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LRRFIP1调控结直肠癌细胞凋亡及相关信号通路的研究进展

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摘　要

结直肠癌(CRC)是全球最常见的消化道恶性肿瘤之一，其发生发展与细胞凋亡密切相关。近年来有多项研究发现，亮氨酸富重复无飞相互作用蛋白1 (LRRFIP1)在多种癌症中呈现表达趋势，并能通过抑制死亡受体通路而削弱肿瘤细胞对凋亡诱导的敏感性。本文围绕“LRRFIP1 – TNFα/FADD – 细胞凋亡”这一轴心，旨在介绍LRRFIP1的分子特征、TNFα/FADD通路的凋亡调控机制、LRRFIP1-TNFα/FADD轴在CRC中的临床意义及靶向策略，并对未来研究方向进行展望，以期为CRC治疗提供新的理论依据。

关键词

LRRFIP1，TNFα，FADD，细胞凋亡，结直肠癌

Progress in Research on LRRFIP1 Regulation of Colorectal Cancer Cell Apoptosis and Related Signaling Pathways

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Abstract

Colorectal cancer (CRC) is one of the most common malignant tumors of the digestive tract worldwide, and its occurrence and development are closely related to cell apoptosis. In recent years, multiple studies have found that Leucine-Rich Repeat Flightless-Interacting Protein 1 (LRRFIP1) shows expression trends in various cancers and can weaken tumor cells' sensitivity to apoptosis induction by inhibiting the death receptor pathway. This article centers on the "LRRFIP1 - TNFα/FADD - cell

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apoptosis" axis, aiming to introduce the molecular characteristics of LRRFIP1, the apoptosis regulatory mechanism of the TNFα/FADD pathway, the clinical significance and targeted strategies of the LRRFIP1-TNFα/FADD axis in CRC, and to project future research directions, intending to provide new theoretical basis for CRC treatment.

Keywords

LRRFIP1, TNFα, FADD, Cell Apoptosis, Colorectal Cancer

1. 结直肠癌的概述

1.1. 发病率、死亡率及全球流行趋势

结直肠癌是全球发病率和死亡率都位居前列的恶性肿瘤[1] [2]。据世界卫生组织和国际癌症研究机构发布的最新全球癌症数据显示，结直肠癌新发病例数位居第三(9.6%)，死亡病例数位居第二(9.3%)，严重威胁人类生命健康[3]。尽管结直肠癌的发病率仍然较高，但得益于时代的发展、治疗的进步以及筛查项目的广泛普及，死亡率开始呈现下降趋势[4]。在许多发展中国家，包括中国，随着生活方式的快速改变，结直肠癌的发病率和死亡率都在迅速增加[5]。在未来的时间里，全球结直肠癌的疾病负担将继续向中低收入国家转移[6] [7]，这凸显了加强早期筛查和预防体系的必要性。

1.2. 主要致病因素和发病机制简介

结直肠癌的发生发展是一个涉及多种因素和机制的复杂过程[8]-[10]。遗传性因素在所有病例中占比不可小觑[11] [12]，其中林奇综合征和家族性腺瘤性息肉病是主要的遗传致病因素[13]。环境和生活方式因素，例如高摄入红肉和加工肉类、低纤维饮食、肥胖、吸烟、过量饮酒以及缺乏体育活动，均已被证明会显著增加疾病风险[14]-[16]。在分子机制层面，结直肠癌的发展可以概括为正常肠上皮细胞在遗传和表观遗传改变的情况下，通过不同的癌变通路，逐步转化为腺瘤，最终发展为腺癌[17] [18]。其中，APC 基因的失活导致 Wnt/β-连环蛋白信号通路的持续激活，使细胞不受控制地增殖，形成最初的微小腺瘤[19] [20]。在 APC 突变的基础上，其他基因突变也会陆续积累出现[21]，而 KRAS 和 PIK3CA 等基因的突变则会推动肿瘤进展，TP53 基因的失活则与恶性转化及侵袭性转移密切相关[22]-[24]。此外，肿瘤微环境中的各种免疫细胞(调节性 T 细胞、细胞毒性 T 细胞、自然杀伤细胞等)、成纤维细胞、血管和淋巴管系统、细胞外基质也通过复杂的相互作用影响肿瘤的发生和发展[25] [26]。

2. LRRFIP1 的简介

2.1. LRRFIP1 的结构与分布

LRRFIP1 (亮氨酸富重复无飞相互作用蛋白 1)是一种由位于 2q37.3 染色体上的基因编码的多功能蛋白[27]，也称为 GCF2。在结构上，其核心功能区域包括 N 端结构域、高度保守的中央卷曲螺旋结构域(Coiled-coil domain)以及 C 端核酸结合结构域。其中，中央卷曲螺旋结构域对于 LRRFIP1 形成同源二聚体至关重要[28]，而 C 端核酸结合结构域的存在则使其能够结合双链 DNA 和双链 RNA [28] [29]。

LRRFIP1 基因通过可变剪接产生多种亚型[27]。这些亚型在组织分布和细胞内定位上呈现差异。研

究表明，LRRFIP1 在人和大鼠的神经元、星形胶质细胞等多种组织细胞中广泛表达[30] [31]。在细胞内部，LRRFIP1 主要定位于细胞质，部分亚型也存在于细胞核内[27]。值得注意的是，其亚细胞定位并非固定不变，在特定病理生理条件下(如脑缺血、氧化应激)会发生动态变化并上调表达[30]。正是这种动态变化，为 LRRFIP1 参与包括癌症在内的多种疾病的调控奠定了基础。

2.2. LRRFIP1 在细胞生物学过程中的作用

LRRFIP1 是一种多功能的调控蛋白，在转录调控、固有免疫应答及信号转导等多种生物学过程中扮演关键角色[32]。首先，LRRFIP1 的核心功能之一是作为转录抑制因子[29]。它能够直接结合特定基因启动子区域的 GC 富集序列，从而抑制下游基因的转录[29]。2025 年的一项新研究进一步揭示了其转录调控的具体机制：在白色脂肪细胞分化模型中，LRRFIP1 能够结合至 E2F6 基因的启动子区域，抑制其转录，从而下调关键分化调节因子 C/EBPα 的表达[33]。这一发现为 LRRFIP1 作为转录因子调控细胞命运提供了直接的分子证据。

其次，LRRFIP1 是胞质核酸识别受体，在机体固有免疫应答中起重要作用[34]。它能够识别并结合胞质中的双链 RNA (dsRNA)，并在病毒感染(如流感病毒)的早期被募集到含有病毒的核内体中[34]。通过激活 β-连环蛋白(β-catenin)通路，LRRFIP1 能够促进 I 型干扰素的产生，从而启动抗病毒免疫应答[34]。在信号转导方面，LRRFIP1 主要参与两条途径：一条是 β-连环蛋白非依赖的 Wnt/非经典途径，影响细胞骨架的重组；另一条是 β-连环蛋白依赖的 Wnt/经典途径，促进 c-myc 和 cyclin D1 等基因的转录[35]。

3. LRRFIP1 影响癌症发生发展的分子机制

3.1. 参与细胞增殖调控

LRRFIP1 作为促癌基因，通过调控关键信号通路驱动结直肠癌细胞的增殖。研究表明，LRRFIP1 能够激活 Akt 和哺乳动物雷帕霉素靶蛋白(mTOR)信号通路[30]。在骨髓增生异常综合征(MDS)中的研究提供了类似的机制线索：LRRFIP1 通过结合并稳定蓬乱蛋白(DVLs)，协同增强 Wnt/β-连环蛋白信号通路的活性，从而促进细胞增殖并抑制凋亡[36]。这提示在结直肠癌中，LRRFIP1 可能通过类似的通路交互作用来驱动细胞周期进程。

3.2. 侵袭和转移相关机制

LRRFIP1 是驱动结直肠癌侵袭和转移的核心因子。体内外实验证实，在结直肠癌细胞中抑制 LRRFIP1 (又名 GCF2)的表达，可以显著减少癌细胞的黏附、迁移和侵袭行为，并在小鼠脾脏注射模型中明显降低肝脏转移灶的数量[37]。其分子机制在于，LRRFIP1 通过整合素信号通路，调控下游小 GTP 酶 RhoA 的活性[37]。而 RhoA 是细胞骨架重组和细胞运动的核心调控者，LRRFIP1 通过增强 RhoA 的活性，最终赋予癌细胞更强的运动性和侵袭性[37]。

3.3. 抗凋亡机制

LRRFIP1 通过激活关键的促生存信号通路，帮助结直肠癌细胞抵抗程序性死亡。如前所述，LRRFIP1 能够激活 PI3K/Akt/mTOR 这条经典的细胞存活信号轴[31]。在 MDS 模型中的研究进一步显示，LRRFIP1 的过表达会伴随抗凋亡蛋白 BCL-2 水平升高和凋亡执行蛋白 Caspase-3 表达下降[36]，这表明其可能通过多层面构建抗凋亡网络，导致癌细胞对化疗药物产生耐受。

3.4. LRRFIP1 在 CRC 中异常表达的上游调控机制

现有证据提示，LRRFIP1 存在 miR-21 介导的转录后负调控[38]，综合遗传学分析已将 LRRFIP1 鉴

定为候选癌基因，其基因突变[37]提示了其在 CRC 发生中的潜在驱动作用，提示遗传学改变可能参与其异常调控。此外，LRRFIP1 定位于染色体 2q37.3 区域[27]，但该区域的拷贝数变异是否参与驱动其异常表达尚待进一步验证。

4. LRRFIP1 与癌症相关信号通路的相互作用

4.1. 经典信号通路

经典信号通路可分为 Wnt/β-连环蛋白信号通路和 PI3K/Akt/mTOR 信号通路[39] [40]。在 Wnt/β-连环蛋白信号通路方面，LRRFIP1 与该通路存在强效相互作用。已有研究报道，LRRFIP1 能够与通路关键转导蛋白蓬乱蛋白(DVL2 和 DVL3)直接相互作用[36] [41]。这种结合可以协同增强 Wnt/β-连环蛋白通路的活性，导致下游 β-连环蛋白水平升高，并驱动 Cyclin D1 等促增殖基因的表达，从而促进细胞增殖，推动肿瘤生长[41]。其次，PI3K/AKT 信号通路是细胞内重要的生存信号通路，在调控细胞增殖、存活、代谢和迁移中发挥关键作用[42] [43]。近年来的研究揭示，LRRFIP1 与 PI3K/AKT 通路存在密切的功能联系。通过 GSEA 分析发现，在胰腺癌中 LRRFIP1 高表达与 PI3K/AKT 信号通路的激活显著相关[44]。功能实验证实，沉默 LRRFIP1 表达可导致 AKT 及其下游底物 GSK-3β 的磷酸化水平降低，从而抑制该通路的活性。值得注意的是，AKT/GSK-3β 轴本身也是 Wnt/β-catenin 通路的上游调控者——AKT 介导的 GSK-3β 磷酸化可抑制其激酶活性，从而减少 β-catenin 的磷酸化降解，导致 β-catenin 在细胞质中积累并转位入核[45] [46]。因此，LRRFIP1 可能通过双重机制调控 Wnt 信号：一方面直接与 DVLs 相互作用促进通路活化，另一方面通过 AKT/GSK-3β 轴间接稳定 β-catenin，形成协同放大效应。

4.2. 非经典信号通路

除了上述经典生长调控通路，LRRFIP1 还深度参与整合素介导的细胞黏附与运动信号。如 3.2 节所述，LRRFIP1 通过整合素信号轴调控下游 RhoA 的活性[37]。这一过程对于癌细胞脱离原发灶、在转移微环境中定植至关重要[37]。此外，基于 LRRFIP1 作为核酸传感器和转录调控因子的多重属性[28] [29] [34]，可以推测其可能在更广泛的非经典通路中发挥功能。其中细胞应激与代谢重编程是一个值得关注的领域。肿瘤微环境中的代谢压力(如缺氧、葡萄糖缺乏、氨基酸耗竭等)和内源遗传物质应激(如胞质 DNA 泄漏)是常见的非经典致癌信号[47]-[50]。LRRFIP1 作为能感知双链 RNA/DNA 的蛋白[28]，可能参与这类应激信号的感知，进而通过调控下游的应激激酶(如 AMPK、mTORC1)或代谢相关的转录因子，影响肿瘤细胞的代谢适应性、自噬活性或促生存炎症反应，从而在肿瘤适应恶劣微环境过程中扮演重要角色。

4.3. TNFα/FADD 通路

肿瘤坏死因子 TNF 是一种具有多种生物学效应的细胞因子[51] [52]，主要由激活的单核巨噬细胞和 T 淋巴细胞产生。由单核巨噬细胞产生的 TNF 命名为 TNFα，由 T 淋巴细胞产生的淋巴毒素称为 TNFβ。TNFα 通过与其受体结合激活下游信号通路，诱导细胞凋亡[53]。

在免疫稳态中，LRRFIP1 的一个明确功能是作为基因的转录抑制子，直接调控 TNFα 的基础表达[54]。TNFα 与胞外的 TNF-R1 受体结合形成 TNF-R1 三聚体，形成的三聚体通过胞内区的死亡结构域招募下游的信号传导蛋白，包括 TRADD、FADD、TRAF2、RIP 等，形成复合体。当 TRADD、FADD 与 TNF-R1 形成复合体后，可活化相关的 caspase，参与细胞凋亡的诱导[55]-[57]。

5. LRRFIP1 作为结直肠癌潜在治疗靶点的研究

5.1. 基于 LRRFIP1 的靶向治疗策略

在靶向治疗策略方面，LRRFIP1 作为胞内蛋白，主要依赖蛋白质相互作用发挥功能[28]，传统小分子

抑制剂的开发面临极大挑战。其功能多样性–同时参与 RhoA 信号、Wnt/β-catenin 通路及转录调控–意味着系统性抑制可能带来免疫或发育相关副作用[35] [37] [58]。目前的研究主要集中在基因沉默和小分子抑制剂两个方面。在基因水平，使用小干扰 RNA (siRNA)在体外和动物模型中敲低 LRRFIP1 的表达，已被证明能有效抑制肿瘤生长、迁移和侵袭[37]。这为基于 RNA 干扰技术的治疗提供了概念验证。虽然针对 LRRFIP1 的特异性抑制剂尚处于早期研发阶段，但针对其相互作用蛋白或下游通路(如 RhoA、整合素)的抑制剂已进入临床前或临床研究，为间接靶向 LRRFIP1 提供了潜在路径。

5.2. 联合治疗方案探讨

由于肿瘤信号网络的复杂性，单独靶向 LRRFIP1 可能不足以完全抑制肿瘤，因此联合治疗策略显得尤为重要。

在化疗联合方面：研究表明，敲低 LRRFIP1 可以增强胰腺癌细胞对传统化疗药物(如吉西他滨)的敏感性[59]。其机制可能是通过激活 JNK/c-Jun 信号通路，从而削弱细胞的凋亡抵抗能力。

与免疫治疗的联合：LRRFIP1 参与塑造肿瘤免疫微环境，其高表达可能与免疫抑制状态相关。因此，联合使用 LRRFIP1 抑制剂与免疫检查点抑制剂(如抗 PD-1/PD-L1 抗体)，有望解除肿瘤细胞的内在生存屏障和外在免疫抑制，产生协同抗肿瘤效果。最新生物信息学研究还发现，LRRFIP1 可能作为谷氨酰胺代谢相关基因，成为骨关节炎等疾病的潜在诊断标志物[60] [61]，这提示其作为疾病生物标志物的潜力可能具有更广泛的应用场景，也为探索其在肿瘤代谢–免疫交互中的作用提供了新思路。

6. 研究现状总结与展望

6.1. 对 LRRFIP1 在结直肠癌中研究成果的总结归纳

当前研究初步表明，LRRFIP1 通过促进增殖、驱动侵袭转移和抵抗凋亡，在结直肠癌中扮演着多重致癌角色。它与 Wnt/β-catenin、PI3K/Akt/mTOR 等核心通路广泛交互，处于肿瘤信号网络的枢纽位置。临床数据关联分析显示，LRRFIP1 的高表达与较晚的 TNM 分期、淋巴结转移及不良预后显著相关，凸显其作为独立预后生物标志物的潜力[37] [62]。在治疗层面，靶向 LRRFIP1 在临床前模型中展现出抑瘤效果，并与化疗、免疫治疗具有协同潜力。

6.2. 分析当前研究存在的问题和挑战

尽管取得进展，该领域仍面临诸多挑战。首先，多数机制研究基于细胞系和异种移植模型，LRRFIP1 在人体复杂免疫微环境中的完整功能仍需在更接近临床的模型(如类器官、人源化小鼠)中验证。其次，对其翻译后修饰(如磷酸化、泛素化)如何精确调控其活性和功能的研究几乎空白。最后，在转化层面，开发高选择性、低毒性的 LRRFIP1 小分子抑制剂仍是主要瓶颈，同时需要建立可靠的生物标志物体系来筛选最可能从治疗中获益的患者群体。

6.3. 对未来研究方向的展望

针对 LRRFIP1 作为潜在治疗靶点的脱靶效应问题，未来研究可从以下几个方向寻求突破：由于 LRRFIP1 主要通过蛋白质-蛋白质相互作用(PPI)发挥功能[63]，且其结合界面通常较为平坦。因此，开发靶向 PPI 的新型干预策略尤为必要。其中，利用 PROTAC (proteolysis targeting chimera)技术实现 LRRFIP1 的选择性降解是一条值得探索的路径，该策略的优势在于可通过事件驱动的药理学模式克服传统抑制剂的局限性[64]。此外，鉴于 LRRFIP1 在 Wnt/β-catenin 信号通路中的关键作用，靶向其下游关键效应分子(如 β-catenin)或相关转录复合物也可能间接调控其功能。为最大限度减少对正常组织的毒性，未来研究还

需结合 CRC 的分子分型，筛选出最有可能从抗 LRRFIP1 治疗中获益的患者群体(如 LRRFIP1 异常表达患者)，从而实现精准靶向。最终，通过多学科合作推动 LRRFIP1 从基础研究走向临床，为结直肠癌患者提供新的精准治疗选择。

参考文献

[1] Zhou, J., Yang, Q., Zhao, S., Sun, L., Li, R., Wang, J., *et al*. (2025) Evolving Landscape of Colorectal Cancer: Global and Regional Burden, Risk Factor Dynamics, and Future Scenarios (the Global Burden of Disease 1990-2050). *Ageing Research Reviews*, **104**, Article 102666. https://doi.org/10.1016/j.arr.2025.102666

[2] Wu, S., Zhang, Y., Lin, Z. and Wei, M. (2025) Global Burden of Colorectal Cancer in 2022 and Projections to 2050: Incidence and Mortality Estimates from GLOBOCAN. *BMC Cancer*, **25**, Article No. 1770. https://doi.org/10.1186/s12885-025-15138-0

[3] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al*. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[4] Zhang, Y., Song, K., Zhou, Y., Chen, Y., Cheng, X., Dai, M., *et al*. (2025) Accuracy and Long-Term Effectiveness of Established Screening Modalities and Strategies in Colorectal Cancer Screening: An Umbrella Review. *International Journal of Cancer*, **157**, 126-138. https://doi.org/10.1002/ijc.35381

[5] Zhang, J.Z., Yang, M. and Wang, X.S. (2024) Epidemiology and Disease Burden of Colorectal Cancer in China, the United States, and Worldwide: A Comparative Analysis and Reflection. *Chinese Journal of Colorectal Diseases* (*Electronic Edition*), **13**, 89-93.

[6] Zhou, H., Wang, Y., Wang, F., Meng, R., Yu, Y., Han, S., *et al*. (2025) Assessing Cross-Country Inequalities in Global Burden of Gastrointestinal Cancers: Slope and Concentration Index Approach. *Discover Oncology*, **16**, Article No. 41. https://doi.org/10.1007/s12672-025-01762-6

[7] Abreu Lopez, B.A., Pinto-Colmenarez, R., Caliwag, F.M.C., Ponce-Lujan, L., Fermin, M.D., Granillo Cortés, A.V., *et al*. (2024) Colorectal Cancer Screening and Management in Low- and Middle-Income Countries and High-Income Countries: A Narrative Review. *Cureus*, **16**, e70933. https://doi.org/10.7759/cureus.70933

[8] Capuozzo, M., Picone, C., Sabbatino, F., Santorsola, M., Caraglia, F., Iervolino, D., *et al*. (2025) Genetic, Epidemiological, Clinical, and Therapeutic Trajectories in Colon and Rectal Cancers. *Cancers*, **17**, Article No. 3438. https://doi.org/10.3390/cancers17213438

[9] Swain, J., Preeti, Mohanty, C., Bajoria, A.A., Patnaik, S., Ward Gahlawat, A., *et al*. (2025) Deciphering the Metabolic Landscape of Colorectal Cancer through the Lens of Ahr-Mediated Intestinal Inflammation. *Discover Oncology*, **16**, Article No. 275. https://doi.org/10.1007/s12672-025-01949-x

[10] Yan, L., Shi, J. and Zhu, J. (2024) Cellular and Molecular Events in Colorectal Cancer: Biological Mechanisms, Cell Death Pathways, Drug Resistance and Signalling Network Interactions. *Discover Oncology*, **15**, Article No. 294. https://doi.org/10.1007/s12672-024-01163-1

[11] 中国家族遗传性肿瘤临床诊疗专家共识(2021 年版)(4)——家族遗传性结直肠癌[J]. 中国肿瘤临床, 2022, 49(1): 1-5.

[12] Silva, M.P.M.E., Sabbaga, J., Najman, H.L., Nascimento, C.D.C., Cotta-Pereira, R.L., Nicoluzzi, J.E.L., *et al*. (2024) From Oncologist to Surgeon-Genetics in Colorectal Metastasis for Surgeons. *Arquivos Brasileiros de Cirurgia Digestiva* (*São Paulo*), **37**, e1689. https://doi.org/10.1590/0102-6720202400075e1869

[13] Møller, P., Ahadova, A., Kloor, M., Seppälä, T.T., Burn, J., Haupt, S., *et al*. (2025) Colorectal Carcinogenesis in the Lynch Syndromes and Familial Adenomatous Polyposis: Trigger Events and Downstream Consequences. *Hereditary Cancer in Clinical Practice*, **23**, Article No. 3. https://doi.org/10.1186/s13053-025-00305-y

[14] Keum, N. and Giovannucci, E. (2019) Global Burden of Colorectal Cancer: Emerging Trends, Risk Factors and Prevention Strategies. *Nature Reviews Gastroenterology & Hepatology*, **16**, 713-732. https://doi.org/10.1038/s41575-019-0189-8

[15] Akhondi, H., Kalteh, E.A. and Lotfi, M.H. (2025) Common Risk Factors in Gastrointestinal Cancers: A Narrative Review. *Medical Principles and Practice*, **34**, 509-526. https://doi.org/10.1159/000547241

[16] Molla, M.D., Symonds, E.L., Winter, J.M., Cock, C. and Wassie, M.M. (2025) Association between Metabolic Obesity Phenotypes and Risk of Colorectal Neoplasia in a South Australian Surveillance Colonoscopy Population. *Preventive Medicine Reports*, **61**, Article 103360. https://doi.org/10.1016/j.pmedr.2025.103360

[17] Alhosani, F., Alhamidi, R.S., Ilce, B.Y., Altaie, A.M., Ali, N., Hamad, A.M., *et al*. (2025) Transcriptome-Wide Analysis and Experimental Validation from FFPE Tissue Identifies Stage-Specific Gene Expression Profiles Differentiating

Adenoma, Carcinoma In-Situ and Adenocarcinoma in Colorectal Cancer Progression. *International Journal of Molecular Sciences*, **26**, Article 4194. https://doi.org/10.3390/ijms26094194

[18] Saskova, K., Landfors, M., Hlavac, V., Seborova, K., Bruha, J., Honkova, K., *et al*. (2026) Patterns of Chromosomal Instability and Epigenetic Alterations in Colorectal Cancer Progression: From High-Grade Dysplasia to Liver Metastases. *Mutagenesis*, **41**, 156-166. https://doi.org/10.1093/mutage/geag010

[19] Brunet Guasch, M., Feeley, N.A., Soriano, I., Thorn, S., Tomlinson, I.P.M., Nicholson, M.D., *et al*. (2025) Mathematical Modeling Quantifies "Just-Right" APC Inactivation for Colorectal Cancer Initiation. *Cancer Research*, **85**, 5113-5127. https://doi.org/10.1158/0008-5472.can-25-0445

[20] Fodde, R., Smits, R. and Clevers, H. (2001) APC, Signal Transduction and Genetic Instability in Colorectal Cancer. *Nature Reviews Cancer*, **1**, 55-67. https://doi.org/10.1038/35094067

[21] Smith, G., Carey, F.A., Beattie, J., Wilkie, M.J.V., Lightfoot, T.J., Coxhead, J., *et al*. (2002) Mutations in APC, Kirsten-Ras, and P53—Alternative Genetic Pathways to Colorectal Cancer. *Proceedings of the National Academy of Sciences*, **99**, 9433-9438. https://doi.org/10.1073/pnas.122612899

[22] Afrăsânie, V.A., Marinca, M.V., Gafton, B., Rusu, A., Froicu, E.M., Sur, D., *et al*. (2025) Navigating Beyond the Surface—Prognostic Significance of KRAS, NRAS, BRAF, PIK3CA, and TP53 Mutations Examined by Exons. *Frontiers in Oncology*, **15**, Article 1557609. https://doi.org/10.3389/fonc.2025.1557609

[23] Öner, M.G., Rokavec, M., Kaller, M., Bouznad, N., Horst, D., Kirchner, T., *et al*. (2018) Combined Inactivation of TP53 and MIR34A Promotes Colorectal Cancer Development and Progression in Mice via Increasing Levels of IL6R and Pai1. *Gastroenterology*, **155**, 1868-1882. https://doi.org/10.1053/j.gastro.2018.08.011

[24] Tang, Y. and Fan, Y. (2024) Combined KRAS and TP53 Mutation in Patients with Colorectal Cancer Enhance Chemoresistance to Promote Postoperative Recurrence and Metastasis. *BMC Cancer*, **24**, Article No. 1155. https://doi.org/10.1186/s12885-024-12776-8

[25] Andac-Aktas, A.B. and Calibasi-Kocal, G. (2025) Immunological Landscape of Colorectal Cancer: Tumor Microenvironment, Cellular Players and Immunotherapeutic Opportunities. *Frontiers in Molecular Biosciences*, **12**, Article 1687556. https://doi.org/10.3389/fmolb.2025.1687556

[26] Chen, Y., Liang, Z. and Lai, M. (2024) Targeting the Devil: Strategies against Cancer-Associated Fibroblasts in Colorectal Cancer. *Translational Research*, **270**, 81-93. https://doi.org/10.1016/j.trsl.2024.04.003

[27] SOURCE Database: LRRFIP1. Princeton University.

[28] Nguyen, J.B. and Modis, Y. (2013) Crystal Structure of the Dimeric Coiled-Coil Domain of the Cytosolic Nucleic Acid Sensor LRRFIP1. *Journal of Structural Biology*, **181**, 82-88. https://doi.org/10.1016/j.jsb.2012.10.006

[29] Liu, Y. and Yin, H.L. (1998) Identification of the Binding Partners for Flightless I, a Novel Protein Bridging the Leucine-Rich Repeat and the Gelsolin Superfamilies. *Journal of Biological Chemistry*, **273**, 7920-7927. https://doi.org/10.1074/jbc.273.14.7920

[30] Zhang, Y., Wang, L., Wang, S., *et al*. (2014) Characterization of Gcf2/LRRFIP1 in Experimental Cerebral Ischemia and Its Role as a Modulator of Akt, mTOR and *β*-Catenin Signaling Pathways. *Neuroscience*, **268**, 48-65.

[31] Li, W.Q., Yu, H.Y., Li, Y.M., Wang, X., *et al*. (2014) Higher LRRFIP1 Expression in Glioblastoma Multiforme Is Associated with Better Response to Teniposide, a Type II Topoisomerase Inhibitor. *Biochemical and Biophysical Research Communications*, **446**, 1261-1267. https://doi.org/10.1016/j.bbrc.2014.03.105

[32] 蒋祝昌, 佘军红. 富含亮氨酸重复序列的结合蛋白 1 的研究进展[J]. 国际生物医学工程杂志, 2012, 35(1): 61-64.

[33] Zhou, L., Jiao, Y., Xue, J., *et al*. (2025) LRRFIP1 Inhibits White Adipocyte Differentiation by Suppressing the E2F6/C/EBP*α* Axis. *Diabetes & Metabolism Journal*.

[34] Yang, P., An, H., Liu, X., Wen, M., Zheng, Y., Rui, Y., *et al*. (2010) The Cytosolic Nucleic Acid Sensor LRRFIP1 Mediates the Production of Type I Interferon via a *β*-Catenin-Dependent Pathway. *Nature Immunology*, **11**, 487-494. https://doi.org/10.1038/ni.1876

[35] Takimoto, M. (2019) Multidisciplinary Roles of LRRFIP1/GCF2 in Human Biological Systems and Diseases. *Cells*, **8**, Article 108. https://doi.org/10.3390/cells8020108

[36] Zhang, M., Li, H., Wang, T., *et al*. (2022) LRRFIP1 Enhances the Wnt/*β*-Catenin Pathway by Binding to DVLs in Myelodysplastic Syndrome. *Chinese Journal of Hematology*, **43**, 410-417.

[37] Wang, F., Li, Y., Zhou, X., *et al*. (2017) GCF2/LRRFIP1 Promotes Colorectal Cancer Metastasis and Liver Invasion through Integrin-Dependent RhoA Activation. *Cancer Letters*, **403**, 91-101.

[38] Li, Y., Li, W., Yang, Y., Lu, Y., He, C., Hu, G., *et al*. (2009) MicroRNA-21 Targets LRRFIP1 and Contributes to VM-26 Resistance in Glioblastoma Multiforme. *Brain Research*, **1286**, 13-18. https://doi.org/10.1016/j.brainres.2009.06.053

[39] Maurice, M.M. and Angers, S. (2025) Mechanistic Insights into Wnt-*β*-Catenin Pathway Activation and Signal Transduction.

Nature Reviews Molecular Cell Biology, **26**, 371-388. https://doi.org/10.1038/s41580-024-00823-y

[40] Petersen, C.H., Mahmood, B., Badsted, C., Dahlby, T., Rasmussen, H.B., Hansen, M.B., *et al*. (2019) Possible Predisposition for Colorectal Carcinogenesis Due to Altered Gene Expressions in Normal Appearing Mucosa from Patients with Colorectal Neoplasia. *BMC Cancer*, **19**, Article No. 643. https://doi.org/10.1186/s12885-019-5833-8

[41] Labbé, P., Faure, E., Lecointe, S., Le Scouarnec, S., Kyndt, F., Marrec, M., *et al*. (2017) The Alternatively Spliced LRRFIP1 Isoform-1 Is a Key Regulator of the Wnt/*β*-Catenin Transcription Pathway. *Biochimica et Biophysica Acta—Molecular Cell Research*, **1864**, 1142-1152. https://doi.org/10.1016/j.bbamcr.2017.03.008

[42] Khezri, M.R., Jafari, R., Yousefi, K. and Zolbanin, N.M. (2022) The PI3K/AKT Signaling Pathway in Cancer: Molecular Mechanisms and Possible Therapeutic Interventions. *Experimental and Molecular Pathology*, **127**, Article 104787. https://doi.org/10.1016/j.yexmp.2022.104787

[43] Han, B., Lin, X. and Hu, H. (2024) Regulation of PI3K Signaling in Cancer Metabolism and PI3K-Targeting Therapy. *Translational Breast Cancer Research*, **5**, 33. https://doi.org/10.21037/tbcr-24-29

[44] Li, J., Tuo, D., Guo, G., Gao, Y. and Gan, J. (2024) The Clinical Significance and Oncogenic Function of LRRFIP1 in Pancreatic Cancer. *Discover Oncology*, **15**, Article No. 123. https://doi.org/10.1007/s12672-024-00977-3

[45] Jere, S.W., Abrahamse, H. and Houreld, N.N. (2023) Interaction of the AKT and *β*-Catenin Signalling Pathways and the Influence of Photobiomodulation on Cellular Signalling Proteins in Diabetic Wound Healing. *Journal of Biomedical Science*, **30**, Article No. 81. https://doi.org/10.1186/s12929-023-00974-8

[46] Jia, H., Bian, C. and Chang, Y. (2025) Exploring the Molecular Interactions between Ferroptosis and the Wnt/*β*-Catenin Signaling Pathway: Implications for Cancer and Disease Therapy. *Critical Reviews in Oncology/Hematology*, **210**, Article 104674. https://doi.org/10.1016/j.critrevonc.2025.104674

[47] Peixoto, A., Ferreira, D., Miranda, A., Relvas-Santos, M., Freitas, R., Veth, T.S., *et al*. (2025) Multilevel Plasticity and Altered Glycosylation Drive Aggressiveness in Hypoxic and Glucose-Deprived Bladder Cancer Cells. *iScience*, **28**, Article 111758. https://doi.org/10.1016/j.isci.2025.111758

[48] Bakhoum, S.F., Ngo, B., Laughney, A.M., Cavallo, J., Murphy, C.J., Ly, P., *et al*. (2018) Chromosomal Instability Drives Metastasis through a Cytosolic DNA Response. *Nature*, **553**, 467-472. https://doi.org/10.1038/nature25432

[49] Shim, A., Chen, Y. and Maciejowski, J. (2025) Activation and Regulation of cGAS-Sting Signaling in Cancer Cells. *Molecular Cell*, **85**, 3807-3822. https://doi.org/10.1016/j.molcel.2025.08.030

[50] Cho, M.G. and Gupta, G.P. (2025) Unveiling cGAS Mechanisms: Insights into DNA Damage and Immune Sensing in Cancer. *DNA Repair*, **153**, Article 103878. https://doi.org/10.1016/j.dnarep.2025.103878

[51] Alim, L.F., Keane, C. and Souza-Fonseca-Guimaraes, F. (2024) Molecular Mechanisms of Tumour Necrosis Factor Signalling via TNF Receptor 1 and TNF Receptor 2 in the Tumour Microenvironment. *Current Opinion in Immunology*, **86**, Article 102409. https://doi.org/10.1016/j.coi.2023.102409

[52] Tucci, G., Pacella, I., Pinzon Grimaldos, A., Rossi, A., Cammarata, I., Zagaglioni, M., *et al*. (2025) TNF Production or TNFR2 Expression Characterize Distinct States of Regulatory T Cells That Cooperate in Treg Expansion in Cancer and Chronic Inflammation. *European Journal of Immunology*, **55**, e70062. https://doi.org/10.1002/eji.70062

[53] Nam, Y.W., Shin, J., Kim, S., Hwang, C.H., Lee, C., Hwang, G., *et al*. (2024) EGFR Inhibits TNF-*α*-Mediated Pathway by Phosphorylating TNFR1 at Tyrosine 360 and 401. *Cell Death & Differentiation*, **31**, 1318-1332. https://doi.org/10.1038/s41418-024-01316-3

[54] Suriano, A.R., Sanford, A.N., Kim, N., Oh, M., Kennedy, S., Henderson, M.J., *et al*. (2005) GCF2/LRRFIP1 Represses Tumor Necrosis Factor Alpha Expression. *Molecular and Cellular Biology*, **25**, 9073-9081. https://doi.org/10.1128/mcb.25.20.9073-9081.2005

[55] Darnay, B.G. and Aggarwal, B.B. (1997) Early Events in TNF Signaling: A Story of Associations and Dissociations. *Journal of Leukocyte Biology*, **61**, 559-566. https://doi.org/10.1002/jlb.61.5.559

[56] Micheau, O. and Tschopp, J. (2003) Induction of TNF Receptor I-Mediated Apoptosis via Two Sequential Signaling Complexes. *Cell*, **114**, 181-190. https://doi.org/10.1016/s0092-8674(03)00521-x

[57] Walczak, H. (2013) Death Receptor-Ligand Systems in Cancer, Cell Death, and Inflammation. *Cold Spring Harbor Perspectives in Biology*, **5**, a008698. https://doi.org/10.1101/cshperspect.a008698

[58] Douchi, D., Ohtsuka, H., Ariake, K., Masuda, K., Kawasaki, S., Kawaguchi, K., *et al*. (2015) Silencing of LRRFIP1 Reverses the Epithelial-Mesenchymal Transition via Inhibition of the Wnt/*β*-Catenin Signaling Pathway. *Cancer Letters*, **365**, 132-140. https://doi.org/10.1016/j.canlet.2015.05.023

[59] Huang, Y., *et al*. (2021) Silencing of LRRFIP1 Enhances the Chemosensitivity of Pancreatic Cancer Cells to Gemcitabine via Activation of the JNK/c-Jun Signaling Pathway. *Pancreatology*.

[60] 基于生物信息学筛选骨关节炎中谷氨酰胺代谢关键基因 LRRFIP1 和 MFSD11 作为新型诊断标志物[J]. Scientific Reports, 2025.

[61] Li, D., Wang, C., Qing, Y., Bao, X., Xu, J., Wang, X., *et al*. (2025) Potential Glutamine Metabolism-Related Biomarkers Were Identified in Osteoarthritis by Bioinformatics. *Scientific Reports*, **15**, Article No. 45797. https://doi.org/10.1038/s41598-025-29541-x

[62] 庹大云, 郭固楠, 张乐佳, 甘进锋, 李金平. GCF2/LRRFIP1 的生物学功能及其在肿瘤中的作用[J]. 黑龙江科学, 2022, 13(6): 114-116.

[63] Fong, K.S.K. and de Couet, H.G. (1999) Novel Proteins Interacting with the Leucine-Rich Repeat Domain of Human Flightless-I Identified by the Yeast Two-Hybrid System. *Genomics*, **58**, 146-157. https://doi.org/10.1006/geno.1999.5817

[64] Oon, C.E., Anbazhagan, P. and Tan, C.T. (2025) Therapeutic Potential of Targeting Ubiquitin-Specific Proteases in Colorectal Cancer. *Drug Discovery Today*, **30**, Article 104356. https://doi.org/10.1016/j.drudis.2025.104356