似物BML-111通过提高中性粒细胞清除效率, 降低血液中细菌浓度[45]。

## 4 结论与展望

LXA4是花生四烯酸经脂氧合酶途径代谢所形成的一种有效抗炎症物质。在多种细胞试验、临床前试验和临床试验中, LXA4的疗效已被充分证

实。其中, LXA4功能性组合的外源性给药促进炎症消散, 极有可能成为一种“热潮”。总而言之, LXA4含量的高低与组织炎症消退能力的强弱直接相关, LXA4具有良好的促炎症消退生物学效应, 和广阔的临床应用前景。

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