特约综述

本实验室研究神经病理性疼痛、炎症痛、癌痛等慢性痛及针刺镇痛的神经生物学机制。主要研究中枢胶质细胞激活的正负性调控因素在慢性痛、慢性痛相关情绪异常和针刺镇痛中的作用。目前的主要研究方向有: 抗炎性脂类介质脂氧素类似物与慢性痛; 炎症小体与慢性痛; 脂氧素参与针刺镇痛的细胞与分子机制。

http://imtm-whocc.fudan.edu.cn/cn/guanyuwomen/lirenlingdao/20130604/100.html

脂氧素的抗炎镇痛与神经保护作用研究进展

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摘要 脂氧素是一类来源于花生四烯酸具有抗炎和促炎症消退的脂类介质。作为炎症过程中的负性调控因子, 被广泛用于治疗各种急慢性炎症、疼痛、脑血管疾病及各种恶性肿瘤。该文将就其在抗炎镇痛和神经保护方面的研究进展作一综述。

关键词 脂氧素; 炎症; 镇痛

The Advances of Lipoxins in Anti-inflammation, Analgesia and Neuroprotection

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Abstract Lipoxins are lipid mediators generated from arachidonic acid that act to anti-inflammation and promote resolution. Lipoxins have emerged as potential anti-inflammatory mediators that be used in various inflammation, chronic pain, cere-brovascular diseases and malignant tumors. In this review, we briefly outline the recent research advances of Lipoxins in inflammation, analgesia and neuroprotection.

Key words lipoxins; inflammation; analgesia

脂氧素(lipoxins, LXs)是来源于花生四烯酸(arachidonic acid, AA), 通过跨细胞途径经由不同脂氧合酶(lipoxygenase, LO)催化AA生成的具有抗炎和促炎症消退的脂类介质[1]。在炎症过程中, 脂氧素通过抑制趋化因子产生, 抑制多形核粒细胞(polymorphonuclear neutrophils, PMN)向炎症部位聚集,

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促进单核/巨噬细胞发挥非炎性吞噬作用, 抑制炎性细胞因子的产生, 被称为炎症过程的“刹车信号”[2-4]。

1 LXs的结构、合成、代谢及受体

1.1 LXs的结构

LXs是Serhan等[5]于1984年首次发现的二十烷类家族中一类AA的代谢产物, 具有典型的三羟基, 四共轭双键结构。根据分子中羟基位置和构象的不同分为四种: LXA4、LXB4、15-epi-LXA4和15-epi-LXB4(图1)[1,3]。15-epi-LXA4又称阿司匹林诱生的LXs(aspirin-triggered lipoxins, ATL), 较LXA4构象更稳定, 半衰期更长[6-7]。

1.2 LXs的合成

LXs主要在炎症过程中通过跨细胞途径, 经不同LO顺序催化AA生成[3-4]。LXs的跨细胞合成途径主要有三条: (1)第一条途径经由5-LO和12-LO催化合成。在血管中, AA在多形核粒细胞PMN内5-LO的催化下生成白三烯(leukotriene A4, LTA4), 血小板通过其表面的P-选择素与PMN黏附, 将LTA4转入血小板内, 在12-LO的催化下合成LXs; (2)第二条途径经由15-LO和5-LO催化合成。AA在单核巨噬细胞、气道上皮细胞和血管内皮细胞内被15-LO催化合成中间产物15S-羟过氧化二十碳四烯酸(15S-hydroperoxyeicosatetraenoic, 15S-HPETE)和15S-羟二十碳四烯酸(15S-hydroxyeicosatetraenoic acid, 15S-HETE), 这些细胞通过胞间黏附分子与PMN相互作用, 将15S-HPETE和15S-HETE传递给PMN, 作为5-LO的催化底物生成LXs; (3)第三条途径是经由阿司匹林(acetylsalicylic acid, ASA)诱发的乙酰化COX-2和5-LO催化合成。在炎症、细胞因子、缺氧等因素作用下, 血管内皮细胞、肠上皮细胞、单核巨噬细胞等表达COX-2, ASA可使这些细胞的COX-2乙酰化并形成ASA-乙酰化COX-2复合体, 乙酰化COX-2丧失原有合成前列腺素的功能, 转换为15R-LO的催化作用, 使花生四烯酸转变为15R-HETE。血管内皮细胞、气道上皮细胞通过与PMN相互作用, 将15R-HETE传递给PMN, 在5-LO催化下合成15-立体异构体(epimer, epi)-LXs, 也称为ATL(图2)[1,3,8-10]。

1.3 LXs的代谢

LXs生成后在局部组织发挥作用, 在单核细胞脱氢酶作用下迅速失活[3]。LXA4被15-羟/oxo-二十碳四烯酸氧化还原酶(15-PGDH)氧化, 形成无活性的15-oxo-LXA4, 经由LXA4/PGE13,14-还原酶/LTB412-羟脱氧酶(PGR/LTB4DH)作用形成13,14-二氢-15-oxo-LXA4, 再经过15-PGDH(15-hydroxyprostaglandin dehydrogenase)作用形成13,14-二氢-LXA4。LXB4被15-PGDH代谢形成5-oxo-LXB4而失活[3,10]。此外, PMN可将LXA4、LXB4代谢为20-羟-LXA4和20-羟-LXB4失活[3,11]。

1.4 LXs受体

LXs通过与其特异性受体结合发挥生物学效应。LXs受体主要有三种, 分别是LXA4受体(lipoxinA4 receptor, ALX)、半胱氨酸白三烯受体(CysLT)和芳烃受体(arylhy-drocarbon receptor, AhR), 其中以ALX最为重要[10,12]。(1)ALX, 又称FPR2或FPRL1, 具有七次跨膜结构, 属于G蛋白耦联受体超家族(G-protein coupled

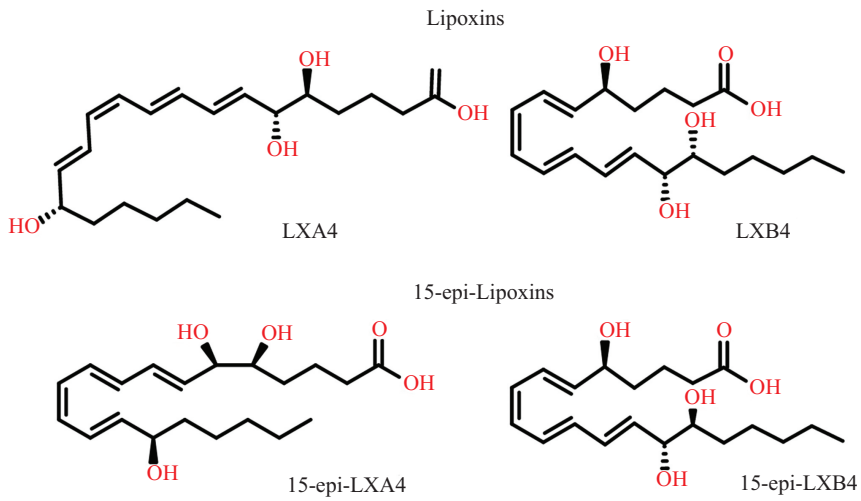

图1 脂氧素的化学结构示意图

Fig.1 The chemical structure of lipoxins

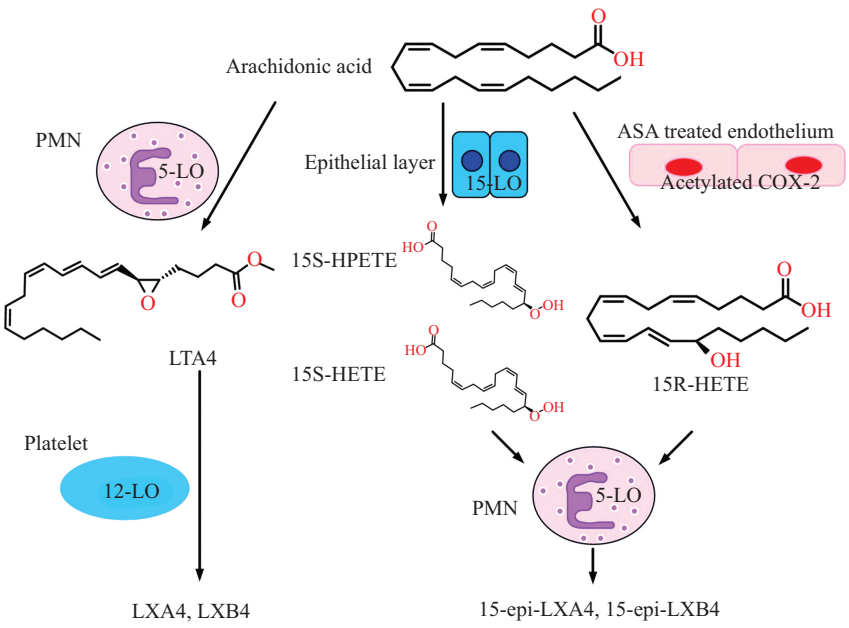

图2　脂氧素及其类似物的合成过程

Fig.2　Biosynthesis of lipoxins and aspirin-triggered lipoxins

receptor super family, GPCR)[13]。人、小鼠和大鼠的ALX的cDNA可读框全长都为1 051 bp, 共编码351个氨基酸残基, 三者在核苷酸和氨基酸序列上分别有74%和65%的同源性, ALX第236~237位丝氨酸残基和第302位酪氨酸残基的突变可引起脂氧素信号的持续激活[14]。ALX主要表达于中性粒细胞、巨噬细胞、嗜酸粒细胞、淋巴细胞、成纤维细胞、消化道上皮细胞、血管内皮细胞等, 在神经系统主要分布于星形胶质细胞, 部分分布于神经元[15-18]。ALX不但具有能够与LXs结合的脂类结合位点, 还具有能够与糖皮质激素诱导的膜联蛋白1(gulcocorticoid-induced annexin 1, ANXA1)结合的肽类结合位点, ANXA1与LXs一起通过作用于ALX的不同位点协同发挥抗炎作用[15-16,19-24]; (2)CysLT, 包括CysLT1和CysLT2, 分别与LTD4和LTC4结合。ALX与CysLT有一定同源性, LXA4可与LTD4竞争性与血管内皮细胞、肾小球系膜细胞的CysLT1结合拮抗LTD4的作用, 也可与LTC4竞争, 与气道上皮细胞的CysLT2结合拮抗LTC4的作用; (3)AhR, LXs还可与小鼠肝细胞内的AhR结合, 通过调节转录因子活性调节相应基因的表达[8,10,25]。

2　LXs的抗炎作用

LXs作为机体内源性产生的抗炎和促炎症消退的脂类介质, 可参与抑制各种肿瘤相关炎症[9,26]、感染性疾病[27]、肺损伤[28-29]、肠炎[24]、妇科炎症[30]等。

2.1　LXs与肿瘤

在小鼠乳头状瘤模型上, 干扰素-γ(interferon-γ, IFN-γ)通过抑制LXA4的表达参与持续性炎症的维持和肿瘤发生, 若外源性给予LXA4则可抑制肿瘤细胞的增生[31]; 在离体培养的HepG2肝细胞系, LXA4及其类似物可通过抑制NF-κB/COX-2信号通路促进肿瘤细胞凋亡, 抑制炎性细胞因子的产生[32]; 在LPS刺激的HepG2肝癌细胞系给予LXA4处理, 可通过抑制NF-κB通路的过度激活, 促进肿瘤细胞凋亡, 抑制其增生迁移和肿瘤血管生成。在小鼠肝癌模型上, 给予LXA4及其类似物可通过抑制血管内皮细胞生长因子(vascular endothelial growth factor, VEGF)的表达, 达到抑制血管增殖抗肿瘤的效应[33]。

2.2　LXs与感染性疾病

在禽流感H5N1病毒感染的小鼠模型上, 给予LXA4, 通过上调细胞信号转导抑制因子-2(suppressor of cytokine signaling-2, SOCS-2)抑制炎症小体(inflammasome)的激活、白介素-1β(interleukin-1β, IL-1β)和IFN-γ的上调, 从而缓解炎症[27]; 在金色葡萄球菌感染造成的小鼠腹膜炎和气道炎症中, 给予ALX激动剂可显著抑制中性粒细胞在炎症部位的增生、聚集[34]; 在大肠埃希菌感染THP-1巨噬细胞系模拟的体外肠炎模型上, 给予ATL可通过激活PI3K通路, 抑制IL-1β、白介素-8(interleukin-8, IL-8)的表达, 缓解炎症[35]; 此外研究发现, 在大鼠盲肠结扎穿刺(cecal ligation

and puncture, CLP)造成的败血症模型上, 静脉给予LXA4及其类似物可通过抑制血浆中显著上调的IL-6和TNF-α, 促进抗炎因子IL-10的表达, 从而缓解症状, 延长大鼠存活时间[36]。

2.3 LXs与肺损伤

与正常人相比, 在慢性阻塞性肺气肿病人痰液中LXA4表达显著下降, LTB4表达上调[37]。给予ALX激动剂可通过抑制中性粒细胞持续聚集、浸润, 缓解气道炎症[38]; 在脂多糖(lipopolysaccharide, LPS)诱导的急性肺损伤模型大鼠上, 给予LXA4可通过抑制PI3K/Akt的磷酸化, 抑制炎性细胞因子白介素-6(interleukin-6, IL-6)和肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)的产生, 缓解肺损伤[39]; 在缺血再灌注诱导的急性肺损伤大鼠模型上, 给予ALX激动剂BML-111, 可通过抑制MAPK信号通路和核转录因子NF-κB的过度激活, 抑制炎性细胞因子IL-1β、IL-6和TNF-α的表达, 从而缓解炎症[40-41]; 在博来霉素诱导的小鼠肺纤维化模型上, 给予ATL可通过抑制粒细胞聚集、肺泡损毁和纤维沉积缓解肺损伤[42]; 此外, 研究表明, 大气污染导致的肺部疾病发病率和致死率的增高, 主要是因为空气中的雾霾颗粒进入体内后打破了机体正常的抗炎和致炎力量间的相对平衡, 导致了疾病的发生[43]。

2.4 LXs与其他炎性疾病

在溃疡性结肠炎患者中, 组织活检发现患处黏膜LXA4和ANNX1表达下降, 增加二者的表达有利于抑制粒细胞浸润促进黏膜破损修复[44]; 在小鼠溃疡性结肠炎模型中, 给予ALX激动剂可显著缓解损伤, 主要是通过抑制炎性细胞因子IL-6、TNF-a、MCP-1和胞间黏附分子VCAM-1、ICAM-1、LFA-1等的表达[45]发挥作用的。

在子宫内膜炎中, LXA4抑制子宫内膜增生主要是通过抑制IL-1β的释放和p38MAPK通路的过度磷酸化[46]; 与正常妇女相比, 孕妇子宫黏膜内LXA4表达显著增加, 在离体培养的子宫肌层细胞上, 给予LXA4可抑制LPS刺激引起的IL-6和IL-8的表达[47]。

3 LXs的神经保护作用

许多神经系统疾病伴随着不同程度的炎症反应, 抑制炎症可有效缓解或改善其症状, LXs作为内源性的抗炎介质在神经系统疾病中的作用受到广泛关注[48]。

3.1 LXs与脑血管疾病

阿尔茨海默病是一种退行性的神经系统疾病, 研究表明, 持续性的炎症与其病理过程密切相关[48]。LXA4的水平在大鼠体内随着年龄增长而逐渐降低[49], 若外源性给予ATL可通过促进巨噬细胞发挥非炎性吞噬作用, 抑制Aβ淀粉样蛋白的沉积, 抑制p38MAPK信号通路从而抑制炎症, 提高认知功能, 改善症状[48,50]; LXA4还可通过作用于大麻素受体(cannabinoid receptor 1, CB1), 协同大麻素抑制Aβ淀粉样蛋白沉积, 改善小鼠认知功能障碍[51]; 此外研究发现, 皮下给予ATL可通过抑制NF-κB活化, 抑制炎性因子表达并促进抗炎因子IL-10和TGF-β表达上调, 从而抑制小胶质细胞的激活, 改善阿尔茨海默病症状[52]。

在结扎大鼠大脑中动脉造成的脑缺血模型上, 静脉注射LXs类似物BML-111, 可通过抑制粒细胞聚集、浸润, 抑制基质金属蛋白酶3、9和胞间黏附分子的表达, 减小梗死面积和脑水肿, 抑制血管通透性增加[48,53]。

3.2 LXs与胶质细胞炎症

在离体培养的人1321N1型星形细胞瘤上, 给予LXA4可通过抑制NF-κB的激活抑制IL-1β诱导的IL-8和胞间黏附分子-1的表达[17]; 在离体培养的大鼠星形胶质细胞中, 预先给予ATL可抑制LPS诱导的NO、PGE2、COX-2和iNOS的表达, 并呈剂量依赖性地抑制NF-κB的活化[54]; 在离体培养的小鼠BV-2细胞系上, 预先给予ATL可抑制LPS诱导的炎性细胞因子IL-1β、IL-6和NO的产生, 主要是通过抑制NF-κB和ERK、p38MAPK信号通路的过度激活导致的[55]; 外源性给予ANXA1可促进脑内小胶质细胞发挥非炎性吞噬作用, 吞噬凋亡的神经元, 抑制炎性细胞因子IL-6、TNF-α和NO的表达, 保护脑组织[56]; 此外, 研究表明在老年小鼠脑内, LXA4的含量与其年龄增长呈负相关, 并且随着LXA4的合成降低, 小鼠表现出焦虑抑郁样行为, 也进一步提示LXs可通过抑制炎症调节脑内微环境, 发挥神经保护作用[49,57]。

4 LXs的镇痛作用

慢性痛又称病理性疼痛、坏痛, 持续日久, 缠绵难愈, 严重影响了患者的生存质量[58]。根据疼痛产生的原因主要分为外周组织损伤诱导的炎症痛, 外

周或中枢神经损伤诱导的神经痛及恶性肿瘤发生增殖、侵润或转移诱导的癌性疼痛[58-59]。近年来研究表明, LXs可参与缓解多种急慢性疼痛[60]。

4.1 LXs与炎症痛

在足底注射角叉菜胶(carrageenan)诱导的大鼠炎症痛模型上, 腹腔给予LXA4、LXB4、ATL或8,9- aLXB4均可缓解大鼠术侧及对侧的热痛敏, 降低痛敏指数, 缓解足底肿胀程度。鞘内给予小剂量的LXs也可显著缓解疼痛, 多次给予可产生累加镇痛效应。免疫荧光实验提示, ALX主要分布于星形胶质细胞, 在小胶质细胞和神经元则未见分布。离体实验结果表明, ATL可抑制ATP诱导的星胶上过度活化的p-ERK、p-JNK。提示, LXs缓解角叉菜胶诱导的大鼠炎症痛主要是通过抑制p-ERK、p-JNK通路的过度活化[14]所致。此外, 研究表明, 鞘内给予LXA4可抑制角叉菜胶诱导的脑脊液中TNF的上调[61]。提示, LXs缓解炎症痛主要与抑制星形胶质细胞释放炎性细胞因子及相关信号通路的过度激活有关。来自同济大学实验室的研究表明, 在完全弗氏佐剂(complete freund's adjuvant, CFA)诱导的大鼠炎症痛模型上, ALX主要分布于星形胶质细胞和神经元, 鞘内给予ANXA1, 可通过与星形胶质细胞和神经元上的ALX结合, 缓解炎症痛, 此镇痛作用可被ALX拮抗剂BOC-1所拮抗[15]。

4.2 LXs与神经痛

在慢性坐骨神经压迫(chronic constriction injury, CCI)诱导的大鼠神经痛模型上, 在造模后第七天单次鞘内及尾静脉给予ATL, 可缓解其机械性痛敏并呈剂量依赖性, 但是对正常大鼠机械痛阈无影响。若预先给予ALX拮抗剂BOC-2, ATL对CCI大鼠的镇痛效应被逆转。鞘内给予ATL可抑制CCI大鼠脊髓中炎性细胞因子IL-1β、IL-6、TNF-α的表达, 抑制Janus激酶2/信号转导和转录激活因子3(Janus kinase/signal transducers and transcription activators, JAK2-STAT3)的过度磷酸化, 并能上调JAK2-STAT3通路的负性调控因子——细胞信号转导抑制因子1和3(suppressor of cytokine signaling 1/3, SOCS1/3)的表达。若预先给予BOC-2, 则可拮抗上述效应。在鞘内分别给予JAK2和STAT3的拮抗剂AG49和S3I-201, 可缓解CCI大鼠机械性痛觉超敏。免疫荧光实验提示, ALX主要分布于脊髓星形胶质细胞和神经元, p-STAT3主要分布于星形胶质细胞。在CCI术后七天, 星形胶质细胞标记物神经胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)表达显著上调。以上提示, 鞘内给予ATL主要通过与脊髓星形胶质细胞上的ALX结合, 抑制炎性细胞因子表达和JAK2-STAT3-SOCS信号通路的过度激活, 从而缓解CCI诱导的大鼠神经痛[62]。进一步实验研究表明, ATL抑制IL-1β的上调主要是通过抑制NALP1(NAcht leucine-rich-repeat protein 1)炎症小体的激活和caspase-1的剪切, 抑制成熟IL-1β的释放, 缓解CCI诱导的神经炎症, 进而降低大鼠机械性痛觉超敏[63]。此外有研究表明, 在慢性压迫背根神经节(chronic compression of dorsal root ganglia, CCD)诱导的大鼠神经痛模型上, 造模后连续三天鞘内给予LXA4可缓解CCD诱导的热痛和机械性痛觉超敏, 并呈剂量依赖性, 可持续至造模后第七天。其镇痛作用主要与LXA4抑制CCD诱导的脊髓中过度激活的NF-κB及炎性细胞因子IL-1β、IL-6和TNF-α的表达相关[64]。

4.3 LXs与骨癌痛

持续进行性炎症与肿瘤微环境的形成密切相关[65], 由原发性肿瘤转移至骨所致的骨癌痛具有不同于炎症痛和神经痛的独特机理[66-67]。在向大鼠胫骨骨髓腔内注入Walker256乳腺癌细胞诱导的大鼠胫骨癌痛模型(cancer-induced bone pain, CIBP)上, 其脊髓背角表现为以胶质细胞显著激活增生和炎性细胞因子分泌为特征的神经炎症[66,68]。鞘内给予LXs及其类似物均可缓解大鼠机械性痛觉超敏, 并以ATL作用更为显著。尾静脉给予不同剂量ATL也观察到类似效果。但若预先给予ALX拮抗剂BOC-2, 则ATL的镇痛效应被拮抗。在骨癌痛大鼠脊髓中, 炎性细胞因子IL-1β、IL-6和TNF-α表达上调, 同时伴有MAPK信号通路的过度活化。鞘内单次给予ATL可显著抑制炎性细胞因子IL-1β和TNF-α的上调, 并能抑制MAPK信号通路的过度激活(未发表结果)。ALX主要分布于星形胶质细胞, 部分分布于神经元, 与之前报道一致。以上结果提示, ATL缓解大鼠骨癌痛, 至少部分是通过抑制其脊髓神经炎症发挥作用的[69]。

4.4 LXs与吗啡镇痛耐受

吗啡耐受是临床应用吗啡镇痛的一个难以避免的副作用, 来自云南省第一人民医院的研究提示: 鞘内给予LXs类似物LXA4Me可通过抑制星形胶质细胞和小胶质细胞的激活, 抑制NF-κB活化, 进而抑制

炎性细胞因子IL-1β、IL-6和TNF-α的表达, 同时促进抗炎因子白介素-10(interleukin-10, IL-10)和转录生长因子-β1(transforming growth factor-β1, TGF-β1)的表达, 从而缓解吗啡耐受导致的热痛敏和机械性痛觉超敏[70]; 来自我们实验室的研究也表明, ATL可通过抑制炎症小体的活化抑制IL-1β的产生, 中止炎症的发展进程, 阻断吗啡耐受的形成(未发表结果)。

5 小结与展望

LXs是一类具有抗炎和促炎症消退的脂类介质, 在生理情况下仅有少量合成, 在病理情况下受到各种炎性刺激后合成显著增加, 作为炎症过程中的负性调控因素发挥抗炎和促炎症消退的作用, 被称为炎症过程中的“刹车信号”。LXs及其类似物主要是通过与其受体结合, 抑制MAPK和JAK-STAT3通路的过度激活, 抑制NF-κB的活化, 抑制各种炎性因子的产生, 同时促进抗炎因子上调, 在各种急慢性炎症、肿瘤、疼痛及脑血管疾病中发挥重要作用。LXs作为机体内源性产生的抗炎脂类介质, 对机体生理功能无影响, 安全、无毒副作用, 有望成为临床抗炎镇痛的新药。

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