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RNA解旋酶DDX5在癌症中的研究进展

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摘　要

恶性肿瘤是威胁人类健康的重大疾病之一，由于肿瘤的异质性和发病机理的复杂性，临床治疗面临巨大挑战。因此，寻找精准的治疗靶点和新型分子标志物已成为肿瘤学研究热点。DDX5 (DEAD-box RNA helicase 5)是DEAD-box蛋白家族的重要成员，在进化上高度保守，主要通过ATP依赖的RNA解旋活性参与多种基因表达调控。研究表明，DDX5在多种癌症中异常表达。因此，深入探究DDX5在癌症发生发展中的调控机制，成为当前癌症研究领域的热点。本论文综述了DDX5蛋白的结构特征及其在转录调节、细胞周期调控和DNA损伤修复等基础生物学过程中的关键作用，重点探讨DDX5通过调控细胞周期、转录因子活性及上皮－间质细胞转化等机制影响多种癌症的发生发展，为进一步研究DDX5作为潜在治疗靶点和预后标志物提供指导。

关键词

DDX5，结构与功能，癌症

Advances in the Study of RNA Deconjugating Enzyme DDX5 in Cancer

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Abstract

Malignant tumors are one of the major diseases threatening human health, and clinical treatment

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faces great challenges due to the heterogeneity of tumors and the complexity of their pathogenesis. Therefore, the search for precise therapeutic targets and novel molecular markers has become a hot spot in oncology research. DDX5 (DEAD-box RNA helicase 5) is an important member of the DEAD-box protein family, which is highly conserved evolutionarily and is involved in the regulation of a wide range of gene expression mainly through ATP-dependent RNA unwinding activity. Studies have shown that DDX5 is aberrantly expressed in a variety of cancers. Therefore, in-depth investigation into the regulatory mechanisms of DDX5 in cancer development and progression has become a major focus in current cancer research. This review summarizes the structural characteristics of the DDX5 protein and its crucial roles in fundamental biological processes including transcriptional regulation, cell cycle control, and DNA damage repair. With a focus on oncogenesis mechanisms, the paper specifically examines how DDX5 influences cancer development and progression through regulating cell cycle dynamics, transcription factor activity, and epithelial-mesenchymal transition (EMT). These comprehensive analyses provide valuable insights for future investigations targeting DDX5 as a potential therapeutic target and prognostic biomarker in cancer research.

Keywords

DDX5, Structure and Function, Cancer

1. 引言

癌症是一种重大疾病，主要是由细胞周期异常调控导致的无限增殖以及免疫系统的异常识别所引起，因其具有较强的增殖和扩散能力，所以被称为“永不愈合的伤口”[1]。数据显示，2022 年我国恶性肿瘤死亡病例高达 257.4 万例[2]，且发病率和死亡率均呈现快速上升趋势[3]。当前临床治疗手段主要包括放疗、化疗和手术切除，并联合免疫检查点抑制剂等生物靶向疗法调控肿瘤微环境，从而杀死癌细胞或抑制癌细胞增殖[4]。尽管多手段联合治疗使患者生存期得到改善，但基于肿瘤干细胞存活及免疫逃逸机制，仍有很大一部分患者会出现局部性复发或转移，导致预后不良[5]。因此，深入探究癌症早期诊断分子标志物和靶向治疗机制是十分必要的。

DDX5 是一种多功能蛋白质，主要通过依赖 ATP 水解产生的能量在多种生物学过程中发挥着关键作用[6]。研究表明，DDX5 在大多数恶性肿瘤中过表达，通过参与肿瘤细胞增殖、侵袭、迁移以及调控多种信号通路，促进癌症的发生发展，例如肺癌、前列腺癌、卵巢癌、胃癌、结肠癌和乳腺癌等[7] [8]。DDX5 作为一种多功能蛋白质，已被确定为治疗各种癌症类型的潜在生物标志物和治疗靶点[7]。本文系统总结 RNA 解旋酶 DDX5 的结构和生物学功能，讨论其在多种癌症中的表达及作用，以期为癌症的临床治疗和 DDX5 靶向新药物的研发提供一定的参考意义。

2. DDX5 的结构

DDX5 又叫 p68，是 RNA 解旋酶 SF2 超家族中 DEAD-box 家族的重要成员[7]。与其他 DEAD-box 解旋酶一样，DDX5 的核心区域是由两个灵活连接的 N 端 RecA 样结构域(NTD)和 C 端 RecA 样结构域(CTD)组成，包含 9 个保守基序(如图 1)，分别是 Q、I、Ia、Ib、II、III、IV、V 和 VI，这些保守区域对 RNA 结合、ATP 结合和水解及分子间相互作用至关重要[9]。NTD 由基序 Q、I、II和III组成，用于 ATP 结合；

CTD 包括基序IV、V和VI，主要表现出 RNA 双链识别结构域；Q 基序存在于催化核心的 N 末端，通过调节蛋白质与 RNA 底物之间的亲和力来影响解旋酶活性[10]。基于 DDX5 蛋白的结构特点，其在整个生命周期中，从 RNA 合成起始到生物活性的表现，都发挥着重要作用。

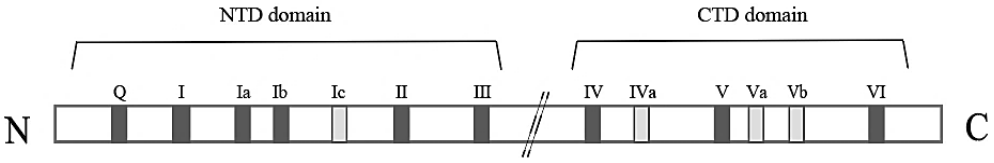

Figure 1. Core sequence of DDX5
图 1. DDX5 核心序列

3. DDX5 的生物学功能

DDX5 作为多功能 RNA 解旋酶，在多种生物学过程中发挥关键作用。在 RNA 代谢方面，它通过促进 U1 小核糖核蛋白和 5'剪接位点解离调控 pre-mRNA 剪接、与 DDX17 协同调控 rRNA 加工以及参与核糖体生物发生[11]。在转录调控中，DDX5 与雌激素受体、雄激素受体、肿瘤抑制因子 p53 和肌生成调节因子 MyoD 等多种转录因子相互作用，并充当其辅助激活因子，从而调控细胞的增殖、侵袭和转移[9] [12]。在细胞周期方面，DDX5 不仅通过参与 Wnt/β-catenin 和 NF-κB 信号通路促进细胞增殖[13]-[15]，同时还作为 p53 的转录共激活因子协同调控细胞周期停滞和凋亡[16]。在 DNA 损伤修复中，DDX5 通过 ATP 依赖性方式识别并清除 DNA:RNA 杂交环，从而维持基因组稳定性和完整性，其缺失导致同源重组修复缺陷，造成了 DNA 损伤积累和基因组不稳定，细胞将进入凋亡状态[17] [18]。另外，DDX5 还可诱导 EMT 产生(如 DDX5 Y593 磷酸化介导的 PDGF 信号) [14]和调控 miRNA (如与细胞增殖相关的 miR-431) [19]，促进细胞增殖和迁移。

4. DDX5 在癌症中的应用

DEAD-box 蛋白家族在细胞维持过程中发挥关键作用，在此基础上，人们发现 DDX5 与细胞增殖和肿瘤转化密切相关[20]。研究表明，DDX5 在多数癌症如结肠癌、肝癌、肺癌和乳腺癌发生发展中发挥关键作用[9]，如表 1。

Table 1. Role of DDX5 in cancer
表 1. DDX5 在癌症中的作用

癌症	作用	调控机制	参考文献
肺癌	+	激活 β-catenin 促进细胞增殖；细胞侵袭	[21] [22]
肝癌	-	调节 Wnt/β-catenin 和 NF-κB 信号通路	[15] [23]
结直肠癌	+	调控 AKT/β-catenin/FOXM1	[24]
胶质母细胞瘤	+	NF-κB p50 亚基激活；下调 DUSP5 激活 ERK	[27] [28]
乳腺癌	+	促进 EMT；DNA 修复	[14] [29]
前列腺癌	+	DDX5/mTOCR1 信号轴	[30]
胃癌	+	激活 mTOR/S6K 信号促进癌症发展	[31]
甲状腺癌	+	激活 Wnt/β-catenin	[13]
子宫内膜癌	+	HDGF/DDX5 相互作用诱导 β-catenin	[32]
卵巢癌	+	AURKA/DDX5/TMEM147-AS1/let-7	[33]

4.1. 肺癌

肺癌是起源于肺部支气管粘膜或腺体的异质性恶性肿瘤，是全球范围内发病率和死亡率最高的恶性肿瘤之一[34]。根据形态不同，主要分为非小细胞肺癌(NSCLC)和小细胞肺癌(SCLC) [35]。王振东等发现，与正常组织内的细胞相比，DDX5 在 NSCLC 细胞中显著表达，通过诱导 β-catenin 的核积累，激活其下游靶基因细胞周期蛋白 D1 和 c-Myc 的转录翻译水平，促进 NSCLC 细胞的增殖和肿瘤生长[21]。在 SCLC 细胞中，DDX5 促进线粒体功能，部分表现为呼吸作用上调，支持癌细胞的能量需求，促进癌细胞侵袭[22]。

4.2. 肝癌

肝癌是全球十大致命癌症之一[36]。研究表明，肝癌经常与慢性肝病一起发生，例如代谢相关脂肪肝病可以使肝细胞发生恶性转化或进展为脂肪型肝炎、肝纤维化，最终导致肝硬化，进而直接从脂肪变性引起肝癌[37] [38]。近年来，DDX5 在肝癌发生发展中的作用逐渐显现。研究表明，慢性肝病患者肝癌的发病率因存在诱发因素而急剧增加，例如肝硬化和 NASH 等[39]，在 NASH 患者体内，低表达的 DDX5 可激活 mTOR 信号通路，加重肝脏脂肪积累并抑制自噬，促进肝癌的发生[23]。在晚期肝细胞癌中，DDX5 缺陷激活 Wnt/β-catenin 信号转导，促进非经典 NF-κB 信号激活和细胞保护性转录因子 NRF2 的表达，从而在索拉菲尼治疗后实现铁死亡逃逸，促进肝癌发展[15]。

4.3. 结肠癌

结肠癌是全球范围内最常见的恶性癌症之一。近年来，尽管化疗、分子靶向治疗和免疫治疗取得了重大进展，但其由于易发生转移和耐药性增强，死亡率仍然很高[40]-[42]。研究发现，DDX5 作为典型的原癌基因，在结肠癌的发生发展中发挥关键作用。在结肠癌中，DDX5 充当 CSN6 的效应因子，通过稳定 PHGDH mRNA 增强核苷酸合成，从而促进结肠癌细胞存活和耐药[43]。另外，DDX5 通过调控 AKT 和 β-catenin 通路，促进结肠癌细胞增殖、迁移和侵袭[24]-[26]。

4.4. 神经胶质细胞瘤

神经胶质细胞瘤是最常见的原发性异质性脑恶性肿瘤，约占脑肿瘤的 50%~60% [44]，由于其高突变等特性，使得该疾病治疗复杂化，复发率高[45]。研究发现，与正常组织相比，DDX5 在神经胶质瘤细胞和组织中过表达。王瑞等利用微阵列分析技术发现了 p68 的新靶点，双特异性磷酸酶 5 (DUSP5)，并且表达呈负相关，二者通过介导细胞外信号调节激酶 ERK 信号通路的激活，促进神经胶质瘤细胞的增殖、侵袭和迁移[28]。他们还发现，p68 通过与 NF-κB p50 的 N 端结合，促进 p50 的核积累和转录活性，诱导胶质瘤细胞增殖和肿瘤生长[27]。

4.5. 乳腺癌

乳腺癌是全球第二大癌症，仅次于肺癌[46]，它是女性死亡的主要原因[47]。近些年，人们发现在乳腺中 DDX5 蛋白表达与乳腺肿瘤的致癌性密切相关。在乳腺癌中，DDX5 通过 Wnt/β-catenin 信号增加 EMT 过程，促进乳腺癌发展[14]。DDX5 与 DNA 修复相关蛋白(BRCA2)相互作用，促进转录染色质内 DNA-RNA 杂交体的解旋与修复，从而促进 BRCA2 缺陷型乳腺癌的发生[29]。

4.6. 其他癌症

据报道，除了上述癌症外，DDX5 还在其他多种癌症的发生发展中发挥重要作用。在胃癌中，DDX5 通过激活 mTOR-S6K1 轴来增强癌细胞增殖[31]。在甲状腺癌细胞中，DDX5 通过激活 Wnt/β-catenin 信号

增强癌细胞增殖、迁移和侵袭[13]。DDX5 和 HDGF 通过激活 β-catenin 促进子宫内膜癌的发生和发展[32]。DDX5 通过激活 mTOCR1 通路，抑制细胞凋亡，促进前列腺癌细胞的增殖[30]。另外，DDX5 直接与 Aurora 激酶 A 结合形成转录共激活因子复合物，诱导致癌基因的转录，通过一系列信号激活脂肪吞噬来增强卵巢癌细胞的耐药性，不利于癌症的治疗[33]。

5. DDX5 在癌症治疗中的应用

研究表明，刘志任团队已成功研发了一种名为 RX-5902 的新型抗癌药物，通过与 Y593 处磷酸化的 DDX5 直接结合，抑制 DDX5 与 β-catenin 相互作用，从而实现抗癌作用[48]。近年来，李凤芝团队研发的分子胶降解剂 FL118 已在临床前得到验证，FL118 强烈结合去磷酸化并通过蛋白酶体降解途径降解 DDX5 蛋白，进而控制多种致癌蛋白的表达，包括存活素、c-Myc 和突变体 Kras，从而实现对人结直肠癌、小儿骨肉瘤、前列腺癌和胰腺癌的抑制作用[49]。另外，基于 circRNA 和 miRNA 的抗癌方法逐渐得到验证。毛小欢等发现在骨肉瘤中，异常表达的 Circ-XPR1 通过吸附具有抑癌作用的 miR-214-5p，促进 DDX5 的表达，从而促进骨肉瘤增殖[50]。因此，Circ-XPR1/miR-214-5p/DDX5 轴是一个新颖且潜在的治疗靶向轴。

6. 总结与展望

随着精准医学与分子诊断技术的快速发展，肿瘤治疗手段和水平也显著提升，但恶性肿瘤固有的高异质性和高转移性，致使临床治疗面临继发性耐药高发和患者生存改善有限等难题。因此深入解析恶性肿瘤发展的多维度调控机制，筛选核心调控靶点，是突破现有的早期诊断效率低下及治疗应答率低的关键手段。DDX5 是一种重要的 RNA 解旋酶，通过调控 NF-κB、PI3K/Akt 和 Wnt/β-catenin 等信号通路，在癌症发生发展中发挥关键作用。基于以上研究，未来可从四个方面深入研究。第一，DDX5 已被发现在癌细胞增殖、迁移和侵袭等过程发挥作用，因此设计和筛选能够特异性靶向 DDX5 的抑制剂或干扰其功能的小分子药物，可以直接或间接阻断细胞的生长和扩散。第二，DDX5 在不同癌症类型中，其作用机制可能存在差异。在肝癌中，DDX5 缺陷可以通过激活 Wnt/β-catenin 信号转导，从而在索拉菲尼治疗后实现铁死亡逃逸，促进肝癌发展；而在乳腺癌中，DDX5 通过维持 β-catenin/TCF4 信号传导的正反馈回路，增加 Wnt 信号介导的 EMT 过程，促进乳腺癌的发展。因此，对这些特异性作用机制的深入剖析，有助于提高治疗的针对性和有效性，减少治疗过程中对正常细胞的损伤，降低副作用。第三，癌症的发生发展是一个涉及多个基因和信号通路相互交织的复杂过程，探究 DDX5 与其他致癌信号通路的相互作用，为开发多靶点联合治疗策略提供理论依据。第四，挖掘 DDX5 作为癌症早期诊断标志物及预后评估指标的潜力，为临床治疗决策提供重要参考。对 DDX5 调控癌症发展作用机制的深入探究，有助于揭示其对癌症的治疗和预防机制，为癌症的治疗和预防提供参考。

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