



Autotaxin表达调控机制及其生物学功能

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国家自然科学基金(批准号: 81972604, 32171138)和细胞增殖及调控生物学教育部重点实验室开放课题资助项目

摘要 Autotaxin(ATX)是催化溶血磷脂酸(lysophosphatidic acid, LPA)生成的关键酶, LPA可以与细胞膜上至少6种G蛋白偶联受体(称为LPA受体1-6)结合, 激活各种信号转导通路, 在多种生理和病理过程中发挥重要作用. ATX的表达在转录、转录后及分泌过程中受到多水平的调控, 近期的研究还发现了ATX表达的表观遗传调控机制. 肿瘤微环境中ATX和LPA可以促进肿瘤细胞的增殖和迁移, 因此ATX-LPA通路被认为是一种潜在的癌症治疗靶点. 目前, 人们已经研发了多种ATX抑制剂, 并发现具有临床应用潜力. 本文重点关注ATX的表达调控机制和生物学功能, 阐释ATX-LPA信号轴调控的生理和病理意义.

关键词 Autotaxin, 溶血磷脂酸, 溶血磷脂酸受体, 表达调控, 生物学功能

Autotaxin(ATX)是一种分泌型糖蛋白, 属于外核苷酸焦磷酸酶/磷酸二酯酶(ENPP)家族, 也称为ENPP2^[1]. ATX最早是从人黑色素瘤细胞A2058的条件培养基中鉴定发现的, 由于ATX可以通过自分泌的方式促进细胞运动, 故被命名为自分泌运动因子^[2]. 随后的研究发现, ATX可以增强NIH3T3细胞在Balb/c裸鼠(Nude mouse)体内的侵袭和转移潜力^[3], 而且ATX在多种恶性肿瘤组织中异常表达, 具有促进肿瘤细胞增殖和迁移的作用. 因此, 近年来ATX作为一种癌症治疗的潜在靶点备受重视. 此外, ATX也在其他多种生理和病理过程中发挥作用. 本课题组和其他实验室的研究表明, ATX的表达调控可以发生在表观遗传、转录和转录后以及分泌等多个层面, ATX表达调控机制的研究和ATX抑制剂的研发为ATX相关疾病的治疗提供

了新的策略.

1 ATX-LPA信号轴

ATX具有溶血磷脂酶D(lysoPLD)活性, 主要功能是将溶血磷脂酰胆碱(lyso-phosphatidylcholine, LPC)水解生成溶血磷脂酸(lysophosphatidic acid, LPA). LPA是迄今为止发现的分子质量最小、结构最简单的甘油磷脂, 作为一种重要的脂质分子, 能够与细胞膜上6种不同的G蛋白偶联受体(LPAR1-6)相互作用, 激活与其偶联的G蛋白 $G_{\alpha_{i/o}}$, $G_{\alpha_{12/13}}$, $G_{\alpha_{q/11}}$, G_{α^5} 等, 并作用于下游的Ras, PI3K, Rho, AC, PLC等信号分子^[4], 这一条信号通路被称为ATX-LPA-LPA受体(LPAR)轴, 通常简称为ATX-LPA信号轴. 另一方面, 细胞外游离的LPA会被细

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胞膜上的脂质磷酸酶LPPs(lipid phosphate phosphohydrolase, LPP)降解为单酰甘油(monoacylglycerol, MAG), 从而下调LPA对LPA受体的激活作用^[5](图1).

2 ATX的结构与亚型

2.1 ATX的结构

ATX蛋白是一种分泌蛋白, 其被合成时以前酶原形式存在. N端的信号肽介导ATX通过内质网-高尔基体途径到达细胞膜, 在分泌过程中信号肽酶去除27个残基的信号肽, 随后位于细胞膜上的ATX被前蛋白转化酶Furin切割, 再去除N端8个氨基酸后分泌到胞外^[6]. 成熟的ATX蛋白由N端两个生长调节素B(somatomedin B, SMB)样结构域、一个核心磷酸二酯酶(phosphodiesterase, PDE)结构域(约400个氨基酸)和一个C端催化无活性的核酸酶(nuclease, NUC)样结构域组成的多结构域蛋白质^[7], 其中NUC结构域通过Cys413-Cys801二硫键与PDE结构域共价连接^[8](图2A). PDE结构域末端伸出长“套索环”(lasso loop)紧紧包裹住NUC结构域, 并从另一边进入NUC结构域的折叠, 加强ATX催化结构域的结构刚性^[9]. 核心催化结构域PDE包含活性催化位点和两个锌离子, 活性位点附近疏水的脂质结合

袋(pocket)可以容纳溶血磷脂等底物. SMB1参与组成的部分疏水的通道用于运输催化产物^[10], SMB2将ATX定位在细胞表面发挥作用^[9]. 此外, ATX蛋白在Asn-53, Asn-410和Asn-524位点被N-糖基化, 其中Asn-524的Man_{8/9}GlcNAc₂聚糖修饰被认为可以与NUC结构域相互作用来稳定核心催化区域的Thr209残基, 从而维持ATX的催化功能^[11,12].

2.2 ATX的亚型

人ATX/ENPP2基因位于第8染色体8q24.1位点, 包含27个外显子, 通过不同的选择性剪接方式可以产生多种剪接亚型(图2B). 最初报道的三种剪接亚型ATX α , ATX β 和ATX γ 被定义为“经典ATX”, 其中ATX β 是一种缺失外显子12和21的亚型, 多分布在人类外周组织中; ATX γ 则只缺失外显子12, 广泛表达于中枢神经系统中; 而ATX α 虽然是最典型的亚型之一, 但在外周组织和神经系统中的含量要远小于其他两种^[13]. 近年又鉴定出了两种新的亚型ATX δ 和ATX ϵ , 分别是ATX β 和ATX α 在连接PDE和NUC结构域的套索环L2连接区中缺少4个氨基酸的剪接变体^[14]. 目前发现的5种ATX具有相似的酶活性, 其中ATX β 是分布最广泛、最常被研究的亚型, 血浆中的ATX就是以ATX β 亚型存在的.

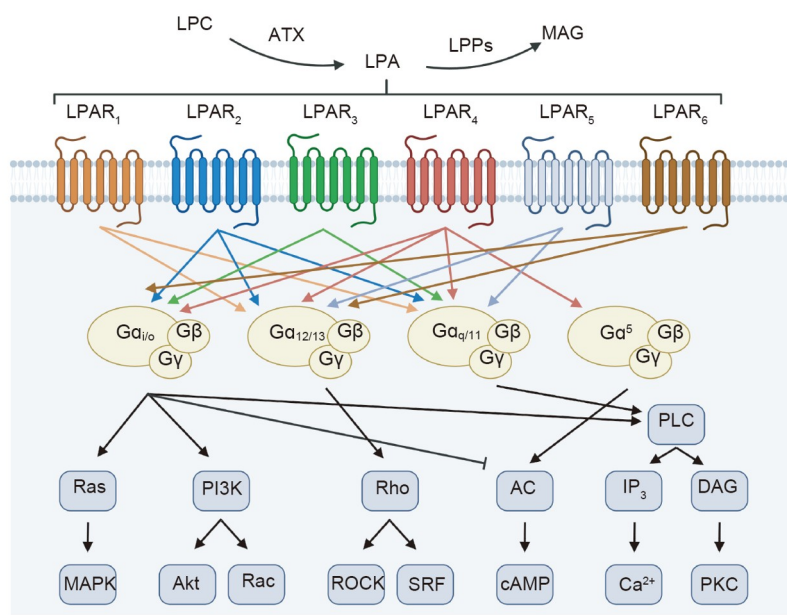


图1 ATX-LPA-LPAR信号通路

Figure 1 ATX-LPA-LPAR signal pathway

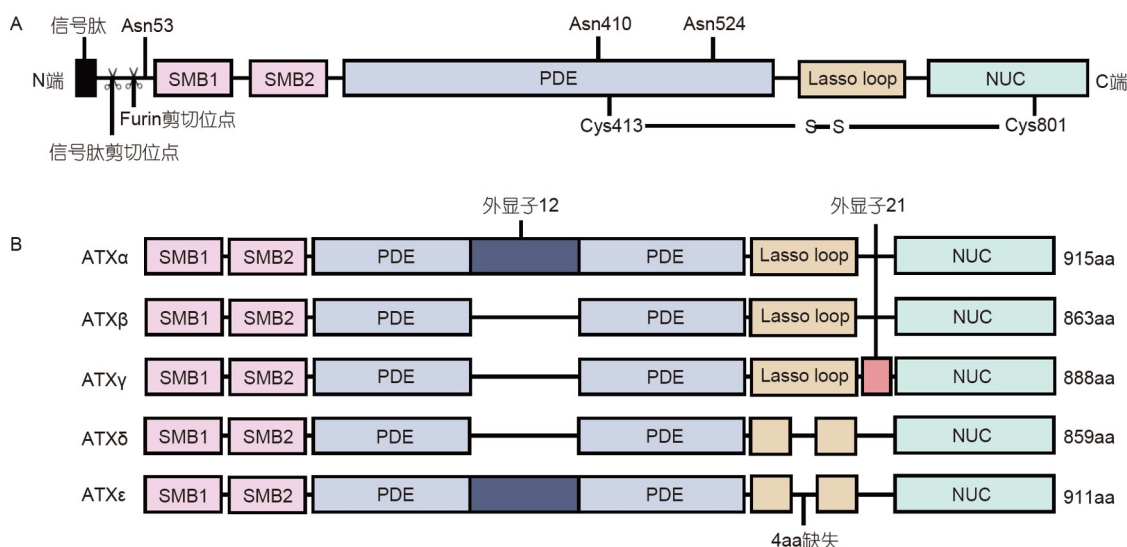


图2 ATX各亚型的结构. A: ATXβ的结构示意图; B: ATX各亚型比较

Figure 2 Domain structure of ATX isoforms. A: Structure of ATXβ; B: comparison of ATX isoforms

2.3 ATX的特殊功能结构域

ATX的N端SMB2结构域中存在RGD整合素结合基序,细胞通过活化的整合素将ATX募集到细胞表面,产生局部高浓度LPA并快速将其递送至靶受体,从而促进LPA信号转导^[9].有研究提出,ATX的C端具有一个少突胶质细胞重塑与组织黏附(Modulator of Oligodendrocyte Remodeling and Focal adhesion Organization, MORFO)调节域,ATX通过MORFO区域与少突胶质细胞表面的嘌呤能受体P2Y₁₂结合,介导ATX与少突胶质细胞的黏附,改变少突胶质细胞的形态并诱导其分化,该通路被认为在少突胶质细胞分化成髓鞘细胞的过程中发挥重要作用^[15].

3 ATX的表达调控机制

ATX的表达调控对细胞微环境中LPA的含量、LPA受体的激活及其下游信号通路有着重要的影响.作为一个分泌型的糖蛋白,ATX的表达受到表观遗传、转录水平、转录后水平、分泌过程、降解机制等多层次的调控(图3).

本课题组之前的工作阐述了组蛋白去乙酰化酶(histone deacetylase, HDAC)抑制剂在多种癌细胞中诱导ATX表达的过程,证明了HDAC3和HDAC7是ATX表达的负性调节因子^[16].其后有研究发现,当用去甲

基化酶UTX处理降低ATX启动子区域的H3K27me3(组蛋白抑制性修饰)水平后,脂多糖(lipopolysaccharide, LPS)诱发的ATX表达水平发生上调^[17];启动子区域特定CpG位点的低甲基化水平会增加ATX的表达^[18].这些工作都表明,ATX的表达受到多种表观遗传调控.此外,研究发现存在一个远距离的增强子,通过与ATX启动子之间相互作用形成的DNA环介导JMJD3-DDX21的募集,促进ATX的转录^[17].

ATX的表达调控还涉及多种转录因子.比如抑制转录因子NFAT1的表达会降低ATX的表达,从而抑制黑色素瘤细胞的生长和转移^[19];AP-1和SP转录因子可以通过CRE/AP-1样元件和ATX启动子区域GA-box之间的相互作用来促进神经母细胞瘤细胞的ATX表达^[20];转录因子Stat3可以通过激活ATX转录来促进乳腺癌细胞的迁移^[21];缺氧条件通过HIF-1α增加肝细胞ATX表达,丙肝病毒也可以通过这条通路增加ATX表达从而促进肝纤维化和肝损伤^[22].此外,转录因子v-Jun, c-Jun和HOXA13均参与ATX转录水平的调节^[23-25].

近年来,ATX表达在转录后水平上的调控也被逐渐阐明.本课题组的研究发现,RNA结合蛋白HuR和AUF1可以直接与ATX mRNA的3'UTR结合影响其稳定性^[26];microRNA-101-3p(miR-101-3p)作为一种肿瘤抑制因子,也可以直接靶向ATX mRNA的3'UTR中的

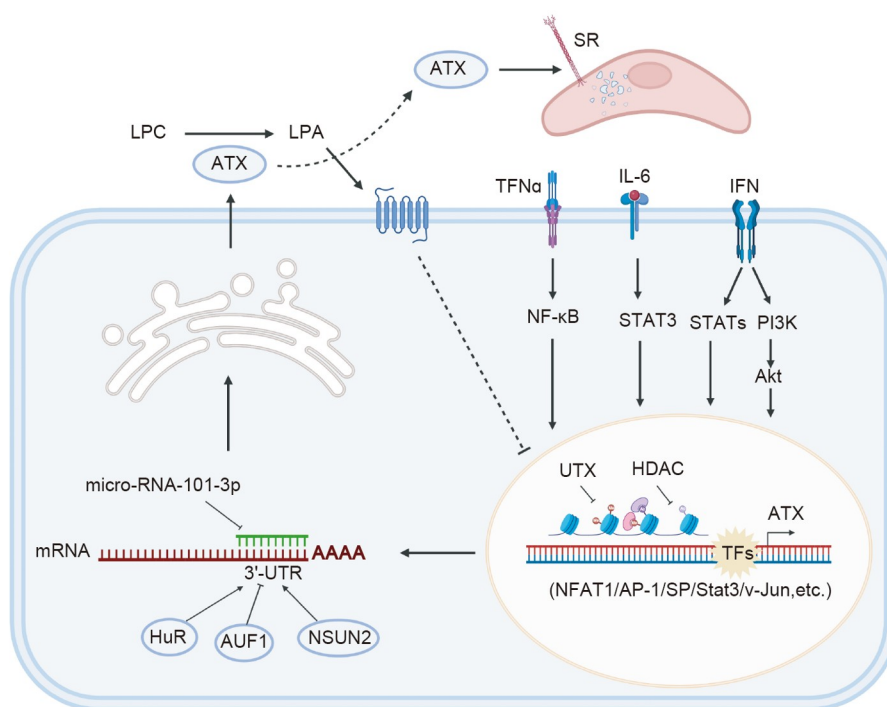


图 3 ATX 的表达调控机制

Figure 3 Mechanisms of ATX expression regulation

保守序列来抑制ATX的表达^[27]。研究还表明, RNA甲基转移酶NSUN2可以在ATX mRNA 3'UTR的C2756处进行甲基化, 促进ATX mRNA从细胞核到细胞质的运输, 进而增强ATX的翻译过程^[28]。有研究发现, NSUN2上调ATX表达可以促进T细胞迁移并加重血管炎症^[29]。

一些炎症细胞因子被证明会影响ATX的表达。肿瘤坏死因子TNF- α 可以通过NF- κ B选择性地促进肝癌Hep3B和Huh7细胞系ATX的表达和分泌^[30]; 白细胞介素IL-6诱导ATX表达, ATX催化产生的LPA也可以驱动IL-6表达, 形成正反馈环路, 介导皮肤纤维化过程^[31]。本课题组的研究发现, Toll样受体(Toll-like receptor, TLR)的多种配体如LPS, CpG寡核苷酸和多聚(I:C)可以诱导THP-1细胞中ATX的产生。TLR受体的激活促进干扰素IFN表达, I型IFN通过自分泌或旁分泌途径, 作用于质膜上的IFNAR, 通过JAK-STAT和PI3K-AKT途径激活ATX表达, 这一过程可以提高微环境中LPA的浓度, 进而促进炎症反应中免疫细胞的迁移^[32]。

ATX作为一种分泌性糖蛋白, N端具有27个氨基酸残基的信号肽, ATX的分泌依赖于信号肽的疏水核

心序列^[33], 同时ATX的Asn53和Asn410的N-糖基化也是分泌所必需的^[34]。本课题组的研究结果显示, ATX C末端的二苯丙氨酸基序(Phe838/Phe839)是ATX-p23相互作用的必需信号, ATX通过p23-Sec24C依赖的内质网分泌途径被选择性运输, 这个途径可被AKT-GSK-3 β 信号调节^[35]。

同时, LPA在循环中的积累会抑制ATX的表达, 形成ATX-LPA的负反馈调节回路^[36]。此外, 循环中的ATX可以在肝窦内皮细胞(liver sinusoidal endothelial cell, LSECs)中通过清道夫受体(scavenger receptor, SR)进行清除^[37], 但是具体的分子机制还有待进一步研究。

4 ATX的功能

4.1 ATX的分布

ATX-LPA轴的功能首先体现在ATX的组织分布上, 无论在胚胎发育阶段还是成熟个体阶段ATX的组织分布既有广泛性又有特殊性。在ddy:slc小鼠(*Mus musculus*)胚胎发育过程中, ATX的表达具有时空特性:

在胚胎发育到8.5天(E8.5)时, ATX主要在神经褶的前端和中脑的最后部区域表达; 到E10.5~11.5时, ATX的表达在神经底板处显著增加; E12.5时, ATX在处于发育时期的乳腺、肠道等器官表达较高; 间充质细胞和平滑肌组织分别在E13.5和E16.5表现出较高的ATX水平; 从E13.5至出生, ATX始终在脉络丛上皮细胞中显示高表达水平^[38]。在成年个体中ATX的分布比较广泛, 在大脑、脂肪组织、胎盘、肠道、淋巴结和视网膜中均可检测到高ATX mRNA水平^[13,39-41], 在肾脏、前列腺、睾丸、胰腺和肺中可以检测到中等ATX mRNA水平^[13], 但在胃、骨骼肌和白细胞中ATX的丰度很低。此外, 大多数生物体液中都存在ATX, 如脑脊液、血浆、精液、腹膜液、尿液中都被发现具有相对较高的ATX水平^[42-45]。已有的研究表明, ATX-LPA轴在多个器官或组织中发挥重要的生理和病理功能(表1)。

4.2 ATX-LPA轴的生理功能

(1) 胚胎发育中的作用. ATX在胚胎发育中起着至关重要的作用, 纯合敲除ATX基因的小鼠胚胎由于缺乏LPA, 显示出了尿囊畸形、神经管缺陷和严重的血管缺陷, 并发生胚胎致死效应^[59-61]。杂合敲除ATX基因小鼠的表型是健康的, 但血浆LPA水平只有野生型小鼠的50%^[59], 这也表明ATX是体内参与LPA生成的关键酶。

(2) 脂肪组织中的作用. ATX在脂肪细胞分化以及肥胖相关的代谢调控中发挥作用。已有的研究表明, 在脂肪细胞系3T3-L1, 3T3-F442A和原代前脂肪细胞的分化过程中, ATX的表达水平发生显著提升^[57,62,63]。ATX

在脂肪组织中高表达, 脂肪组织特异性敲除ATX基因可以导致小鼠血浆中LPA的水平下降了38%; 喂食高脂肪食物后, 与野生型对照组小鼠相比, 脂肪组织特异性敲除ATX的小鼠体重增加较小, 胰岛素抵抗减弱, 表明ATX是脂肪性肥胖中的关键物质^[58]。本实验室的研究发现, IL-6家族的细胞因子IL-6, LIF, CT-1等可以通过gp130-JAK-STAT3通路上调脂肪细胞ATX的表达, 使用gp130抑制剂SC144则可以抑制脂肪细胞中ATX的表达, 并显著改善高脂饮食诱导的肥胖小鼠的胰岛素敏感性^[63]。此外, ATX既可以被炎性因子促进表达又可以增强肥胖个体的炎症, 脂肪组织特异性ATX敲除小鼠的脂肪组织和血浆中IL-6, TNF- α 和MCP-1等炎症因子含量显著降低^[58]。因此, ATX被认为可以调节脂肪性肥胖, 并在肥胖相关的糖脂代谢紊乱中发挥作用。

(3) 生殖系统中的作用. ATX-LPA轴在生殖系统中的功能被广泛研究。在哺乳动物卵泡中, 绝大多数卵母细胞减数分裂停滞在中期 I, 为未成熟状态, 卵泡液中的LPA可以通过MAPK信号通路磷酸化连接蛋白connexin关闭卵母细胞和卵丘细胞之间的缝隙链接, 降低卵母细胞内的cAMP含量, 激活分裂进程从而促进其成熟^[64]。同时输卵管液中也含有LPA, 加速了胚胎通过输卵管的运输过程, 并促进了胚胎发育^[65]。ATX被发现大量存在于卵泡液中, 且正常孕妇血清中的ATX活性显著高于非孕妇, 这种活性随着孕周逐渐提高并在分娩后迅速恢复到孕前水平^[65], 有研究认为胎盘在其中起到一定作用^[66]。在动物研究中人们发现猪在整个动情周期和妊娠过程的子宫中都能检测到大量ATX^[67], 牛的子宫中也检测到了充足的LPA和LPA受

表 1 ATX-LPA轴的生理和病理功能

Table 1 Physiological and pathological functions of ATX-LPA axis

水平	分布	生理或病理功能
系统水平	神经系统	神经管发育、轴突生长、神经胶质细胞分化、髓鞘形成、神经性疼痛、神经退行性疾病、脊髓损伤 ^[46]
	免疫系统	淋巴细胞趋化迁移、淋巴细胞归巢、树突细胞趋化反应、多种炎症性疾病 ^[47]
	循环系统	血小板聚集、动脉粥样硬化、钙化性主动脉瓣狭窄 ^[48]
	生殖系统	精子发生 ^[49,50] 、妊娠维持、胎盘植入、分娩 ^[51]
器官水平	视网膜	眼压调节、血-视网膜屏障的维持 ^[40,52]
	肾	系膜细胞增殖、肾小管细胞增殖、肾纤维化 ^[53]
	肺	慢性阻塞性肺病、肺纤维化 ^[54,55]
	肝	星状细胞增殖、酒精性肝病、肝纤维化 ^[56]
组织水平	脂肪组织	前脂肪细胞增殖分化、营养性肥胖、胰岛素抵抗 ^[57,58]

体表达^[68]。以上这些研究都说明, ATX-LPA轴在胚胎发育和妊娠进程中具有重要作用。

LPA信号对于雄性生殖功能也具有潜在作用。在哺乳动物睾丸中能够检测到ATX和数种LPA受体的表达, 小鼠中LPAR1/2/3同时缺失会导致无精子症的患病率增加, 过表达LPP1的小鼠会过度降解LPA, 精子发生受阻^[49,50]。此外, 在精卵结合过程中, LPA被认为可以激活精子PKC α 参与顶体反应, 也可以促进精子进入卵细胞质的过程^[69]。

(4) 免疫系统中的作用。ATX-LPA轴参与免疫调节。ATX在淋巴器官的高内皮小静脉(high endothelial venules, HEV)中高表达, 形成局部高浓度LPA, 诱导T细胞的趋化反应, 促进T细胞的跨内皮迁移(transendothelial migration, TEM), 引导T细胞从血液归巢进入淋巴器官的过程^[39,70,71]。除此之外, 其他免疫细胞, 如B细胞、NK细胞、肥大细胞、嗜酸性粒细胞、树突状细胞等的细胞表面均有LPA受体分布^[47]。树突状细胞(dendritic cell, DC)被发现在未成熟状态下和成熟状态下表达不同的LPA受体, LPA可以诱导未成熟DC发生钙瞬变(Ca²⁺ transient)、肌动蛋白聚合和趋化作用, 这种反应在DC成熟过程中消失; 在成熟DC中LPA起到抑制IL-12和TNF分泌, 促进IL-10分泌的作用^[72]。总的来说, ATX-LPA轴在免疫系统中主要参与免疫细胞运输、迁移过程, 并被认为是可能参与适应性免疫反应的启动。

(5) 肌肉修复中的作用。骨骼肌的再生特性是依靠肌纤维基底层下方的肌肉干细胞(卫星细胞)响应肌肉损伤或肌营养不良发生分化完成的。在卫星细胞中条件性敲除ATX或LPAR1受体, 或肌肉注射ATX抑制剂都会阻碍ATX诱导肌肉损伤后发生的肌肉修复和再生^[73]。以上研究结果表明, ATX-LPA-LPAR1这一信号通路在骨骼肌修复过程中具有重要的作用。

(6) 循环系统中的作用。ATX可以储存在静息状态血小板的 α 颗粒中, 当血小板被活化时会释放ATX, ATX与血小板 β_3 整合素结合促进LPA的产生, 通过LPAR5受体来激活信号通路^[48]。血液中的LPA激活血小板形成血小板聚集体, 增强血小板纤连蛋白的交联, 从而在血管壁损伤后促进凝血和修复作用^[74]。LPA还能有效激活内皮细胞上的LPAR1/3受体, 促进白细胞和血管壁的黏附作用和跨壁迁移, 同时刺激内皮细胞的增殖、迁移和新血管的形成^[48]。LPA还可以诱导一氧化氮合酶介导的血管舒张及血栓素A2介导的血管

收缩来影响血管张力^[75]。除此之外, 还有研究发现ATX与细胞间黏附分子1(intercellular adhesion molecular-1, ICAM-1)协同增加内皮细胞的黏附作用^[76]。

4.3 ATX-LPA轴的病理生理功能

(1) 恶性肿瘤中的作用。ATX在多种恶性肿瘤细胞中高水平表达, 并在肿瘤发生和癌细胞侵袭中起关键作用。在恶性程度极高的多形性胶质母细胞瘤研究中, 发现ATX在侵袭细胞和肿瘤核心细胞中表达, 氧化应激可以刺激ATX的表达, 并通过ATX-LPA轴增加胶质母细胞瘤的侵袭能力^[77]。过表达ATX可以增强乳腺癌细胞系的侵袭能力, 乳腺癌细胞分泌的炎症因子(如TNF和IL-1 β)可以增加乳腺脂肪组织中ATX的生成, ATX-LPA信号又可以进一步促进炎症因子的产生, 同时乳腺癌细胞表面的整合素还能招募ATX, 促进癌细胞定向迁移^[78]。肝细胞癌(hepatocellular carcinoma, HCC)患者的血清中ATX活性和血浆LPA含量显著升高, 与多种慢性肝病发展相关的肝毒性刺激在鼠中会提高肝细胞ATX表达, 导致肝脏星状细胞(hepatic stellate cell, HSC)活化、放大促纤维化信号, 而肝细胞ATX特异性敲除会减弱HCC的发展^[79]。

对肿瘤干细胞(cancer stem cell, CSC)的研究显示, 肿瘤治疗中的耐药性通常归因于CSC的存在和其特异性的蛋白表达。LPA被发现可以刺激CSC相关基因如OCT4, SOX2, 药物转运蛋白基因等的表达^[80], 抑制ATX, LPAR1, LPAR2受体可以减少卵巢癌中CSC样细胞的产生^[81]。在脑肿瘤研究中发现, LPAR4可以促进血管网络形成, 恢复血脑屏障功能, 从而增强PD1-PDL1疗法的抗癌作用^[82], 表明各种LPA受体可能在不同肿瘤的发展和防治中发挥不同的作用。

(2) 慢性肾病中的作用。慢性肾病(chronic kidney disease, CKD)是由各种原因引起的慢性肾脏结构和功能障碍, 包括原发性肾小球肾炎、糖尿病肾病、自身免疫性疾病等诱因, 随着肾功能的持续衰竭, 慢性肾病可能发展为终末期肾病(end-stage renal disease, ESRD)^[83]。发展过程中, 细胞外基质中胶原蛋白和纤连蛋白的逐渐累积, 这些蛋白分散在肾小管之间, 称为肾小管间质纤维化(tubulointerstitial fibrosis, TIF), 肾功能的持续下降与肾组织纤维化息息相关, 因此以抗纤维化为基础的治疗方法在对抗ESRD转化方面具有巨大潜力^[84]。

ATX和LPAR1的表达水平在糖尿病肾病和其他慢性肾病,如单侧输尿管阻塞(unilateral ureteral obstruction, UUO)模型小鼠的肾皮层中均出现了上调^[85,86]。有研究发现,LPAR1-Rho/ROCK通路可以诱导结缔组织生长因子(connective tissue growth factor, CTGF)的表达,LPAR1敲除的UUO模型小鼠能通过降低CTGF的产生有效防止肾纤维化^[87],LPAR1/3阻断剂ki16425处理肾病小鼠模型可以减轻肾纤维化程度^[88]。LPA通过LPAR1-PI3K/AKT信号通路诱导TGF- β 表达,TGF- β 又可以反过来促进ATX表达形成正反馈加速肾纤维化进程^[89]。另一项关于肾缺血再灌注损伤(ischemia-reperfusion injury, IRI)的研究则阐明了LPA通过LPA2信号通路诱导TGF- β 表达促进肾纤维化的机理^[89]。综上所述,肾脏出现损伤时ATX和LPA会发生富集,促进肾纤维化,因此靶向ATX或LPA受体的药物来降低相关因子的表达,可能会成为治疗肾纤维化的一种新策略。

(3) 妊娠异常中的作用。先兆子痫(pre-eclampsia, PE)是一种妊娠期综合征,表现为多系统器官功能紊乱,是胎儿畸形或生长受限及孕产妇死亡的常见原因^[90]。在胎盘早期发育中,绒毛外滋养层细胞迁入子宫内膜形成母体和胎儿混合脉管系统的过程十分关键^[90],而这个过程在先兆子痫患者中受到干扰,是先兆子痫发病的核心因素^[91]。ATX在整个妊娠期间大量存在于胎盘中,主要由胎盘滋养层表达^[92]。而先兆子痫患者胎盘中ATX的表达较低,这导致了这些患者外周血液中ATX和LPA含量也随之下降^[93]。随后的研究发现,正常妊娠时除了LPAR4以外的其余5种LPA受体在胎盘中的表达量都出现上调;与正常妊娠相比,先兆子痫患者胎盘中LPAR3的表达量又进一步升高^[94],这可能是对ATX和LPA含量降低的一种代偿性反应。因此,先兆子痫患者的胎盘异常应与ATX-LPA轴信号通路受阻有关。

血管内皮生长因子(vascular endothelial growth factor, VEGF)为先兆子痫疾病发展中的关键物质,胎盘中可溶性VEGF受体1(sVEGFR1,一种VEGF的生理拮抗剂)的生成增加会降低VEGF的活性,从而导致先兆子痫血管功能的紊乱^[95]。ATX分泌的下调会导致sVEGFR1的增加及VEGFR2的减少^[96],LPA也可以通过LPAR1/3调控过氧调节蛋白150(ORP150,一种促进蛋白质折叠的内质网伴侣蛋白)在翻译后水平促进VEGF分泌^[97]。也就是说,胎盘内ATX的减少会抑制

VEGF信号通路,从而导致血管生成紊乱,引起胎盘发育异常和先兆子痫等妊娠疾病。

(4) 关节炎中的作用。类风湿性关节炎(rheumatoid arthritis, RA)的发病特点是伴有滑膜细胞增殖和炎性细胞浸润引起的增生性滑膜^[98]。滑膜成纤维细胞(synovial fibroblasts, SFs)是引起滑膜性关节炎的主要细胞类型,在炎症环境和表观遗传变化的影响下被激活并增生^[99]。在小鼠关节炎模型和人类患者的关节中,均在SFs中检测到大量ATX表达^[100]。在SFs中进行ATX条件敲除,或进行全身LPAR1受体敲除的小鼠中,关节炎的发病症状被大大缓解,这表明ATX-LPA信号是关节炎的重要驱动因素^[100,101]。利用药物Ki16425阻断LPAR1/3受体也可以表现出明显的抗关节炎作用,提供了治疗RA的新思路^[102]。

(5) 心血管疾病中的作用。动脉粥样硬化是一种慢性的动脉疾病,通常伴随着炎症、血管重塑和硬化斑块的形成。LPA有促进血栓形成的功能,有助于动脉粥样硬化斑块的发展。氧化低密度脂蛋白(oxidized low-density lipoprotein, oxLDL)作为ATX的转运蛋白参与动脉粥样硬化中LPA的局部产生过程,从各种细胞类型(如脂肪组织、血管内皮细胞等)分泌到血浆中的ATX也可以被血小板的整合素募集,参与动脉粥样硬化的发展过程^[48]。动脉粥样硬化引起的炎症可以增加内皮细胞ATX和LPA受体的表达,促进形成新生血管,从而使斑块病变恶化^[103]。动脉粥样硬化斑块的破裂是急性冠状动脉综合征(acute coronary syndrome, ACS)的重要病因。LPA通过LPA2-NF κ B信号通路上调巨噬细胞基质金属蛋白酶9(matrix metalloproteinase 9, MMP-9)的表达,可以增加硬化斑块的不稳定性^[104]。因此,LPP3作为LPA清除蛋白可以预防动脉粥样硬化斑块的形成和发展,并降低相关并发症的风险^[105]。

钙化性主动脉瓣狭窄(calcific aortic valve stenosis, CAVS)是一种慢性的多因素瓣膜疾病,病理变化包括进行性纤维化和主动脉瓣膜矿化。与正常组织相比,CAVS组织中LPAR1的表达量增加了1.5倍。由oxLDL携带的ATX催化LPA生成,进而通过LPAR1-RhoA/ROCK-NF κ B信号通路促进主动脉瓣矿化^[106]。LPAR1通路的激活上调了骨形态发生蛋白2(bone morphogenetic protein 2, BMP2)的表达,从而引起成骨矿化反应^[106]。除了oxLDL外,脂蛋白A(lipoprotein A)被发现可以作为ATX的载体,参与CAVS的病变。脂蛋白A携

带的ATX活性甚至要高于oxLDL携带的ATX, 因此血液循环中的脂蛋白A被认为是一种潜在的CAVS疾病标志物^[107].

4.4 ATX的其他催化活性

除了LPA, ATX还可以催化产生LPA类似物环磷酸cPA, cPA以与白蛋白结合的形式存在于哺乳动物的血清中^[108,109]. cPA功能中最突出的就是抑制细胞增殖、抑制肿瘤细胞的浸润和转移, 这与LPA的功能恰恰相反. cPA可以引起成纤维细胞中cAMP水平的升高, 从而抑制由蛋白激酶A(protein kinase A, PKA)介导的磷酸化引起的MAPK活性, 起到抗有丝分裂的作用^[110]; cPA还能直接抑制细胞周期调节蛋白Cdc25, 影响G1/S检查点, 导致细胞周期停滞^[111]. 化学合成的cPA类似物被认为是ATX活性的有效抑制剂, 具有临床应用潜力^[112].

ATX还具有将鞘氨醇磷酸胆碱(sphingosine phosphate choline, SPC)作为底物, 水解生成鞘氨醇-1-磷酸(sphingosine-1-phosphate, S1P)的能力^[113]. S1P作用于与LPA受体不同的GPCR, 目前已知的有5种S1P受体(S1PR1-5), 通过激活小GTP酶Rho进行信号传导. 由于S1P和LPA能够调节细胞骨架动力学、细胞迁移和细胞增殖等过程, 又都对胚胎血管发育和内皮完整性至关重要, 二者均被归类为重要的具有生物活性的脂质介质^[114].

4.5 ATX抑制剂的开发和应用

在肿瘤发生发展过程中, ATX-LPA轴可以通过促进细胞迁移、肿瘤侵袭、血管生成等发挥作用, 因此抑制ATX活性阻断LPA生成将是肿瘤治疗的重要方法.

此外, ATX也被视为肺纤维化、肾纤维化、肝炎、关节炎等疾病的潜在靶点^[115]. 目前, 已经有几种ATX抑制剂达到了药物开发的临床或临床前阶段(表2).

GLPG1690作为ATX的竞争性抑制剂已经进入特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)III期临床试验^[116,117], 它可以结合ATX的疏水口袋和疏水通道防止LPA的形成^[118]. 最近有研究将GLPG1690应用在乳腺癌小鼠模型中, 显著降低了癌细胞的增殖并增强了放疗诱导的凋亡^[119].

PF-8380是另一种有效的ATX抑制剂^[120], 它对ATX的抑制可以阻碍肿瘤细胞侵袭, 并增强人和小鼠胶质母细胞瘤细胞系的放射敏感性^[121]. 应用PF-8380还可以通过降低肥胖小鼠的血液LPA水平来减少高脂饮食引起的心脏肥大、机能失调和炎症反应^[122], 而且还可以减轻博来霉素引起的肺纤维化^[123].

ONO-8430506是一种新的ATX抑制剂^[124], 可以降低血浆ATX活性. 施加这种抑制剂可以大幅度延缓小鼠乳腺癌的生长和肺转移^[125], 还可以降低甲状腺癌中16种炎症介质的水平, 并使肿瘤体积缩小^[126].

S32826是一种被广泛用于体外研究的纳摩尔级别ATX抑制剂^[127]. 本实验室研究发现, 使用HDAC抑制剂TSA处理肿瘤细胞会促进ATX产生, ATX-LPA信号轴保护癌细胞抵抗TSA诱导凋亡, 而在施加S32826后这种抗凋亡效应被消除. 与ATX抑制剂的联合使用, 可以促进HDAC抑制剂诱导肿瘤细胞凋亡的作用^[16].

还有一些化合物, 如HA155, HA130, RB011等被发现具有一定抑制ATX活性的功能^[128~130], 以上这些抑制剂的进一步应用还需依靠更多的研究和临床数据. 此外值得注意的是, 抑制ATX活性可能会对正常生

表 2 ATX抑制剂的种类和研发进展

Table 2 ATX inhibitors and their research progress

抑制剂名称	抑制剂的性质	抑制方式	研发进度	应用范围
GLPG1690	LPC类似物 ^[118]	竞争性抑制	III期临床试验 ^[116,117]	肺纤维化 ^[116,117] 、乳腺癌 ^[119]
PF-8380	LPC类似物 ^[120]	竞争性抑制	动物试验 ^[121,122]	胶质母细胞瘤 ^[121] 、肥胖 ^[122] 、肺纤维化 ^[123]
ONO-8430506	LPC类似物 ^[124]	竞争性抑制	动物试验 ^[125]	乳腺癌 ^[125] 、甲状腺癌 ^[126]
S32826	LPA类似物 ^[127]	竞争性抑制	细胞试验 ^[127]	体外ATX活性抑制及细胞实验 ^[116,127]
HA155	硼酸衍生物 ^[128]	竞争性抑制	动物试验 ^[128]	体内ATX活性抑制 ^[128]
HA130	硼酸衍生物 ^[129]	混合型抑制	动物试验 ^[129]	体内ATX活性抑制 ^[129]
RB011	DNA分子 ^[130]	核酸适配体	动物试验 ^[130]	体内ATX活性抑制 ^[130]

理功能造成一定影响, 尤其是面对处于备孕或妊娠等特殊状态的患者, 相关药物的应用要更加谨慎小心。

5 展望

ATX和ATX-LPA轴在肿瘤发生和癌症进展中具有重要意义, 但到目前为止ATX在癌细胞中的表达机制仍不完全清楚, 不同LPA受体在不同种类癌细胞中的具体作用也待探究。同时ATX的表达具有一定的组织特异性, 在前述的多项研究中ATX条件敲除已经成为了探究ATX功能的有力工具, 如在脂肪组织^[58]、肌肉干细胞^[73]、肝细胞^[79]、滑膜成纤维细胞^[100]中进行的

ATX敲除。在各组织细胞中分别进行ATX的条件敲除不仅可以揭示ATX在不同组织中的具体功能, 还有助于深入探讨其在特定组织的疾病发展过程中的作用及其作用机制。此外, 细胞外ATX的活性调控、分布调控以及ATX的降解机制也都是具有吸引力的研究方向。

随着研究的继续深入, 更多ATX功能和表达调控机制会被阐明, 干预ATX-LPA信号轴的手段也将更加丰富, 并被应用于各种疾病的临床治疗。由于ATX的复杂生理功能, ATX抑制剂在进入临床试验后, 可能对于特定生理状况的患者中具有潜在的副作用, 如何正确认识并尽可能规避这些风险也是研究者需要关注的问题。

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Expression regulation mechanisms and biological functions of Autotaxin

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Autotaxin (ATX) is a key enzyme to produce lysophosphatidic acid (LPA). LPA interacts with at least six specific G protein-coupled receptors on cell membrane, named LPA receptor 1-6, to activate various signal pathways, and plays important roles in physiological and pathological processes. The expression of ATX is regulated at multiple levels in the process of transcription, post-transcription and secretion, and the epigenetic regulation of ATX expression has been clarified recently. ATX and LPA in the tumor microenvironment promote cell proliferation and migration, therefore ATX-LPA signaling pathway is regarded as a potential cancer therapeutic target. Several ATX inhibitors have been developed with clinical application potential. In this review, we will focus on the expression regulation mechanisms and biological functions of ATX, and demonstrate the physiological and pathological significance of ATX-LPA signaling axis.

autotaxin, LPA, LPA receptor, expression regulation, biological function

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