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·专家论坛·

白血病抑制因子在肿瘤发生发展中的作用与靶向治疗策略

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[摘 要] 白血病抑制因子(LIF)属IL-6家族,是一种多效性细胞因子,因最早被发现能够抑制小鼠髓系M1白血病细胞增殖并诱导其终末分化而得名。LIF广泛参与器官、神经发育与再生和免疫调节等反应,对于肿瘤的发展同样具有重要的作用。与抑制白血病细胞生长的作用相反,LIF通常促进多种类型实体瘤的发展,高表达的LIF能够促进肿瘤的发生发展、转移、耐药和肿瘤免疫逃逸等,与患者的不良预后相关。聚焦LIF生理和病理的功能作用及其所调控信号通路的整体性,寻找新的靶向药物,对于LIF通路靶向治疗策略的开发具有重要意义。

[关键词] 白血病抑制因子;肿瘤免疫;靶向治疗;细胞因子
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Leukemia inhibitory factors: the critical role in tumor development and implications for targeted therapy strategies

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[Abstract] Leukemia inhibitory factor (LIF) is a pleiotropic cytokine of the interleukin-6 (IL-6) family, which was first identified as being able to inhibit the proliferation of mouse myeloid M1 leukemia cells and induce their terminal differentiation. LIF is widely involved in the regeneration of organs, neural development, and immune regulation, and also plays an important role in the development of tumors. In contrast to its inhibitory effect on the proliferation of leukemia cells, LIF typically facilitates the progression of many solid tumors. Elevated expression of LIF has been observed to contribute to the development, metastasis, treatment resistance, and evasion of immune response in tumors, hence correlating with a poor prognosis in patients. Focusing on the functions of LIF physiology and pathology and the holistic nature of the signaling pathways it regulates and searching for new targeted drugs is important for the development of targeted therapeutic strategies for the LIF pathway.

[Key words] leukemia inhibitory factor (LIF); tumor immunity; targeted therapy; cytokine
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白血病抑制因子(leukemia inhibitory factor, LIF)是IL-6超家族的多功能细胞因子[1]。LIF由180个氨基酸组成,有7个糖基化位点,其分子量为38 000~67 000,具体大小取决于糖基化修饰的长度,而非糖基化蛋白的分子量约20 000~25 000[2]。LIF的特征是含3个二硫键的四α螺旋束拓扑结构,在小鼠和人类之间

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高度保守[3-4]。

LIF mRNA有LIF-D(分泌型)、LIF-M(分泌和细胞内)和LIF-T(细胞内)三种不同的异构体,它们产生于不同的起始密码子,这些异构体使LIF能够发挥自分泌和或旁分泌效应[5]。这三种亚型以高度组织和细胞类型依赖性的方式表达,LIF-D通常是细胞中最丰富的形式,目前对其研究最为广泛[6]。

LIF通过与白血病抑制因子受体(leukemia inhibitory factor receptor,LIFR)和糖蛋白130(glycoprotein 130,gp130)组成膜受体复合物,介导信号转导,由于缺乏内在的酪氨酸激酶活性,LIFR依赖gp130来执行LIF介导的作用[7]。gp130/LIFR复合物通过胞内结构与JAK酪氨酸激酶家族相关联,当LIF与LIFR结合会激活触发gp130的募集从而形成异二聚体受体复合物,迅速激活的JAK家族激酶导致STAT3与STAT1蛋白的磷酸化,STAT3和STAT1会二聚化并转位到细胞核,从而调节基因表达[8-9]。除JAK/STAT1/3信号通路之外,LIF还能够激活PI3K/Akt、mTORC1/p70s6K、Hippo/YAP和MAPK等信号通路[7,10-11],在肿瘤细胞的增殖和转移过程中起着重要作用。

1　LIF在生物过程和疾病中的多种功能

LIF作为一种多能细胞因子,在造血、神经、肌肉、内分泌、生殖系统等几乎所有器官系统中都具有不同的活性。其多功能性也体现在研究者对其命名的不同,例如,分化抑制因子(differentiation inhibitory factor,DIA)[12]、肝细胞刺激因子(hepatocyte stimulating factor,HSF)[13]、神经元分化因子(cholinergic neuronal differentiation factor,CNDF)[14],也有报道[15]称之为黑色素瘤衍生的脂蛋白脂肪酶抑制蛋白。

1.1　多功能干细胞自我更新

与其在小鼠髓系白血病M1细胞中的促分化作用相反,LIF对小鼠正常胚胎干细胞显示出分化抑制作用,能够维持胚胎干细胞的多能性并刺激其自我更新[16]。LIF能促进狨猴诱导多能干细胞(induced pluripotent stem cell,iPSC)的增殖,并通过调节PI3K/Akt信号通路,激活Tbx-3来维持其自我更新[17],JAK/STAT和PI3K/Akt通路也参与LIF对小鼠胚胎干细胞多能性的维持和调节[18-20]。此外,LIF在小鼠和人类的肠道干细胞(intestinal stem cell,ISC)中都有表达,LIF敲除小鼠模型和肠类器官培养系统中的研究结果[21]表明,小鼠缺乏LIF会损害肠上皮细胞在生理条件下的发育和更新,降低其数量和功能。

1.2　神经发育和再生

LIF在神经发生和再生过程中发挥重要作用。在大鼠模型中,胎儿-母体LIF信号以自分泌/旁分泌方式诱导胎儿大脑中IGF-1和IGF-2的分泌,IGF信号转导调节PI3K/Akt通路以及神经祖细胞(neural progenitor cell,NPC)产生的神经元的分化和成熟,有助于大脑皮质发育[22]。LIF信号转导调节发育中人类大脑皮层组织和前脑类器官的外径向胶质细胞(outer radial glia,oRG)干细胞;LIF治疗还增加了皮质培养物中抑制性中间神经元(inhibitory interneuron,IN)的产生,这表明LIF信号转导可以促进中间神经元与oRG的分化[23]。LIF蛋白在坐骨神经损伤的大鼠雪旺细胞中大量表达,抑制或升高的LIF分别增加或降低雪旺细胞的增殖率和迁移能力,周围神经损伤体内应用针对LIF的siRNA可促进雪旺细胞迁移和增殖、轴突生长和髓鞘形成[24]。

1.3　组织器官发育和再生

LIF参与不同组织器官的发育和再生。LIF在体外促进成肌细胞(骨骼肌的前体)的增殖,并抑制其向肌管分化[25]。同时,LIF参与受损肌肉的再生,缺乏LIF会降低小鼠肌肉损伤后的肌肉再生能力[26]。

LIF还能调节骨骼重塑过程,以恢复受损区域,维持血液中的钙含量,并对饮食和激素做出反应。LIF可促进骨髓基质细胞向成骨细胞分化,抑制其向脂肪细胞分化,从而促进骨形成[27-28]。LIF通过与成骨细胞表面结合,增强缺损骨的重建,在体外和体内诱导骨形成[29-30]。

1.4　感染、炎症及免疫应答

Ⅱ型肺泡细胞(type Ⅱ alveolar cell,ATⅡ)是肺炎期间LIF产生的主要来源,上皮细胞LIFR信号转导有助于肺炎期间的组织保护,与LIF依赖性肺细胞凋亡调控相对应[31-32]。调节性T(regulatory T,Treg)细胞能够产生高水平的LIF,LIF通过抑制IL-6诱导的IL-17A蛋白释放来支持Foxp3(Treg细胞谱系转录因子)的表达并降低Th17型细胞谱系转录因子RORγt的表达来诱导Treg细胞的产生[33-34],因此,LIF似乎可以通过促进Treg细胞分化和抑制Th17型细胞分化来产生耐受性。另一方面,LIF会调节DC的成熟,导致半成熟和耐受性DC的发育[35]。

2　LIF与肿瘤

LIF最初被确定认为能够抑制白血病细胞的增殖,但是随后的众多研究表明LIF在不同类型的实体瘤中具有致癌作用。在乳腺癌、结直肠癌、胰腺癌、黑色素瘤及前列腺癌等多种肿瘤中都观察到了LIF的异常升高,并且在不同类型的肿瘤中LIF也发挥着

不同的作用。人类蛋白质图谱收集的数据显示,几乎所有细胞和健康组织类型都会产生LIF[36],而在肿瘤中LIF mRNA由上皮癌细胞和周围的基质细胞(成纤维细胞、单核细胞、T细胞和巨噬细胞)表达[37]。

2.1 LIF促进肿瘤细胞干性

肿瘤干细胞(cancer stem cell,CSC)是肿瘤细胞的一个独特的亚群,具有不断自我更新和分化的能力,它们是肿瘤耐药和复发的主要驱动者[38]。在胶质母细胞瘤(glioblastoma,GBM)中,TGF-β通过Smad依赖性诱导LIF产生,随后激活JAK-STAT途径诱导GBM起始细胞(GBM-initiating cell,GIC)的自我更新能力[39]。乳腺癌细胞受肿瘤相关成纤维细胞(cancer associated-fibroblast,CAF)产生的LIF刺激,能够激活LIFR信号从而诱导Nanog与Oct4的表达,增加乳腺癌干细胞标志物$CD24^-/CD44^+$水平[40]。此外,LIF也被确定为骨肉瘤中干细胞样特性的超级增强子(super-enhancer,SE)控制的调节因子,通过由LIF/STAT3途径激活的NOTCH1信号传导调节干性相关基因表达,赋予肿瘤细胞干细胞样特征[41]。

2.2 LIF促进肿瘤生长与侵袭

LIF已被证明在多种类型肿瘤的转移中发挥重要作用。在肿瘤组织中,除肿瘤细胞以自分泌LIF的方式调节肿瘤发展外,其他细胞如肿瘤相关成纤维细胞、肿瘤相关脂肪细胞、肿瘤相关巨噬细胞(tumor-associated macrophage,TAM)等细胞也可以通过旁分泌来调节肿瘤微环境(tumor microenvironment,TME)。乳腺癌中的肿瘤相关脂肪细胞产生的LIF激活STAT3信号促进乳腺癌细胞的迁移和侵袭,同时STAT3能够诱导乳腺癌细胞CXC基序趋化因子配体(C-X-C subfamily chemokine ligand,CXCL)的分泌,CXCL又可反过来激活ERK1/2/NF-κB/STAT3信号以促进肿瘤相关脂肪细胞中LIF的表达[42]。前列腺癌中的circSCAF8可以通过与miR-140-3p和miR-335结合来调节LIF表达并激活LIF/STAT3途径,导致前列腺癌细胞的生长和转移[43]。此外,LIF还参与基质成纤维细胞的激活,LIF介导依赖于TGF-β的肌动蛋白收缩性和细胞外基质重塑,从而导致体外和体内癌细胞的侵袭[44]。

2.3 LIF诱导免疫抑制

TAM是TME中最丰富的免疫抑制细胞。在多数人类肿瘤中,TAM的浸润与LIF的过表达相关,并且巨噬细胞内高表达LIFR对于其发挥免疫抑制作用也是不可或缺的。卵巢癌腹水中高含量的LIF 和IL-6促使单核细胞分化为TAM样细胞[45],与之类似,在胃癌中高表达的SOX9基因通过促进LIF分泌,诱导单核细胞极化为TAM,来源于TAM的CCL2与IL-10进一步抑制T细胞功能[46]。另一方面,LIF增加CCL2表达以促进TAM的募集,并将巨噬细胞中CXCL9基因进行表观遗传沉默来抑制细胞毒性$CD8^+$ T细胞的浸润[47]。在前列腺癌细胞中,LIF表达以NF-κB依赖方式受到TLR9信号转导的调节,LIF的分泌会促进PMN-MDSC细胞的积累和免疫抑制活性,对T细胞的增殖产生强烈的抑制作用[48]。

2.4 LIF引发耐药性

长期以来,CAF一直被认为是胰腺导管腺癌(pancreatic ductal adenocarcinoma,PDAC)TME中的主要基质细胞和促肿瘤成份,由CAF组成的致密增生的结缔组织阻碍了化疗药物的递送,增强了PDAC对化疗的抗性。IL-1介导的胰腺星状细胞自分泌LIF诱导激活JAK/STAT信号转导并促进炎症相关成纤维细胞(inflammatory CAF,iCAF)的形成,iCAF在PDAC的进展、化疗耐药性方面发挥着重要作用[49]。肿瘤细胞产生的LIF通过激活STAT3信号通路,刺激巨噬细胞形成促瘤的M2型表型从而促进胃癌对化疗药物的耐药[50]。LIF在结肠癌中过度表达,通过STAT3/ID1/MDM2通路降解p53,p53的缺失导致结直肠癌细胞和结直肠异种移植瘤细胞对化疗药物的耐药性[51]。自分泌和旁分泌LIF信号通过STAT1/PI3K/Akt依赖性途径上调骨髓细胞白血病序列1(myeloid cell leukemin-1,Mcl-1)的表达来促进胆管癌的化学耐药性[52]。

2.5 肿瘤中对LIF的调节

肿瘤的调控是非常复杂的,LIF在不同的细胞和组织中通过不同的机制以高度依赖环境的方式进行精确调控,这有助于LIF在生理和病理过程中发挥复杂的功能,包括调控表观遗传修饰和微环境中的应激信号,以及调节细胞因子和致癌的转录因子的表达。

2.5.1 表观遗传学

有研究[53]表明,乳腺癌中LIF的表达是通过其启动子区域内的DNA去甲基化和组蛋白甲基化状态的变化进行表观遗传上调的。在乳腺癌发生期间,LIF启动子区域的甲基-CpG结合蛋白MeCP2占有率和组蛋白H3-Lys9-二甲基化(转录抑制的标志)等非活性表观遗传标志显著降低,而H3-Lys4-二甲基化水平(转录激活的标志)增加。研究[41]发现,组蛋白H3-Lys27-三甲基化去甲基化酶UTX能维持癌细胞的增殖,损害组蛋白H3-Lys27-三甲基化的积累,诱导LIF基因位点的组蛋白H3-Lys27-乙酰化,最终导致LIF表达增加。

2.5.2 抑癌基因

HU等[54]研究证实,LIF是肿瘤抑制因子p53的直接转录靶标,p53与LIF基因第一个内含子中的p53

结合元件结合,上调包括子宫在内的小鼠各种组织中的基础LIF表达水平。据报道[55],敲低WIP1或SIRT1可稳定p53并能增强髓母细胞瘤中LIF的转录并诱导细胞凋亡。

2.5.3　应激与致癌基因

缺氧是实体瘤中广泛存在的一种特征,结直肠癌中的缺氧会稳定缺氧诱导因子2α(hypoxia-inducible factor 2α,HIF-2α),导致HIF-2与LIF启动子区域中的两个缺氧反应元件结合,增强LIF的转录[56]。雄激素剥夺治疗刺激前列腺肿瘤启动子ZBTB46的丰度增加,并通过SNAI1的转录调控促进EMT,ZBTB46能与LIF基因的启动子区域结合并诱导LIF表达以促进前列腺癌的肿瘤生长和治疗耐药性[57]。也有报道[58]证实,LIF是骨髓细胞系中STAT5的直接转录靶标,STAT5与LIF启动子结合,并且在激活 JAK2/STAT5通路后增加LIF表达。锌指E-Box结合同源盒1(zinc finger E-box binding homeobox 1,ZEB1)是能促进EMT的转录因子,在结直肠癌、乳腺癌、胰腺癌、骨肉瘤、肺癌等肿瘤中显示出促癌作用[59]。但一项研究[60]显示,在超过50%的GBM中观察到ZEB1缺失,在15%的低级别胶质瘤(Ⅱ级和Ⅲ级)中观察到缺失,杂合性经常丧失。而ZEB1与LIF的启动子区域结合并抑制神经胶质瘤肿瘤干细胞中的LIF表达,从而抑制神经胶质瘤肿瘤干细胞的自我更新并促进其分化。

3　LIF作为潜在的肿瘤生物标志物

BRESSY等[61]研究发现,PDAC组织中的癌细胞和基质细胞均表达LIF,但只有基质细胞可以分泌LIF。在PDAC患者血清和PDAC小鼠模型中,LIF滴度与肿瘤内神经密度呈正相关。这项研究结果表明,LIF是一种候选血清生物标志物和诊断工具,也是一种可能的治疗靶点,可限制胰腺癌相关神经重塑(pancreatic cancer-associated neural remodeling,PANR)在PDAC病理生理学和转移进展中的影响。单变量和多变量Cox回归分析发现,胰腺肿瘤组织中LIF的表达是导致总生存率和无复发生存率低的独立危险因素。LIF的过度表达与淋巴结转移、病理分期等临床病理特征不良有关。胰腺癌患者的血清LIF水平高于健康对照组。综合来说,血清LIF比其他生物标志物(CA199和CEA)更能有效地预测淋巴结和远处转移[62]。鼻咽癌患者血清LIF水平与放射抵抗和局部肿瘤复发呈正相关[63]。在食管腺癌患者中,治疗反应差的患者血清LIF水平明显更高[64]。GBM患者的全基因组测序结果显示,LIF与CCL2在mGBM(multifocal GBM)中间充质亚型肿瘤病灶中高度富集,诱导产生类似于间充质亚型GBM的表型,并与GBM患者的不良预后相关[65]。此外,LIF在血清中的升高与接受免疫检查点阻断(immune checkpoint blockade,ICB)治疗的肿瘤患者的不良预后相关,循环中LIF的水平与TME中三级淋巴结构形成水平呈反比,因此,LIF也被确定为一种新的ICB抗性的生物标志物[66-68]。

上述研究结果提示了LIF可用作肿瘤早期诊断和预测患者对肿瘤治疗反应的生物标志物的可能性。然而,使用血清LIF水平作为生物标志物存在一定的局限性。例如,单独升高的LIF血清水平不能明确肿瘤类型。因此,需要LIF和每种特定肿瘤类型的其他生物标志物的组合用于早期诊断。此外,LIF可由其他疾病如感染和炎症诱导,因此在确定血清LIF水平升高的原因时应谨慎。

4　LIF通路的靶向策略

LIF通路在许多实体瘤进展中的重要作用,揭示其具有作为肿瘤治疗靶点开发的潜力。目前已开发出LIF的小分子抑制剂和中和抗体用于肿瘤的治疗,实验结果证实,中和抗体以及阻断LIFR能够有效地抑制肿瘤的进展。

4.1　小分子抑制剂

由YUE等[69]根据LIF/LIFR晶体结构设计合成的小分子化合物EC330与EC359是有效的LIFR抑制剂,EC330对LIFR表现优异的结合能力,但EC330具有类固醇骨架,可能与糖皮质激素受体等类固醇受体结合从而引起不必要的不良反应。在此基础上对EC330进行结构修饰得到化合物EC359,保留了对LIFR结合效力的同时减少了与类固醇受体的相互作用,EC359在BT-549细胞模型中表现出与EC330相当的抑制活性。与EC330相同,EC359直接与LIFR结合以有效阻断LIF/LIFR相互作用,EC359处理减弱了LIF/LIFR途径(包括STAT3、mTOR和AKT)的激活,能够有效抑制三阴性乳腺癌(triple negative breast cancer,TNBC)的侵袭能力,诱导TNBC细胞凋亡并抑制TNBC异种移植瘤的生长[70]。在Ⅱ型子宫内膜癌(endometrial cancer,EC)的研究[71]中,EC359在两种不同患者来源的异种移植模型和离体患者来源的类器官中能够显著抑制移植瘤进展,提示LIFR抑制剂EC359可能成为治疗Ⅱ型EC的新的小分子疗法。

米非司酮作为一种类固醇拮抗剂,具有抗孕激素活性,临床被批准用于药物流产,同时米非司酮也对乳腺癌、卵巢癌等多种肿瘤有抗肿瘤活性[72-74]。DI GIORGIO等[75]利用EC359的结构对美国FDA批准的药物数据库进行相似性筛选,将米非司酮鉴定为有效的LIFR拮抗剂,体外实验表明其能够抑制PDAC细胞中LIF/JAK/STAT3通路而抑制癌细胞增殖和迁移。

4.2 中和抗体

LIF的中和抗体已被证明能够在多种不同类型的实体瘤中有效拮抗LIF的致癌作用。研究[76]表明,LIF中和抗体可以阻断LIF对葡萄糖的代谢促进作用并抑制肿瘤生长,还能逆转由LIF诱导的肿瘤耐药性。例如,LIF中和抗体与吉西他滨协同作用能清除PDAC小鼠模型中生长的肿瘤[77]。MSC-1(AZD0171)是Northern Biologics/Celgene公司开发的首个抗LIF人源化单克隆抗体,通过与LIF结合来阻断下游JAK/STAT3通路的激活。在一项在晚期实体瘤的临床试验(NCT03490669)中,AZD0171在所有剂量下都表现出较好的安全性与良好的耐受性,在患者肿瘤内观察到p-STAT3的减少,$CD8^+$ T细胞的浸润增加和M1∶M2巨噬细胞比例的偏移,总的来说有利于患者的抗肿瘤免疫应答。另一方面,由于人类肿瘤样本中的LIF表达与不良的患者预后和对ICB治疗的耐药性有关,因此临床试验结果支持MSC-1与免疫检查点抑制剂的联合运用[78]。这种假设在结肠癌小鼠模型中得到了验证,MSC-1的治疗促使巨噬细胞获得抗肿瘤与促炎功能,与PD-1单抗联用增强了抗肿瘤反应[79]。为进一步验证MSC-1的疗效,在另一项临床Ⅱ期试验(NCT04999969)中与度伐利尤单抗(durvalumab)联用治疗晚期PDAC。

另一种由加科思药业开发的JAB-BX300单抗,已在中国获批新药临床新药试验申请(Investigational New Drug,IND),将开展Ⅰ/Ⅱa期晚期实体瘤临床试验。

4.3 来源于中药的小分子化合物

笔者所在课题组先前研究[80]表明,来源于木兰科辛夷的化合物木兰脂素(magnolin)具有良好的抗肿瘤活性。结肠癌中LIF通过促进STAT3磷酸化增加Mcl-1转录表达,木兰脂素能够抑制LIF进而阻断STAT3/Mcl-1信号转导来促进肿瘤细胞自噬和细胞周期停滞。另一种从龙葵中提取的生物碱——澳洲茄边碱(solamargine),可以通过LIF/p-STAT3通路使TAM重新极化以抑制肝细胞癌(hepatocellular carcinoma,HCC)的生长和EMT,同时通过调节巨噬细胞、MDSC、DC和T细胞群体来影响TME中的其他免疫细胞发挥抗HCC的作用[81]。盐酸水苏碱是来源于脓疮草的生物碱,研究[82]表明盐酸水苏碱能与LIF结合,通过上调p-AMPK来诱导肿瘤细胞自噬、周期阻滞和细胞衰老来抑制肝癌细胞生长。

此外,三氧化二砷作为中药砒霜中的主要有效成分,使用三氧化二砷治疗显著减少了Hep3B和Huh7 HCC细胞系中的$CD133^+$干细胞数量并诱导HCC中CSC的分化,还能通过协同5-FU与顺铂抑制LIF/JAK1/STAT3和NF-κB信号通路,增强化疗药物的细胞毒作用[9]。

5 结 语

多功能性细胞因子LIF在肿瘤进展中发挥着重要作用,靶向LIF是针对许多LIF过表达类型肿瘤的一种有前途的治疗策略。靶向LIF的策略包括抑制LIF的过表达以及阻断其在肿瘤中致癌的关键信号通路。小分子抑制剂的开发为靶向LIF治疗肿瘤提供了一种可行的治疗策略,遗憾的是,由于特异性与抑瘤效果不理想而未能进入临床试验。另一种LIF的中和抗体作为单一药物已被证明是一种潜在的肿瘤治疗新策略——以LIF为治疗靶点的人源化抗LIF抗体(MSC-1)疗法目前已在进行Ⅰ期临床试验,表现出良好的安全性,期待与ICB疗法联用能增强抗肿瘤疗效。

鉴于LIF通路在肿瘤发展中的重要性,亟须开发更多的新药以满足未来临床治疗的需求。更深入地了解LIF过表达的机制和LIF在不同肿瘤中的下游信号通路对于开发针对肿瘤中LIF的更有效策略是必要的。值得注意的是,LIF不仅由癌细胞产生并以自分泌方式发挥作用,还可由TME产生并以旁分泌方式发挥作用。LIF在肿瘤病理过程中发挥着重要而复杂的作用,探寻LIF在这些过程中的确切作用和机制,深入了解LIF在治疗肿瘤过程中的关键作用,进而寻求更加优良的潜在治疗方案,这对未来靶向LIF治疗肿瘤策略的应用至关重要。

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