LRG1在炎症性疾病和肿瘤中的研究进展

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摘要 富含亮氨酸的α2-糖蛋白-1(leucine-rich α-2 glycoprotein 1, LRG1)是亮氨酸重复序列蛋白家族的重要成员。LRG1在炎症、血管生成、纤维化、细胞黏附、细胞凋亡以及细胞活性等生物过程中都发挥着关键的调控作用。在探讨LRG1各种致病机制的同时, 它作为诊断、预后和监测疾病发生的生物标志物的潜能也被挖掘。该文对LRG1在炎症性疾病和肿瘤中的作用机制进行综述, 旨在提供一个对LRG1更全面的认知, 并且实现LRG1在临床诊断和治疗方面的可能。

关键词 富含亮氨酸的α2-糖蛋白-1; 炎症性疾病; 肿瘤; 生物标志物

Research Progress on Leucine-Rich α2-Glycoprotein-1 in Inflammatory Diseases and Tumors

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Abstract LRG1 (leucine-rich α2-glycoprotein-1) is an important member of the leucine-repeat sequence protein family. LRG1 plays a key regulatory role in biological processes such as inflammation, angiogenesis, fibrosis, cell adhesion, apoptosis and cell activity. While various pathogenic mechanisms of LRG1 have been explored, its potential as a biomarker for diagnosis, prognosis and monitoring of diseases has also been extensively investigated. This article reviews the mechanisms of LRG1 in inflammatory diseases and tumors, aiming to provide a more comprehensive understanding of LRG1 and to realize the possibilities of LRG1 in clinical diagnosis and therapy.

Keywords leucine-rich α2-glycoprotein-1; inflammatory diseases; tumor; biomarker

富含亮氨酸的α2-糖蛋白-1(leucine-rich α-2 glycoprotein 1, LRG1)由位于人类19p13.3的*lrg1*基因编码[1], HAUPT与BAUDNER[2]在1977年首次从人类血清中将其分离。生理条件下, LRG1在肝脏和中性粒细胞中结构性表达, 并且在内皮细胞和巨噬细胞中合成[3]。然而, 作为富含亮氨酸重复序列(leucine-rich repeat sequence, LRR)家族中的一个高度保守的成员, LRG1的生物学功能到目前为止还没有完全被阐释。近年来的研究发现, LRG1在肿瘤、炎症性疾病、眼部疾病、血液系统疾病、免疫系统疾病、内分泌系统疾病、呼吸系统疾病和神经系统疾病中都表达异常。尤其是在炎症性疾病和肿瘤中, LRG1作为一种新的标志物, 对疾病的诊断和预后非常重要。同时, LRG1调控不同的信号通路, 在肿瘤发生发展中的作用机制也被揭露。本综述旨在全面地描述LRG1在炎症性疾病和肿瘤中的作用和应用研究进展。

1 LRG1的结构

1985年, TAKAHASHI等[4]确定了LRG1的氨基酸序列。LRG1由一条多肽链组成, 上面附着一个半

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乳糖胺和四个葡糖胺寡糖, 它有两个链内二硫键。这种大小为50 kDa的糖基化蛋白含有312个氨基酸, 其中亮氨酸残基占氨基酸组成的16.62%[4]。在对LRG1的氨基酸进行测序时发现, LRG1至少包含八个重复的共同序列。每个序列由24个氨基酸残基组成, 在亮氨酸、脯氨酸和天冬酰胺上呈现出周期性的规律[4]。

这种共享序列被称为富含亮氨酸的重复序列(leucine-rich repeat sequence, LRR)。一个LRR分为高度保守序列和可变序列。直至目前, 根据可变序列的不同, 已经确定了9个LRR类别[5]。LRR存在于43万多种生物的蛋白质中, 形成了LRR超家族。含有LRR的蛋白质位于细胞内、跨膜和细胞外区域, 具有不同的功能。一些研究者认为, LRR的主要功能是为蛋白质之间的相互作用提供结构框架, 包括免疫反应、细胞黏附、血小板聚集、植物抗病和病原体识别等[6-7]。

2 LRG1与炎症性疾病

2.1 LRG1在炎症中的作用

LRG1在中性粒细胞(neutrophilic granulocyte, NE)中表达, 从早期的粒细胞分化一直持续到嗜中性粒细胞阶段[1]。LRG1存在于NE的过氧化物酶阴性颗粒中[8], 在炎症刺激和微生物感染后释放, 一度被认为是急性时相反应蛋白中的一员。LRG1的表达受到多种细胞因子的刺激, 包括肿瘤坏死因子-α[9]、白介素-6(interleukin-6, IL-6)、白介素-1β(interleukin-1β, IL-1β)[10]、白介素-22[11]。有研究发现, IL-6和IL-1β分别通过转录因子STAT3和NFκB发出信号, 协同促进LRG1的表达[10]。胞外的LRG1可能通过诱导*L*-选择素[12]和趋化因子CXCL-1[13]的表达来促进NE的内皮黏附, 从而有助于NE在损伤部位的募集。LRG1还有助于NE的功能成熟[14]、辅助性T细胞17的细胞分化和增殖[15]。除了上述作用之外, LRG1通过调控转化生长因子-β1(transforming growth factor-β1, TGF-β1)及其下游途径, 发挥促进炎症[15]、纤维化[16]、病理性血管生成[17]的作用, 导致一系列炎症性疾病的发生。

2.2 LRG1与炎症性疾病的关系

2.2.1 LRG1与自身免疫性疾病 LRG1的产生在系统性炎症时升高, 有时它比c-反应蛋白(c-reactive protein, CRP)更具有炎症性标志物的优势。CRP是急性炎症后的下游介质, 主要依赖IL-6在肝脏合成[18]。SERADA等[19]报道, 血清中LRG1的水平是监测溃疡性结肠炎(ulcerative colitis, UC)活动的良好的预测指标, 特别是在那些CRP较低的UC患者中。SHINZAKI等[20]进一步发现, LRG1在判断UC患者的内镜下黏膜愈合活动方面比CRP更有效, 可以避免患者频繁的内镜评估。除此之外, 当临床使用IL-6阻断治疗炎症性疾病时, LRG1可比CRP更好地监测疾病的治疗效果, 这在类风湿性关节炎[21]和青少年特发性关节炎[22]中都有体现。

2.2.2 LRG1与纤维化疾病 纤维化是机体对各种刺激的慢性炎症反应的最终结果, 是指包括胶原在内的细胞外基质成分过度沉积而引起的各种组织的过度生长、硬化或瘢痕[23]。LIU等[24]发现, LRG1在常驻的心脏成纤维细胞中结构性表达, 通过与TGF-β竞争结合TGF-β受体来调节TGF-β的生物利用度。*LRG1*的缺失会导致TGF-β信号的过度活跃, 从而加重心肌纤维化和心功能不全。一些研究证实, LRG1的表达减少与心脏老化、血管特性异常、心肌细胞特性改变以及心力衰竭患者的纤维化加剧有关[25]。此外, LRG1通过调节TGF-β, 抑制炎症因子和纤维化因子的分泌, 减弱肾脏间质纤维化[26]。但是, 当LRG1在体内过量表达会促进病理性血管生成而加剧增生性瘢痕的形成[27]。LRG1的过表达通过激活TGFβ1/SMAD3通路而加剧了肾脏纤维化的进程[16]。

2.2.3 LRG1与2型糖尿病的慢性并发症 2型糖尿病(type 2 diabetes, T2D)的神经病变、视网膜病变和血管并发症是导致T2D发病率和死亡率的主要因素。一些研究发现, LRG1与T2D的这些病理变化有着密不可分的关系。LRG1水平升高是T2D患者动脉僵化、内皮功能紊乱、外周动脉病变[28]、增殖性糖尿病视网膜病变[29]和糖尿病肾病[17]的潜在标志物。GURUNG等[30]采用全基因组方法提供了基因影响血浆LRG1增加T2D患者肾功能快速下降的证据。一项平均随访7年的前瞻性研究发现, 高浓度的LRG1与T2D患者心力衰竭的风险增加有关, LRG1可能作为TGF-β信号转导途径的调节者参与T2D患者心力衰竭的发病机制[31]。最近的一项研究表明, LRG1是一种脂肪因子, 其表达和分泌与人类和小鼠的肥胖呈正相关, LRG1在介导肥胖引起的肝脏萎缩和胰岛素抵抗中起关键作用[32]。

2.2.4 LRG1与心脑血管疾病 炎症、血管再生和组织纤维化在心脑血管疾病中起着重要作用。研究

表明, LRG1是急性冠状动脉综合征[33]、心力衰竭[34]、心房颤动[35]和心源性卒中[36]的潜在标志物, 有助于早期预警上述疾病的发生, 改善患者的预后。此外, 人类脑脊液(cerebrospinal fluid, CSF)中的LRG1水平可能是中枢神经系统炎症性疾病的敏感生物标志物[37]。MIYAJIMA等[38]发现, 认知功能随着CSF中LRG1浓度的增加而下降, LRG1在大脑中的过度表达会引起记忆问题。

2.2.5 LRG1与感染性疾病 脓毒症是一种由于宿主对感染的反应失调而导致出现危及生命的器官功能障碍的严重疾病。儿童脓毒症是引起世界范围内儿童高发病率和死亡率的主要原因之一。有研究发现, 当胎儿肝脏不成熟时, LRG1能比CRP更准确、更早地检测出胎儿感染, 从而避免胎儿发生致命的败血症[39]。进一步的蛋白组学研究表明, 由可溶性白介素2α链受体、血清淀粉样蛋白-A1和LRG1三种蛋白组成的检测小组, 可以诊断儿童脓毒症[40]。脓毒症相关性脑病(sepsis-associated encephalopathy, SAE)是脓毒症严重的并发症之一。MIAO等[41]研究发现, LRG1在脓毒症模型小鼠中升高, 沉默*LRG1*通过抑制TGF-β/SMAD1通路减轻SAE的脑损伤, 提示LRG1可能是治疗SAE的一个潜在靶点。

急性阑尾炎是最常见的小儿外科急症, 由于诊断和治疗的延误, 可能会导致严重的并发症。有报道称, 在对患儿尿液进行脱水调整后, 尿液中LRG1将成为儿童阑尾炎的一个新的生物标志物[42]。YAP等[43]发现LRG1是排除儿童阑尾炎的一个非侵入性工具。一项在儿童中的前瞻性队列研究报告称, LRG1可能区分急性复杂性阑尾炎和急性非复杂性阑尾炎, 有助于尽快启动适当的治疗[44]。然而, 在成人阑尾炎的鉴别中, LRG1的表现并不理想[45]。除此之外, 在机体接种卡介苗后, 比起CRP和红细胞沉降率, LRG1可以更好地衡量抗结核治疗的效果[46]。最近的一项研究发现, 在第三期牙周炎患者中, LRG1局部和全身的表达都有所增加[47]。以上研究都说明LRG1与炎症性疾病密切相关, 无论是作为生物标志物还是潜在的治疗靶点, 都有巨大的价值。

3 LRG1与肿瘤

3.1 LRG1在肿瘤中的作用

3.1.1 LRG1与血管生成 血管生成是一个正常而复杂的生理过程。它是指血细胞通过内皮细胞的“发芽”, 在原有的血管系统中形成新的血管, 向组织提供氧气和营养物质[48]。生理性的血管生成是维持生理平衡和组织完整性的关键过程, 相反, 异常加速或者病理性的血管生成却与多种疾病密切相关。许多研究发现, LRG1作为一种新的血管生成因子, 通过调控不同的途径参与血管生成(图1)。

转化生长因子β1(transforming growth factor-β1, TGF-β1)在血管生成中起着重要作用, 并且高度依赖环境, 在抗血管生成和促进血管生成的功能中进行角色转换[49]。TGF-β1主要与其特定的TGF-β I型受体(TβR1)和TGF-β II型受体(TβR2)相互作用, 从而激活两种不同的I型受体信号: ①激活素受体样激酶1(activin receptor-like kinase 1, ALK1)-SMAD1/5/8信号, 促进内皮细胞增殖、迁移和小管形成, 发挥促血管生成作用; ②激活素受体样激酶5(activator receptor-like kinase 5, ALK5)-SMAD2/3信号, 抑制内皮细胞增殖、迁移和小管形成, 发挥抗血管生成功能。同时, 内皮糖蛋白(endoglin, ENG)作为共同受体, 平衡ALK1和ALK5途径[50]。LRG1与ENG结合, 在TGF-β1存在时促进T-βRII-ALK1-SMAD1/5/8途径信号转导, 打开TGF-β1血管生成开关[12,17,51-52]。研究表明, LRG1的存在对血管的健壮生长起着必要的作用[51]。

低氧诱导因子(hypoxia-inducible factor, HIF-1), 是由构成性表达的HIF-1α亚基和HIF-1β亚基组成的异源二聚体, 介导对组织氧合变化的适应性反应, 是低氧反应中最重要的转录调节因子[53]。HIF-1能激活与血管生成、葡萄糖代谢、细胞增殖和存活、侵袭和转移有关的各种蛋白质的转录编码基因, 血管内皮生长因子(vascular endothelial growth factor, *VEGF*)就是HIF-1的靶基因之一。ZHANG等[54]发现, LRG1促进了结直肠癌细胞HIF-1α基因和蛋白的表达, 而*HIF-1α*敲除则抑制了LRG1诱导的VEGF-A的表达。这表明, LRG1可能针对HIF-1α途径诱导结直肠癌细胞的血管生成。另一项研究发现, LRG1能直接上调VEGF-A、B、C、D和VEGF受体-1(VEGFR-1)、VEGFR-2和VEGFR-3的间质表达, 促进碱烧伤小鼠模型的角膜新生血管和淋巴管生成[55]。最近, HE等[56]研究发现, LRG1在胃癌中发挥促进血管生成的作用, 而这一作用是通过激活LRG1下游通路SRC/STAT3/VEGFA实现的。

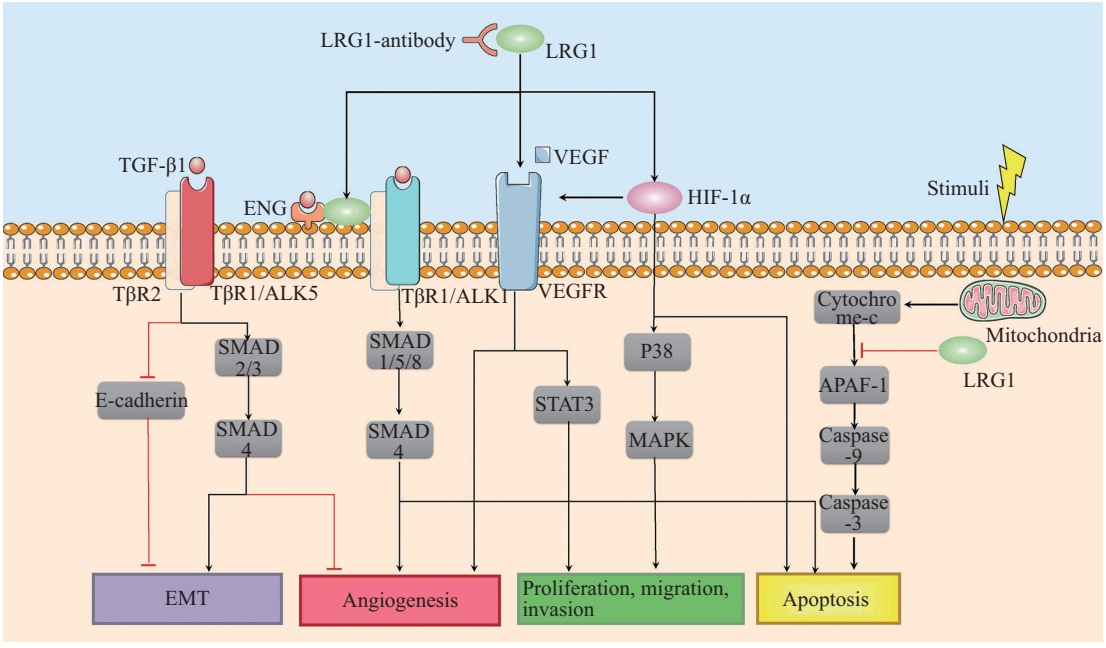
3.1.2 LRG1与细胞凋亡 十几年前, 研究者就发现LRG1是细胞色素c(cytochrome c, Cyt c)的细胞外配

体, 它可以作为血清干扰的抑制剂, 提高酶联免疫吸附实验量化人体血清中总Cyt c的灵敏度[57]。近年来的研究表明, LRG1参与了由Cyt c调节的细胞凋亡过程(图1)。在应对各种压力刺激时, Cyt c从线粒体中释放出来并与细胞质凋亡蛋白酶激活因子-1(apoptotic protease activating factor-1, APAF-1)结合, 引起APAF-1的构象变化, 使dATP/ATP结合并裂解Caspase-9前体, 然后激活下游Caspase并最终导致细胞死亡[58]。LRG1与Cyt c的结合抑制了Cyt c和APAF-1之间的相互作用, 从而保护淋巴细胞[59]、MCF-7乳腺癌细胞[60]免受细胞外Cyt c诱导的凋亡, 而稳定地敲除*LRG1*则会促进胶质母细胞瘤细胞的凋亡[61]。然而, 值得注意的是, 在缺血/再灌注损伤[62]和急性心肌梗死[63]中, LRG1分别通过调节TGFβ-AKL1-SMAD1/5信号通路和HIF-1α促进细胞的凋亡和自噬, 加剧了机体的损伤。

3.1.3 LRG1与细胞增殖、迁移、侵袭 TGF-β超家族蛋白存在于正常细胞和转化细胞中, 广泛参与细胞的增殖、迁移和侵袭[64]。LRG1通过上调细胞中的TGF-β抑制E-钙黏蛋白的表达, 促进上皮–间充质转化(epithelial-mesenchymal transition, EMT)过程, 同时LRG1激活了TGF-β/SMAD信号通路, 增强了细胞的增殖、迁移和侵袭(图1)。LRG1的这一调控机制在胶质瘤细胞[65]、胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)细胞[66]、胃癌细胞[67]、非小细胞肺癌(non-small cell lung cancer, NSCLC)[52]中都有体现。相反, LRG1通过负向调节TGF-β信号转导途径, 抑制了食道癌细胞的迁移和侵袭[68]。一些研究表明, LRG1刺激MAPK/p38信号通路, 促进甲状腺癌细胞[69]和间充质干细胞的迁移[9], 以及PDAC细胞的增殖、迁移和侵袭[70]。此外, LRG1通过调节EGFR/STAT3信号转导促进黑色素瘤细胞迁移、侵袭、黏附和肺部转移[71]。

3.2 LRG1与肿瘤的关系

3.2.1 LRG1与胰腺癌 胰腺癌(pancreatic cancer,



LRG1: 富含亮氨酸的α2-糖蛋白-1; TGF-β1: 转化生长因子-β1; TβR2: 转化生长因子-β-II型受体; TβR1/ALK5: 转化生长因子-β-I型受体/激活素受体样激酶5; TβR1/ALK1: 转化生长因子-β-I型受体/激活素受体样激酶1; ENG: 内皮糖蛋白; VEGF: 血管内皮生长因子; VEGFR: 血管内皮生长因子受体; STAT3: 信号转导转录激活因子3; HIF-1α: 低氧诱导因子-1α; MAPK: 丝裂原活化蛋白激酶; APAF-1: 凋亡蛋白酶激活因子-1; EMT: 上皮–间充质转化。

LRG1: leucine-rich α2 glycoprotein 1; TGF-β1: transforming growth factor-β1; TβR2: transforming growth factor-β type II receptor; TβR1/ALK5: transforming growth factor-β type I receptor/activin receptor-like kinase 5; TβR1/ALK1: transforming growth factor-β type I receptor/activin receptor-like kinase 1; ENG: endoglin; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; STAT3: signal transducer and activator of transcription 3; HIF-1α: hypoxia-inducible factor-1α; MAPK: mitogen-activated protein kinase; APAF-1: apoptosis protease activating factor; EMT: epithelial-mesenchymal transition.

图1 LRG1在血管生成、细胞凋亡和细胞增殖、迁移、侵袭中的作用机制

Fig.1 The mechanism of LRG1 in angiogenesis, apoptosis and cell proliferation, migration and invasion

PC)是高度致命的恶性肿瘤, 特别是胰腺导管腺瘤(pancreatic ductal adenocarcinoma, PDAC)。PC通常在早期不表现出特异性症状, 导致确诊延迟和高死亡率。LRG1在PC患者血清中表达增加[72], 并且预示着PC患者的肿瘤晚期和预后不良[70]。LRG1与金属蛋白酶组织抑制剂1、CA19-9联合组成的检测小组, 在早期检测PDAC中发挥巨大潜能, 尤其是在CA19-9低于阈值的前PDAC中[73-74]。LRG1的存在弥补了CA19-9诊断PC的一些缺陷, 如因缺乏岩藻糖基转移酶而不产生CA19-9导致的假阴性以及因胆道梗阻而出现的假阳性。在PDAC风险较高的T2D患者中, LRG1也参与了由11种蛋白质组成的多个生物标志物小组, 提高了早期诊断PDAC的准确性[75]。

3.2.2 LRG1与结直肠癌 大肠癌(colorectal cancer, CRC)是全球第二大常见癌症[76]。结肠镜检查是检测CRC的金标准。然而由于其侵入性, 不可能对所有群体进行大规模的普查。近年来, 寻找适合大规模普查的新型非侵入性标志物的工作从未停止。有研究发现, LRG1在CRC组织中的表达明显高于正常组织[54]。随着从正常组织向CRC组织的过渡, LRG1在组织中的表达逐渐增加, LRG1可能是影响CRC患者预后的一个独立风险因素[77]。LRG1在预后更差的右侧结肠癌患者的血清胞外囊泡中有所增加, 其促进肿瘤转移的作用比左侧结肠癌更明显[78]。粪便中由结合珠蛋白和LRG1组成的蛋白质小组被确定为高危腺瘤和CRC的检测对象[79]。

3.2.3 LRG1与肺癌 对肺癌患者尿液中的蛋白分析显示, LRG1的表达增加[80]。在NSCLC患者肺组织[52]和尿液外泌体[81]中, LRG1的表达均升高。尿液外泌体中LRG1的水平与肺癌的预后相关, LRG1的水平升高将缩短肺癌患者的生存时间[82]。

3.2.4 LRG1与其他类型的肿瘤 LRG1在胃癌[67]、乳腺癌[83]、子宫肌瘤[84]、肾透明细胞癌[85]、肝内胆管癌[86]、卵巢癌[87]和前列腺癌[88]中表达水平升高, 并且预示着更低的生存率, 表明LRG1可能是这些肿瘤的预后标志物。然而值得注意的是, LRG1在头颈部鳞状细胞癌[89]和肝细胞癌[90]中表达下降, 并且抑制肿瘤发生和侵袭。在患有局部前列腺癌并进行了根治性前列腺切除术的患者中, 高水平LRG1预示了更低的生化复发和进展为去势抵抗性前列腺癌的风险[91]。这表明, LRG1的表达水平升高对前列腺全切除患者的预后是有利的。在胶质母细胞瘤中也发现了类似的结果, 升高的LRG1是其预后的独立有利因素[92]。表1总结了LRG1在不同肿瘤中的表达水平和调节作用。

4 展望与总结

LRG1调节中性粒细胞分化和血管生成, 还在细胞增殖、迁移、侵袭和细胞凋亡的过程中发挥重要作用。循环中LRG1水平的改变, 与多种炎症性疾病和肿瘤的发生、活动、预后密切相关。特别是LRG1与其他生物标志物联合使用, 能更准确和及时地诊断一些复杂疾病, 这在临床实践中拥有巨大的应用价值。此外, LRG1在多种疾病的发生和发展中扮演着重要角色, 这为一些疾病的治疗提供了新思路。一方面, 阻断LRG1可能用作控制相应疾病的手段。KALLENBERG等[96]报道了一种名为Magacizumab的人源化阻断LRG1的IgG4抗体, 该抗体在体内和体外小鼠模型中都抑制致病性血管生成和血管渗漏。随后, 一种包含Magacizumab在内的新型的抗体–药物结合物被合成, 它通过靶向LRG1定位于皮下肿瘤部位, 提高了黑色素瘤小鼠的生存率[97]。然而, 另一方面, LRG1的存在是有益的。研究表明, 外源性LRG1促进了糖尿病小鼠的角膜伤口的修复和神经再生[98], 并加速正常小鼠的角质形成和皮肤伤口修复[99]。YIN等[100]发现LRG1与其特异性受体Latrophilin-2相互作用, 改善了高糖环境下小鼠体内的血管生成和神经营养。在小鼠阴茎内注射LRG1能完全恢复因糖尿病导致的勃起障碍[100]。

综上所述, LRG1在多种炎症性疾病和肿瘤的诊断和治疗方面都有广阔的临床应用前景。然而, 在大多数疾病中, LRG1的升高是引起病理异常的原因还是病理损伤代偿性升高的结果还有待阐明。此外, 众多研究证实, LRG1在不同肿瘤中的表达和作用存在异质性, 甚至在同一类型肿瘤中研究结果也有所不同, 提示LRG1在不同肿瘤中的具体作用机制还需要在未来进一步探究。而当体外应用LRG1发挥一些有益作用时, 需要严格调节它的功能以防止炎症反应以及病理性血管生成的发生。最后, 现阶段的研究大都集中于蛋白组学和基础实验, 未来需要挖掘更多来自临床的实验证据。

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表1 LRG1在不同肿瘤中的变化与作用

Table 1 Changes and roles of LRG1 in different cancers

肿瘤类型 Type of cancer	定位 Location	表达 Expression	作用 Roles	参考文献 References
Pancreatic cancer	Serum	Increase	Identifying patients with pancreatitis LRG1 increases with the stage of pancreatic cancer	[93]
Colorectal cancer	Tumor tissue	Increase	An independent risk factor affecting prognosis of colorectal cancer	[77]
Liver cancer	Tumor tissue	Increase	High expression of LRG1 is associated with poor prognosis Prognostic risk factor for postoperative intrahepatic cholangiocarcinoma	[86]
	Tumor tissue	Decrease	LRG1 inhibits metastasis	[90]
Lung cancer	Urinary exosomes	Increase	Elevated levels of LRG1 predict shorter survival times	[82]
NSCLC	Lung tissue	Increase	Inducing proliferation, migration. Enhancing invasion	[52]
Glioblastoma	Tumor tissue	Increase	High expression of LRG1 is an independent favorable prognostic factor	[92]
Oral cancer	Serum	Increase	Early diagnostic and screening tool	[94]
Breast cancer	Tumor tissue	Increase	High expression of LRG1 is associated with poor prognosis	[83]
Gastric cancer	Serum	Increase	Diagnostic marker of gastric cancer High expression of LRG1 is associated with poor prognosis	[67]
	Tumor tissue	Increase	LRG1 stimulates proliferation and angiogenesis	[56]
Ovarian cancer	Serum	Increase	LRG1 is associated with tumor load	[87]
Retinoblastoma	Tumor tissue	Increase		[95]
Head and neck squamous cell carcinoma	Tumor tissue	Decrease	LRG1 is related to the occurrence of tumors Early diagnostic tool	[89]
Clear cell carcinoma of the kidney	Tumor tissue	Increase	Low-level LRG1 is associated with longer survival in patients	[85]
Melanoma	Tumor tissue	Increase	LRG1 promotes migration, invasion, adhesion, and lung metastasis	[71]
Thyroid cancer	Tumor tissue	Increase	High expression of LRG1 predicted poor survival and late tumor stage	[69]
Prostate cancer	Serum	Increase	High-level of LRG1 is associated with higher risk of disease-progression and mortality	[88]
	Serum Tumor tissue		High-level of LRG1 predicts reduced risk of disease recurrence and progression in prostate cancer patients who undergo prostatectomy	[91]

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