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· 基础研究 ·

富亮氨酸 α 2糖蛋白1在乳腺癌中的表达及其功能的生物信息学分析

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摘要

背景与目的: 富亮氨酸 α 2糖蛋白1 (LRG1) 是富亮氨酸重复序列 (LRR) 家族蛋白成员, 近些年研究显示 LRG1 在恶性肿瘤的发生、上皮间质转化、侵袭转移、异常血管生成、预后预测中发挥重要作用。然而 LRG1 在乳腺癌中的表达、预后、功能和潜在机制方面尚待阐明。本研究旨在通过生物信息学方法系统分析 LRG1 在乳腺癌中的表达及意义。

方法: 使用 TCGA、Breast Cancer Gene-Expression Miner、UALCAN、Kaplan-Meier Plotter、GeneMANIA、DAVID 等多个数据库对 LRG1 在乳腺癌中的表达与临床病理特征关系、预后价值、相互蛋白作用网络及功能富集进行综合分析。

结果: TCGA 数据库分析显示, LRG1 mRNA 在乳腺浸润癌中的表达量明显高于正常组织 (23.461 vs. 8.357, $P < 0.001$)。在不同分子亚型中, luminal 型乳腺癌中 LRG1 mRNA 表达量为 37.462 (9.930~74.197), 高于 HER-2 阳性型乳腺癌和三阴性乳腺癌 (TNBC) (均 $P < 0.01$); I、II、III 期乳腺癌中 LRG1 mRNA 的表达水平均高于正常乳腺组织 (均 $P < 0.05$)。Breast Cancer Gene-Expression Miner 数据库分析显示, 雌激素受体 (ER) 和 (或) 孕激素受体 (PR) 阳性乳腺癌中 LRG1 mRNA 的表达水平高于 ER 和 (或) PR 阴性乳腺癌, HER-2 阴性乳腺癌中 LRG1 mRNA 表达高于 HER-2 阳性型乳腺癌 (均 $P < 0.05$); 淋巴结阳性乳腺癌 LRG1 mRNA 表达量高于淋巴结阴性乳腺癌 ($P < 0.0001$)。用 GEPIA 在线平台对 TCGA 数据库中乳腺癌数据进行生存分析发现, LRG1 高表达患者总生存率 (OS) 及无复发生存率 (RFS) 均低于低表达患者, 但差异无统计学意义 ($HR=0.81$, $P=0.200$; $HR=0.70$, $P=0.064$); 用 Kaplan-Meier plotter 对 TCGA 中乳腺癌数据进行生存分析发现, LRG1 的表达与 luminal A 型、luminal B 型、HER-2 阳性型乳腺癌的 OS 无明显关系 (均 $P > 0.05$), 但在 basal-like 亚型中, LRG1 低表达患者 OS 明显优于 LRG1 高表达患者 ($HR=3.12$, 95% $CI=1.54\sim6.29$, $P < 0.001$)。使用 GeneMANIA 数据库进行分析, 共筛选出 20 个与 LRG1 相互作用蛋白质, GO 富集分析显示, LRG1 及其共表达相关的 20 个蛋白富集于细胞外区, 外泌体, 血液微粒, 受体复合物等结构中, 参与细胞的血管生成调控、上皮间质转化、缺氧反应等相关生物学过程。

结论: LRG1 在乳腺癌组织中表达上调, 并可预测部分不良乳腺癌亚型的预后, LRG1 可能为乳腺癌治疗提供新的靶点。

关键词

乳腺肿瘤; 富亮氨酸 α 2糖蛋白1; 预后; 计算生物学

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Bioinformatics analysis of expression of leucine-rich $\alpha 2$ glycoprotein 1 in breast cancer and its function

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Abstract

Background and Aims: Leucine-rich $\alpha 2$ glycoprotein 1 (LRG1) is a member of the leucine-rich repeat (LRR) protein family. Recent studies have shown that LRG1 plays an important role in the occurrence, epithelial-mesenchymal transformation, invasion and metastasis, abnormal angiogenesis and prognosis of malignant tumors. However, the research on the expression, prognosis, function and potential mechanism of LRG1 in breast cancer remains to be elucidated. The purpose of this study was to systematically analyze the LRG1 expression in breast cancer and its significance based on bioinformatics approaches.

Methods: The expression of LRG1 in breast cancer and its relationship with clinicopathologic characteristics, prognostic value, interacting protein networks and functional enrichment were systematically analyzed by using the TCGA, Breast Cancer Gene-Expression Miner, UALCAN, Kaplan-Meier Plotter, GeneMANIA, DAVID and other databases.

Results: TCGA database analysis showed that the mRNA expression of LRG1 in breast invasive carcinoma was significantly higher than normal tissues (23.461 vs. 8.357, $P < 0.001$). Among different molecular subtypes, LRG1 mRNA expression level in luminal subtype breast cancer was 37.462 (9.930–74.197), which was higher than that in HER-2 positive subtype and triple-negative subtype (both $P < 0.01$); the LRG1 mRNA expression levels in stage I, II and III breast cancer were all higher than that in normal breast tissue (all $P < 0.05$). Breast Cancer Gene-Expression Miner database analysis showed that the LRG1 mRNA expression levels in estrogen receptor (ER) and (or) progesterone receptor (PR) positive breast cancer were higher than those in ER and (or) PR negative breast cancer, and the LRG1 mRNA expression level in HER-2 negative breast cancer was higher than that in HER-2 positive breast cancer (all $P < 0.05$); the LRG1 mRNA expression level in lymph node-positive breast cancer was higher than that in lymph node-negative breast cancer ($P < 0.000 1$). Analysis of the TCGA survival data using the GEPIA online platform showed that both the overall survival (OS) and recurrence-free survival (RFS) rates in patients with high LRG1 expression were lower than those in patients with low LRG1 expression, but the differences did not reach a statistical significance ($HR = 0.81$, $P = 0.200$; $HR = 0.70$, $P = 0.064$); analysis of the TCGA survival data using Kaplan-Meier plotter revealed that LRG1 expression was not significantly correlated with the OS in luminal A, luminal B, and HER-2 positive subtypes (all $P > 0.05$), but in the basal-like subtype breast cancer, the OS in patients with low LRG1 expression was better than that in patients with high LRG1 expression ($HR = 3.12$, 95% $CI = 1.54-6.29$, $P < 0.001$). Using the GeneMANIA database for analysis, a total of 20 proteins interacting with LRG1 were screened. GO enrichment analysis showed that the LRG1 and the 20 its co-expression associated proteins were enriched in the extracellular regions, exosomes, blood particles, receptor complexes and other structures, and were involved in cell angiogenesis regulation, epithelial-mesenchymal transformation, hypoxia response and other relevant biological processes.

Conclusion: LRG1 expression is upregulated in breast invasive carcinoma and can predict the prognosis of some unfavorable subtypes of breast cancer. LRG1 may provide a new target for breast cancer treatment.

Key words Breast Neoplasms; Leucine-Rich α 2 Glycoprotein 1; Prognosis; Computational Biology

CLC number: R737.9

目前, 乳腺癌已成为威胁女性健康最常见的恶性肿瘤之一, 其发病率逐年上升。世界卫生组织国际癌症研究机构 (international agency for research on cancer, IARC) 发布的2020年全球最新癌症数据显示: 乳腺癌新发病例226万例, 已超过肺癌成为全球第一大癌症^[1]。近年来, 随着新型药物的开发和精准治疗的不断推进, 乳腺癌的治疗已由传统经验模式过渡到基于不同分子分型的个体化精准治疗时代^[2-3]。不断开发新的分子标志物和靶向治疗药物, 可以更精准化地改善乳腺癌患者的预后。

富亮氨酸 α 2 糖蛋白 1 (leucine-rich- α -2-glycoprotein1, LRG1) 是富亮氨酸重复序列 (leucine-rich repeat, LRR) 蛋白家族成员, 也是最早被发现的含有LRR结构的蛋白。近些年研究显示 LRG1 在肿瘤的发生、上皮间质转化、侵袭转移、异常血管生成、预后预测中扮演着重要角色^[4-7]。然而, 目前LRG1在乳腺癌组织中表达与临床病理特征的关系、预后价值、分子功能和作用机制尚未阐明。本研究旨在通过生物信息学方法, 明确LRG1在乳腺癌中的表达特点及其与预后的关系, 以期揭示LRG1在乳腺癌发生发展中的作用, 为进一步探索LRG1的分子机制奠定基础。

1 材料与方法

1.1 数据采集

癌症基因组图谱 (the cancer genome atlas, TCGA) 数据库 (<http://www.tcg.org>) 中包括乳腺癌组织及正常组织中RNA-seq的测序结果^[8]。利用UALCAN在线工具 (<http://www.ualcan.path.uab.edu>)^[9]分析TCGA数据库中LRG1 mRNA的表达情况。

1.2 生存分析

利用GEPIA (<http://gepia.cancer-pku.cn>)^[10]、Kaplan-Meier plotter (<http://kmplot.com/analysis>)^[11]平台获取TCGA数据库中乳腺癌患者的临床特征及生存资料, 分析LRG1的表达与总生存期 (overall survival, OS) 和无复发生存期 (recurrence-free survival, RFS) 之间的关系, 并绘制Kaplan-Meier曲线。

1.3 功能分析

利用GeneMANIA数据库^[12]绘制LRG1相关的蛋白、遗传相互作用通路和蛋白共表达网络。利用DAVID数据库^[13]进行基因功能富集分析, 了解与LRG1相互作用的关键基因以及参与的细胞组分、生物过程、生物功能。

1.4 统计学处理

使用TPM (transcripts per million) 作为LRG1 mRNA表达量度, 表达量使用中位数 (四分位间距) 来表示。采用Kaplan-Meier生存曲线对LRG1高、低表达组患者进行生存比较, 计算95%置信区间 (CI) 的危险比 (HR) 和Log-rank *P*值。统计检验均采用双侧检验, *P*<0.05为差异有统计学意义。

2 结果

2.1 LRG1在乳腺癌中的表达及其与分子亚型、分期、淋巴结转移关系

使用UALCAN在线工具分析TCGA中1 097例乳腺浸润性癌和114例正常乳腺组织的数据, 结果显示LRG1 mRNA在正常乳腺组织中位表达量为8.357 (4.402~14.021), 在乳腺癌组织中表达量为23.461 (3.158~63.676), LRG1在乳腺癌组织中表达明显高于正常乳腺组织 (*P*<0.000 1) (图1)。

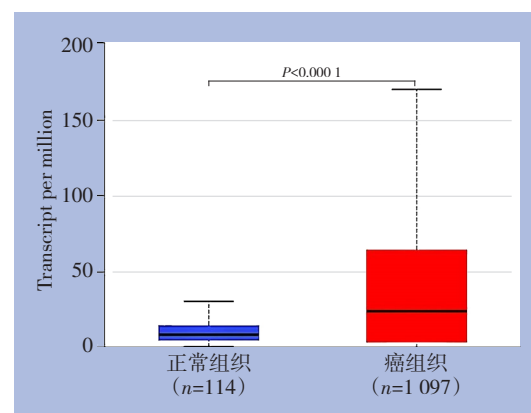


图1 LRG1在乳腺浸润性癌及癌旁正常组织中表达 (UALCAN)

Figure 1 LRG1 expressions in invasive breast carcinoma and normal tissue (UALCAN)

进一步分析乳腺癌不同亚型中LRG1的表达, 566例luminal型乳腺癌中LRG1表达量为37.462 (9.93~74.197), 高于HER-2阳性型和三阴性乳腺癌 (triple-negative breast cancer, TNBC) ($P < 0.01$)。37例HER-2阳性型乳腺癌组织中LRG1表达量为3.609 (0.852~29.732), 116例TNBC组织中表达量为1.028 (0.516~4.027) (图2)。

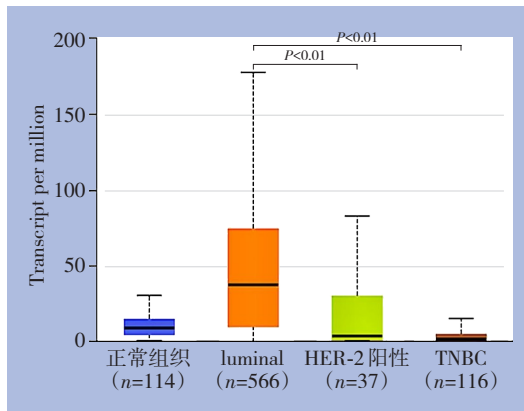


图2 LRG1在乳腺癌不同亚型中表达 (UALCAN)

Figure 2 LRG1 expressions in different subtypes of breast cancer (UALCAN)

进一步分析LRG1在不同临床分期乳腺癌中表达情况。183例I期乳腺癌组织中LRG1表达量为34.684 (3.036~84.648), 615例II期乳腺癌中表达量为22.553 (3.036~84.648), 在247例III期乳腺癌中表达量为22.677 (4.347~52.772), 在20例IV期乳腺癌组织中表达量为13.667 (3.931~22.511)。I、II、III期乳腺癌中LRG1 mRNA的表达水平均高于

正常乳腺组织 (均 $P < 0.05$) (图3)。

分析Breast Cancer Gene-Expression Miner数据库 (包含TCGA数据库中1 034例乳腺癌)^[14]中3 911例ER阳性、551例ER阴性、3 498例PR阳性和828例PR阴性乳腺癌, 发现LRG1在ER、PR双阳性乳腺癌中的表达明显高于ER、PR均阴性乳腺癌, 差异有统计学意义 ($P < 0.000 1$)。ER阳性、PR阳性组表达水平高于ER阴性、PR阳性组, 差异有统计学意义 ($P < 0.000 1$)。3 582例HER-2阴性组LRG1表达高于661例HER-2阳性组, 差异有统计学意义 ($P < 0.000 1$) (图4)。根据淋巴结转移情况进一步分析显示, LRG1在1 646例淋巴结阳性患者中的表达高于2 415例淋巴结阴性组, 差异具有统计学意义 ($P = 0.007 0$) (图5)。

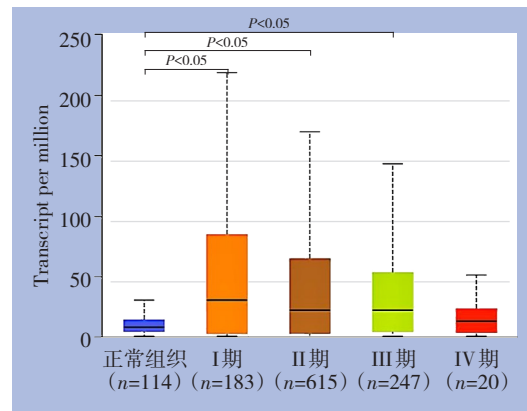


图3 LRG1在乳腺癌不同分期中表达 (UALCAN)

Figure 3 LRG1 expressions in breast cancer of different stages (UALCAN)

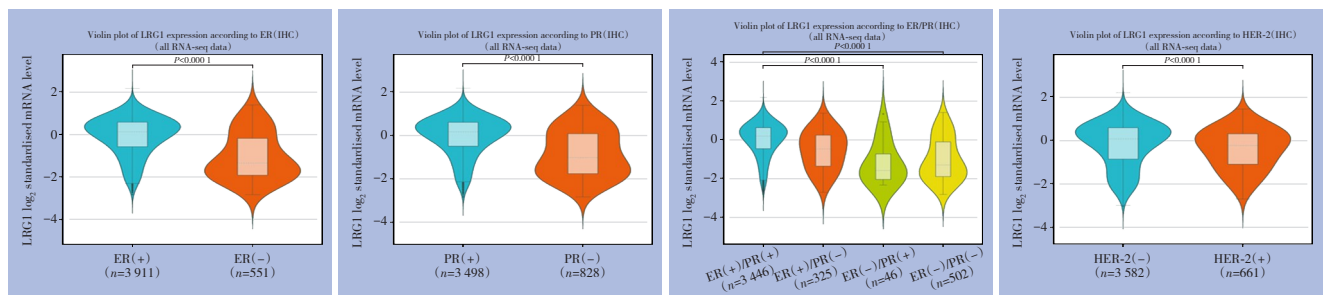


图4 LRG1在不同激素受体状态乳腺癌中的表达 (bc-GenExMiner)

Figure 4 LRG1 expressions in breast cancer with different hormone receptor statuses (bc-GenExMiner)

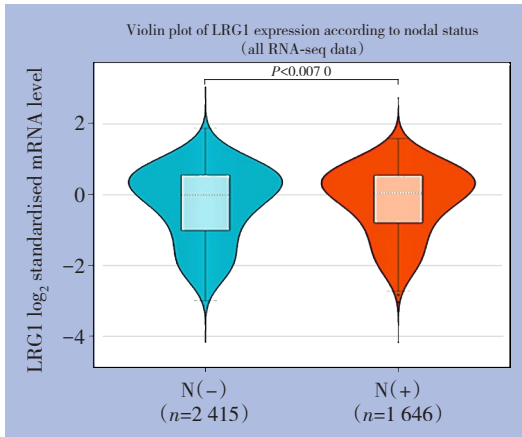


图5 LRG1在不同淋巴结状态乳腺癌中的表达 (bc-GenExMiner)

Figure 5 LRG1 expressions in breast cancer with different lymph node statuses (bc-GenExMiner)

2.2 LRG1 的表达与乳腺癌预后关系

利用 GEPIA 在线平台，分析 TCGA 数据库中 1 070 例乳腺浸润性癌患者的 OS 及 RFS，并绘制生存曲线。结果显示：随着随访时间的延长，535 例 LRG1 高表达组患者 OS 及 RFS 均低于 535 例低表达组，但差异未达统计学意义 ($HR=0.81, P=0.2$; $HR=0.7, P=0.064$) (图 6)。利用 Kaplan-Meier plotter 在线工具分析 TCGA 数据库中不同分子亚型预后，LRG1 的表达与 luminal A 型、luminal B 型、HER-2 阳性型乳腺癌的 OS 无明显关系 (均 $P>0.05$)，但在 basal-like 亚型中，LRG1 的表达却与 OS 明显相关，LRG1 表达低的患者 OS 更好 ($HR=3.12, 95\% CI=1.54\sim 6.29, P=0.000 84$) (图 7)。

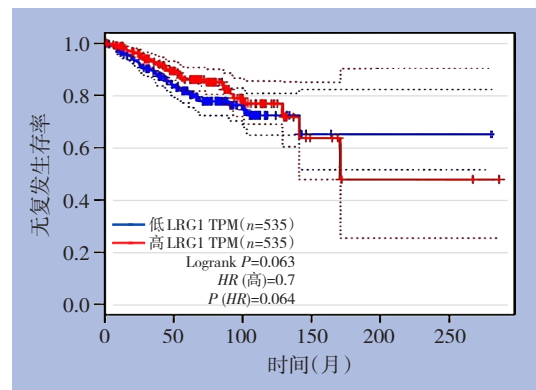
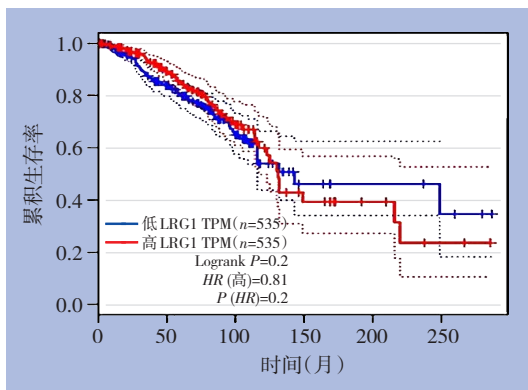


图6 LRG1 表达与乳腺癌的预后的关系 (GEPIA)

Figure 6 Relationship of LRG1 expression with the prognosis of breast cancer (GEPIA)

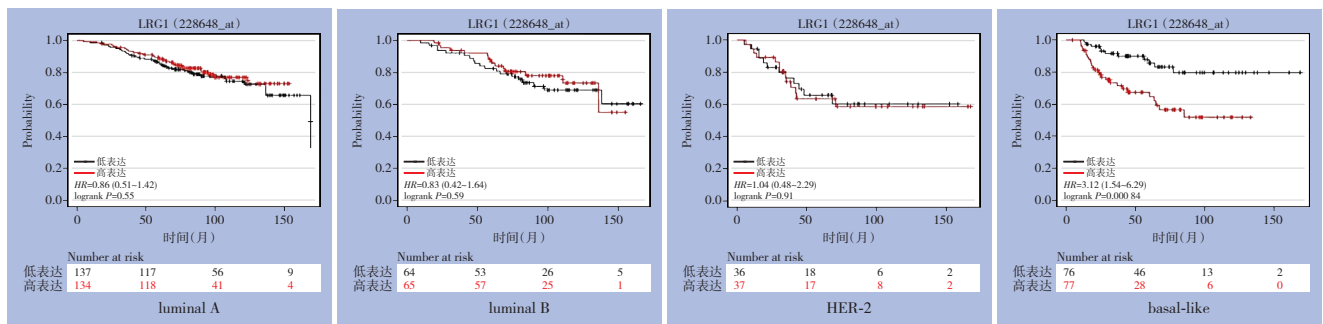


图7 不同分子亚型乳腺癌中 LRG1 的表达与 OS 的关系 (Kaplan-Meier plotter)

Figure 7 Relationship of LRG1 expression with the OS in breast cancer of different subtypes (Kaplan-Meier plotter)

2.3 LRG1 相互蛋白作用网络预测及功能分析

利用 GeneMANIA 数据库分析筛选出 20 个与 LRG1 相互作用蛋白质，分别为 CYCS、NME2、ACVRL1、ENG、TGFB1、TGFB2、CFB、FGGY、

C2、SDS、ORM2、HAL、CEBPA、CRP、C4BPA、CEBPE、SAA2、IGFALS、HAMP、PJA1。其相互作用关系包括物理相互作用、共表达、相互预测、共定位，遗传相互作用 (图 8)。

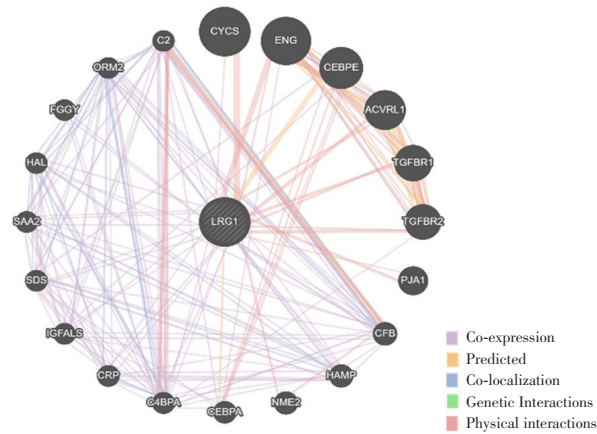


图8 LRG1相互作用蛋白网络分析

Figure 8 Analysis of LRG1 interacting protein network

2.4 GO分析

利用DAVID数据库进行GO富集分析,结果显示,LRG1及其共表达相关的20个蛋白富集于细胞外区,外泌体,血液微粒,受体复合物等结构中,共同参与细胞的血管生成调控、上皮间质转化的转化、缺氧反应等相关生物学过程(图9)。

3 讨论

早期研究^[15]认为LRG1可能是中性粒细胞早期分化的标志物。随着分子生物学不断发展,LRG1其他功能陆续被发现:它不仅参与细胞蛋白间的相互作用,同时在信号转导、细胞黏附及细胞发育过程中也发挥重要作用,尤其在肿瘤的发生、上皮间质转化、侵袭转移和异常血管生成中也扮演了重要角色。

LRG1在多种恶性肿瘤组织中的表达呈上调状

态。Hong等^[6]发现肾透明细胞癌中LRG1存在过表达,并与患者生存率呈负相关。Li等^[16]报道在非小细胞肺癌的尿样和肺癌组织中LRG1表达明显升高。Andersen等^[17]通过Western blot技术检查了58例卵巢癌患者血清、肿瘤组织和细胞系中LRG1的表达,与对照组相比,LRG1在卵巢癌患者的血清和肿瘤组织中均存在表达上调。在胰腺疾病中,与慢性胰腺炎患者和健康志愿者相比,胰腺癌患者血清中LRG1水平显著升高,并且LRG1表达水平随着胰腺癌疾病进展而升高^[18]。本研究结果发现LRG1在浸润性乳腺癌组织中表达明显高于正常组织。笔者先前研究^[19]通过免疫组化技术检测了330例原发性乳腺癌组织中LRG1蛋白的表达,结果显示,LRG1蛋白在乳腺癌组织中的阳性表达率为58.48%(193/330),较正常乳腺组织明显升高。根据数据库的分析和蛋白表达的验证表明,乳腺癌组织中LRG1mRNA与蛋白表达均明显上调。TCGA数据库中显示LRG1在不同分子亚型中表达存在差异性,luminal型乳腺癌中LRG1表达显著高于HER-2阳性型乳腺癌和TNBC。但不同观点认为LRG1和PLCL1的表达与luminal亚型无关。先前的研究^[19]同样未发现LRG1蛋白在不同分子亚型中未呈现差异。分析原因,可能与研究入组样本数和组织异质性相关,未来仍需进一步扩大样本量再次进行验证。

LRG1在肿瘤发生和发展过程中的作用仍不明确。Zhong等^[21]报道沉默LRG1可减少细胞周期蛋白B、D1和E的表达,并使细胞抑制在G_{0/1}期。脑胶质瘤细胞中LRG1过表达后出现TGF- β 1、P-Smad2和P-Smad3蛋白水平上调,E-cadherin蛋白水平下降,而Smad2/3的活化可促进细胞侵袭和迁

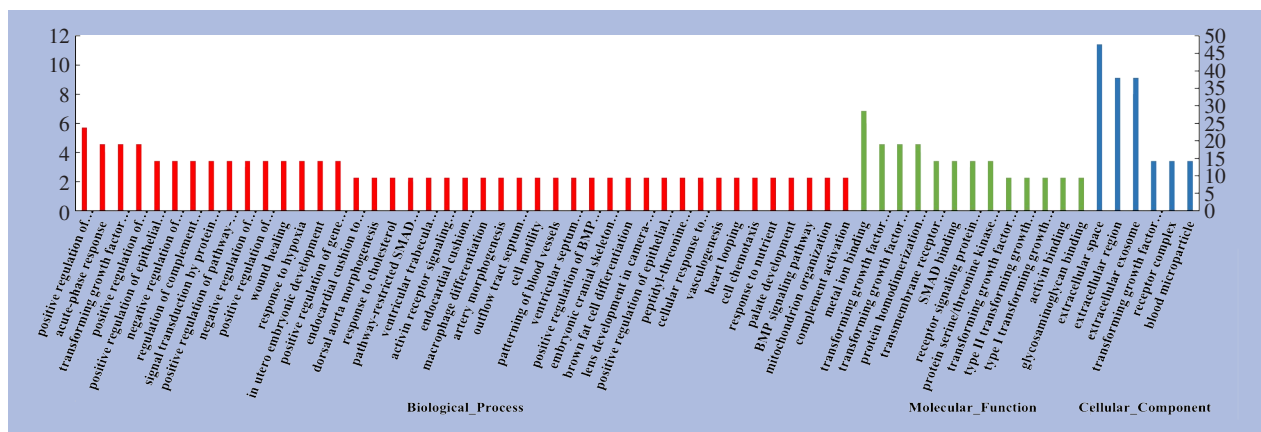


图9 LRG1相关蛋白参与的细胞生物学过程、分子功能及细胞组分

Figure 9 Cellular biological processes, molecular functions and cellular components of LRG1 related proteins

移^[22]。LRG1在视网膜血管疾病可能是通过TGF- β 信号传导通路促进肿瘤血管生成^[23-25]。李金梅等^[26]报道胃癌组织中LRG1蛋白的表达与肿瘤微血管密度(MVD)相关,推测LRG1通过调节TGF- β 信号通路促进胃癌中微血管的生成。Ronald等^[27]研究证实LRG1与凋亡激活因子1(Apaf-1)竞争性结合细胞色素c(Cyt c),抑制MCF-7细胞凋亡。Ban等^[28]报道LRG1在甲状腺癌中表达与存活率低和肿瘤分期晚相关。本研究发现LRG1在淋巴结阳性组患者中的表达高于淋巴结阴性组,提示LRG1与乳腺癌局部进展可能有关。富集分析发现LRG1及其共表达相关的20个蛋白富集于细胞胞外区、外泌体、血液微粒及受体复合物等结构中,共同参与了细胞的血管生成调控、上皮间充质的转化、缺氧反应等相关生物学过程。LRG1在肿瘤的发生、发展中可能涉及多个通路,通过进一步的基础研究实验阐明其作用机制,可能为乳腺癌提供新的治疗靶点,从而进一步改善患者预后。

LRG1在肿瘤预后预测方面也有相关报道。Sun等^[7]报道在III期结直肠癌中,LRG1蛋白表达与MVD和其他临床病理参数密切相关,包括肿瘤T分期、组织分化和血管浸润,Cox多元回归分析显示LRG1蛋白是DFS和OS独立的不良预测因素。梁栋等^[29]报道在子宫内膜癌患者中,LAPTM4B-35、LRG1高表达患者术后5年生存率差于低表达者。Wang等^[30]研究显示,LRG1在肝癌组织中的表达显著增加,LRG1与OS、DFS密切相关,多元Cox回归模型分析表明LRG1是OS和DFS的独立不良预后因素。在本研究中,TCGA数据库中生存分析结果显示:LRG1的表达与luminal A型、luminal B、HER-2阳性型乳腺癌的OS无明显关系,但在basal-like亚型中,LRG1的表达与OS呈显著相关,LRG1低表达的患者OS更好($HR=3.12$, $95\% CI=1.54\sim 6.29$, $P<0.001$)。LRG1在basal-like亚型乳腺癌中具体作用仍不明确。Hanif等^[31]报道LRG1表达上调可导致TNBC细胞中出现明显FEC化疗方案药物耐药,可能导致不良预后。其他观点^[20]认为LRG1表达与乳腺癌的OS和无进展生存期相关,推测可能原因是后者纳入研究人群主要为既往接受新辅助治疗的乳腺癌患者。LRG1在乳腺癌中预后预测价值未来仍需大样本数据进行验证。

本研究仅对数据库中乳腺癌LRG1的表达进行了差异分析和预后探索,缺少体内和体外实验证据支持。此外,对于LRG1在乳腺癌中的具体作用机制

缺乏了解,后期将通过设计具体实验进一步探索LRG1在乳腺癌发生发展中的机制。

综上所述,LRG1在乳腺癌组织中呈现高表达,淋巴结阳性患者中LRG1表达明显高于阴性组,且与basal-like亚型乳腺癌患者不良预后相关。在未来抗肿瘤治疗中,LRG1有可能作为一种新的肿瘤分子标志物,为乳腺癌的诊断和治疗提供新的思路。

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参考文献

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020[J]. CA Cancer J Clin, 2020, 70(1):7-30. doi: 10.3322/caac.21590.
- [2] 江泽飞,许凤锐. 乳腺癌精准治疗:20年探索历程[J]. 中国实用外科杂志, 2020, 40(1): 83-88. doi: 10.19538/j. cjps. issn1005-2208.2020.01.15.
- [3] 江泽飞,李健斌,李峰. 乳腺癌治疗决策:经验到循证精准到智能[J]. 中国实用外科杂志, 2018, 38(11): 1222-1226. doi: 10.19538/j. cjps. issn1005-2208.2018.11.02.
- [4] 江泽飞, Li JB, Li F. Breast cancer treatment: From experience to evidence, from precision to artificial intelligence[J]. Chinese Journal of Practical Surgery, 2018, 38(11): 1222-1226. doi: 10.19538/j. cjps. issn1005-2208.2018.11.02.
- [5] Zhang Q, Huang R, Tang Q, et al. Leucine-rich alpha-2-glycoprotein-1 is up-regulated in colorectal cancer and is a tumor promoter[J]. Onco Targets Ther, 2018, 11:2745-2752. doi: 10.2147/OTT.S153375.
- [6] Zhong ME, Chen Y, Xiao Y, et al. Serum extracellular vesicles contain SPARC and LRG1 as biomarkers of colon cancer and differ by tumour primary location[J]. EBioMedicine, 2019, 50:211-223. doi: 10.1016/j. ebiom.2019.11.003.
- [7] Hong Q, Wang S, Liu S, et al. LRG1 May Accelerate the Progression of ccRCC via the TGF- β Pathway[J]. Biomed Res Int, 2020, 2020:1285068. doi: 10.1155/2020/1285068.
- [8] Sun DC, Shi Y, Wang LX, et al. Leucine-rich alpha-2-glycoprotein-1, relevant with microvessel density, is an independent survival prognostic factor for stage III colorectal cancer patients: a retrospective analysis[J]. Oncotarget, 2017, 8(39): 66550-66558. doi: 10.18632/oncotarget.16289.
- [9] Wang Z, Jensen MA, Zenklusen JC. A Practical Guide to The Cancer Genome Atlas (TCGA)[J]. Methods Mol Biol, 2016, 1418: 111-141. doi: 10.1007/978-1-4939-3578-9_6.
- [10] Chandrashekar DS, Bashel B, Balasubramanya SAH, et al. UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses[J]. Neoplasia, 2017, 19(8):649-658. doi: 10.1016/j. neo.2017.05.002.
- [11] Tang Z, Li C, Kang B, et al. GEPIA: a web server for cancer and

- normal gene expression profiling and interactive analyses[J]. *Nucleic Acids Res*, 2017, 45(W1): W98–102. doi: [10.1093/nar/gkx247](https://doi.org/10.1093/nar/gkx247).
- [11] Nagy Á, Munkácsy G, Györfy B. Pancancer survival analysis of cancer hallmark genes[J]. *Sci Rep*, 2021, 11(1):6047. doi: [10.1038/s41598-021-84787-5](https://doi.org/10.1038/s41598-021-84787-5).
- [12] Warde-Farley D, Donaldson SL, Comes O, et al. The GeneMANIA prediction server: biological network integration for gene prioritization and predicting gene function[J]. *Nucleic Acids Res*, 2010, 38(Web Server issue):W214–220. doi: [10.1093/nar/gkq537](https://doi.org/10.1093/nar/gkq537).
- [13] Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources[J]. *Nat Protoc*, 2009, 4(1): 44–57. doi: [10.1038/nprot.2008.211](https://doi.org/10.1038/nprot.2008.211).
- [14] Jézéquel P, Gouraud W, Ben Azzouz F, et al. bc-GenExMiner 4.5: new mining module computes breast cancer differential gene expression analyses[J]. *Database (Oxford)*, 2021, 2021: baab007. doi: [10.1093/database/baab007](https://doi.org/10.1093/database/baab007).
- [15] O'Donnell LC, Druhan LJ, Avalos BR. Molecular characterization and expression analysis of leucine-rich alpha2-glycoprotein, a novel marker of granulocytic differentiation [J]. *J Leukoc Biol*, 2002, 72(3):478–485.
- [16] Li Y, Zhang Y, Qiu F, et al. Proteomic identification of exosomal LRG1: a potential urinary biomarker for detecting NSCLC [J]. *Electrophoresis*, 2011, 32(15): 1976–1983. doi: [10.1002/elps.201000598](https://doi.org/10.1002/elps.201000598).
- [17] Andersen JD, Boylan KL, Jemmerson R, et al. Leucine-rich alpha-2-glycoprotein-1 is upregulated in sera and tumors of ovarian cancer patients[J]. *J Ovarian Res*, 2010, 3:21. doi: [10.1186/1757-2215-3-21](https://doi.org/10.1186/1757-2215-3-21).
- [18] Furukawa K, Kawamoto K, Eguchi H, et al. Clinicopathological Significance of Leucine-Rich α 2-Glycoprotein-1 in Sera of Patients with Pancreatic Cancer[J]. *Pancreas*, 2015, 44(1): 93–98. doi: [10.1097/MPA.0000000000000205](https://doi.org/10.1097/MPA.0000000000000205).
- [19] Zhang YS, Han L, Yang C, et al. Prognostic Value of LRG1 in Breast Cancer: A Retrospective Study[J]. *Oncol Res Treat*, 2021, 44(1/2):36–42. doi: [10.1159/000510945](https://doi.org/10.1159/000510945).
- [20] Ramirez-Ardila DE, Ruigrok-Ritstier K, Helmijr JC, et al. LRG1 mRNA expression in breast cancer associates with PIK3CA genotype and with aromatase inhibitor therapy outcome[J]. *Mol Oncol*, 2016, 10(8):1363–1373. doi: [10.1016/j.molonc.2016.07.004](https://doi.org/10.1016/j.molonc.2016.07.004).
- [21] Zhong D, Zhao S, He G, et al. Stable knockdown of LRG1 by RNA interference inhibits growth and promotes apoptosis of glioblastoma cells in vitro and in vivo[J]. *Tumour Biol*, 2015, 36(6): 4271–4278. doi: [10.1007/s13277-015-3065-3](https://doi.org/10.1007/s13277-015-3065-3).
- [22] Valcourt U, Kowanez M, Niimi H, et al. TGF-beta and the Smad signaling pathway support transcriptomic reprogramming during epithelial mesenchymal cell transition [J]. *Mol Biol Cell*, 2005, 16(4):1987–2002. doi: [10.1091/mbc.e04-08-0658](https://doi.org/10.1091/mbc.e04-08-0658).
- [23] Amer R, Tiosano L, Pe'er J. Leucine-Rich α -2-Glycoprotein-1 (LRG-1) Expression in Retinoblastoma[J]. *Invest Ophthalmol Vis Sci*, 2018, 59(2):685–692. doi: [10.1167/iovs.17-22785](https://doi.org/10.1167/iovs.17-22785).
- [24] Chen C, Chen X, Huang H, et al. Elevated plasma and vitreous levels of leucine-rich- α 2-glycoprotein are associated with diabetic retinopathy progression[J]. *Acta Ophthalmol*, 2019, 97(3):260–264. doi: [10.1111/aos.13633](https://doi.org/10.1111/aos.13633).
- [25] Wang X, Abraham S, McKenzie JA, et al. LRG1 promotes angiogenesis by modulating endothelial TGF-beta signalling[J]. *Nature*, 2013, 499(7458):306–311. doi: [10.1038/nature12345](https://doi.org/10.1038/nature12345).
- [26] 李金梅, 刘艳茹, 陈红, 等. 胃癌中LRG1的表达与肿瘤微血管生成的关系[J]. *广东医学*, 2018, 39(19):2903–2906. doi: [10.3969/j.issn.1001-9448.2018.19.012](https://doi.org/10.3969/j.issn.1001-9448.2018.19.012).
- Li JM, Liu YR, Chen H, et al. Relationship between LRG1 expression and tumor microangiogenesis in gastric cancer[J]. *Guangdong Medical Journal*, 2018, 39(19): 2903–2906. doi: [10.3969/j.issn.1001-9448.2018.19.012](https://doi.org/10.3969/j.issn.1001-9448.2018.19.012).
- [27] Jemmerson R, Staskus K, Higgins L, et al. Intracellular leucine-rich alpha-2-glycoprotein-1 competes with Apaf-1 for binding cytochrome c in protecting MCF-7 breast cancer cells from apoptosis[J]. *Apoptosis*, 2021, 26(1/2): 71–82. doi: [10.1007/s10495-020-01647-9](https://doi.org/10.1007/s10495-020-01647-9).
- [28] Ban Z, He J, Tang Z, et al. LRG1 enhances the migration of thyroid carcinoma cells through promotion of the epithelial-mesenchymal transition by activating MAPK/p38 signaling[J]. *Oncol Rep*, 2019, 41(6):3270–3280. doi: [10.3892/or.2019.7123](https://doi.org/10.3892/or.2019.7123)
- [29] 梁栋, 李维茹, 钟沛文, 等. 子宫内瘤组织LAPTM4B-35和LRG1表达变化及其临床意义[J]. *山东医药*, 2018, 58(36):71–73. doi: [10.3969/j.issn.1002-266X.2018.36.020](https://doi.org/10.3969/j.issn.1002-266X.2018.36.020).
- Liang D, Li WR, Zhong PW, et al. Expression of LAPTM4B-35 and LRG1 in endometrial carcinoma and its clinical significance[J]. *Shandong Medical Journal*, 2018, 58(36): 71–73. doi: [10.3969/j.issn.1002-266X.2018.36.020](https://doi.org/10.3969/j.issn.1002-266X.2018.36.020).
- [30] Wang CH, Li M, Liu LL, et al. LRG1 expression indicates unfavorable clinical outcome in hepatocellular carcinoma[J]. *Oncotarget*, 2015, 6(39): 42118–42129. doi: [10.18632/oncotarget.5967](https://doi.org/10.18632/oncotarget.5967).
- [31] Mohamad Hanif EA. Dysregulation of non-histone molecule miR205 and LRG1 post-transcriptional de-regulation by SETD1A in triple negative breast cancer[J]. *Mol Biol Rep*, 2019, 46(6):6617–6624. doi: [10.1007/s11033-019-05079-w](https://doi.org/10.1007/s11033-019-05079-w).

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