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Tumor Discovery

REVIEW ARTICLE

WD repeat domain 4 in tumorigenesis: Molecular mechanisms, cancer-type specific roles, and therapeutic potential

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Abstract

WD repeat domain 4 (WDR4) is an essential member of the WD-repeat protein family, known for its regulatory roles in cellular processes critical to cancer development, including RNA modification, protein stability, cell cycle progression, and apoptosis. Studies have shown that WDR4 plays a pivotal role in tumorigenesis across various cancer types, with a particular focus on breast cancer in this study, where its overexpression is closely associated with aggressive tumor characteristics and poorer patient outcomes. As a scaffold protein, WDR4 is involved in N7-methylguanosine tRNA methylation and ubiquitin-mediated protein degradation, thereby regulating RNA stability, protein synthesis, and cell survival. This review provides a comprehensive analysis of WDR4's molecular mechanisms, its oncogenic functions across different cancer types, and its interactions with other key factors in the tumor microenvironment, further exploring its potential role in tumor progression. As research on WDR4 progresses, we not only gain a deeper understanding of its complex role in tumor biology but also uncover new therapeutic avenues. In particular, the potential of WDR4 as a biomarker and therapeutic target is increasingly recognized. Despite the challenges faced in its clinical application, such as the difficulty in developing targeted therapies and managing side effects, the future prospects of WDR4 in cancer diagnosis and treatment remain promising, and it is expected to emerge as an effective therapeutic target in the near future.

Keywords: WD repeat domain 4; Tumorigenesis; RNA modification; Tumor microenvironment; Cancer-type specificity; Targeted therapy

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1. Introduction

1.1. Molecular and functional overview of WD repeat domain 4 (WDR4)

WDR4 belongs to the WD-repeat protein family, defined by the presence of WD40 repeat motifs that enable extensive protein-protein interactions.[1] These WD40 domains form a stable beta-propeller structure (Figure 1), providing WDR4 with a large interaction surface that supports its role as a scaffold protein in critical cellular pathways. Located on chromosome 21q22.3, *WDR4* encodes a protein consisting of 311 amino acids,

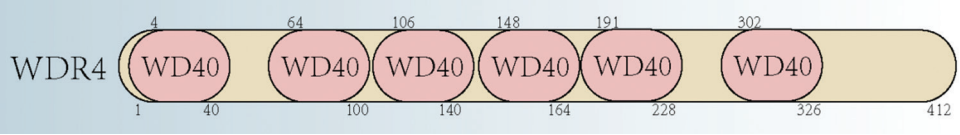


Figure 1. The protein structure of WDR4. WDR4 is composed of multiple WD40 domains
Abbreviations: WDR4: WD repeat domain 4.

that contributes to essential processes in normal cellular function and disease states, including transcriptional regulation, signal transduction, protein degradation, and cell cycle progression.[2]

Functionally, WDR4 plays a pivotal role in RNA metabolism, particularly in m7G modification of transfer RNA (tRNA).[3] This post-transcriptional modification is critical for stabilizing tRNA, enhancing translation fidelity, and ensuring efficient protein synthesis.[4,5] In the biological characteristics of malignant tumor cells, the stability of RNA molecules and the efficiency of their translation processes constitute the fundamental mechanisms driving the rapid proliferation and growth of cancer cells. By modulating tRNA methylation, WDR4 affects RNA stability and translation efficiency, driving the increased protein synthesis required for oncogenesis.[6,7] Consequently, the dysregulation of WDR4 leads to a cellular environment conducive to tumorigenesis, positioning WDR4 as a significant factor in malignant transformation.[8,9]

In addition to its role in RNA modification, recent studies have shown that WDR4 regulates protein stability through interactions with the ubiquitin-proteasome system.[10] Specifically, WDR4 facilitates the degradation of tumor suppressor proteins and enhances the stability of proteins involved in cell cycle progression and resistance to apoptosis.[11] This mechanism may promote tumor cell proliferation and survival by selectively modulating the degradation and maintenance of critical proteins.[12,13] Therefore, WDR4 plays a crucial role not only through RNA modification pathways but also by influencing protein stability, making it a potential therapeutic target in cancer biology.

This dual role in RNA modification and protein stability enables WDR4 to regulate several tumor-promoting processes, underscoring its potential as a therapeutic target in oncology.

1.2. Relevance of WDR4 in cancer

The oncogenic functions of WDR4 in multiple malignancies have been studied, including hepatocellular carcinoma (HCC),[14-16] lung cancer,[17-19] head and neck squamous cell carcinoma,[20] adrenocortical carcinoma,[21] prostate adenocarcinoma,[22,23] esophageal squamous cell carcinoma,[24] hepatoblastoma,[25] and Wilms tumor,[26] where its overexpression or polymorphism has been linked to tumor progression, metastasis, and poor patient prognosis. In HCC, high expression of WDR4 is associated with aggressive disease features, including advanced tumor stage and reduced survival, as it supports RNA modifications that promote the synthesis of oncogenic proteins by forming a complex with methyltransferase like 1 (METTL1), which cooperatively regulates the m7G modification of mRNA in HCC cells. WDR4 effectively modulates both the expression of mRNA and the protein levels of the *METTL1* gene. Moreover, the impact of WDR4 on tRNA m7G levels directly mediates the translation of TRIM28, which in turn enhances the stemness of cancer stem cells. This process contributes to the development of resistance to lenvatinib and promotes tumor progression in HCC. In lung cancer, WDR4 has been shown to influence cell cycle regulation and apoptosis, facilitating rapid cell division and enhanced survival under conditions of cellular stress. Similarly, in head and neck squamous cell carcinoma, elevated expression of WDR4 is linked to disease progression by regulating RNA translation through RNA modification. This process impacts critical signaling pathways, including the PI3K/AKT/mTOR pathway, which are essential for promoting oncogenic protein synthesis.[20] This regulation facilitates tumor growth and may contribute to the aggressive behavior characteristic of this malignancy.

This multifaceted role of WDR4 across cancer types suggests that its oncogenic mechanisms may vary depending on the specific molecular context and the surrounding tumor microenvironment. Understanding the precise molecular functions and signaling interactions of WDR4 in different types of cancer is essential to identifying its potential as a therapeutic target and designing targeted strategies to selectively inhibit its activity in cancer cells.

2. Molecular mechanisms of WDR4 in tumorigenesis

2.1. Structural and functional aspects of WDR4

The oncogenic mechanisms of WDR4 in cancer are mainly attributable to its unique structural properties, particularly its WD40 repeat domains,[27] which form a stable beta-propeller structure capable of binding diverse cellular partners, such as METTL1.[28] This structure enables WDR4 as a scaffold protein that coordinates cellular complexes in RNA modification and protein turnover pathways.

2.1.1. RNA modification and tumorigenesis

WDR4's role in RNA metabolism is particularly evident in its involvement in M7G modification of tRNA, which stabilizes tRNA molecules and improves translation fidelity.[29] Dysregulation of this modification in cancer cells contributes to rapid protein synthesis, supporting the increased cellular proliferation and metabolic demand associated with tumorigenesis.[6] In HCC, WDR4 overexpression has been shown to enhance m7G modification, resulting in the translation of oncogenic proteins that promote cell survival and proliferation.[30] By specifically improving the translation efficiency of these tumor-promoting proteins, WDR4 drives cellular processes that support malignancy, highlighting its potential as an oncogene in RNA metabolism.

2.1.2. Interaction with the ubiquitin-proteasome system

WDR4 also interacts with the ubiquitin-proteasome system, influencing protein stability by promoting the degradation of tumor suppressor proteins. For instance, in cancer, WDR4 facilitates the ubiquitination and degradation of p53, a crucial tumor suppressor, enabling cancer cells to evade apoptosis.[11] This ability to degrade tumor suppressors while stabilizing cell cycle regulators allows WDR4 to support cell proliferation and survival, which are critical for tumor progression. WDR4-mediated ubiquitination of protein tyrosine phosphatase, non-receptor type 23 (PTPN23) leads to its proteasomal degradation, thereby inhibiting the lysosomal transport and degradation of wild-type epidermal growth factor receptor (EGFR), EGFR mutants, and c-MET. Through this mechanism, WDR4 maintains EGFR and c-MET signaling, promoting the proliferation, migration, invasion, stemness, and metastasis of non-small cell lung cancer. In addition, WDR4-mediated ubiquitination of promyelocytic leukemia (PML) enhances lung tumor growth. Specifically, the degradation of PML induced by WDR4 triggers the secretion of a series of cell surface or secreted factors, including CD73, urokinase-type plasminogen activator receptor, and serum amyloid A2, which initiate paracrine signaling that stimulates cell migration, invasion, and metastasis.[13] WDR4-induced ubiquitination and degradation of Arhgap17 activate Rac1, which prevents the cell cycle exit of granule neuron precursor (GNP), thus supporting GNP proliferation and ultimately facilitating cell cycle progression, a process essential for cerebellar development and motor function.[31] By modulating the ubiquitin-proteasome pathway, WDR4 effectively tilts the balance between cell survival and apoptosis in favor of tumor progression. However, current research suggests that WDR4's role in protein degradation might be interconnected with its function in tRNA modification, although the exact mechanisms may differ. Figure 2 illustrates the molecular mechanisms of WDR4 in tumorigenesis.

2.2. Regulation of cell cycle and apoptosis

WDR4's influence on cell cycle progression and apoptosis is fundamental to its role in tumorigenesis. Through interactions with cell cycle regulators and apoptotic pathways, WDR4 promotes cell proliferation while inhibiting programmed cell death, creating a cellular environment conducive to tumor growth.

2.2.1. Cell cycle control

In several types of cancer, WDR4 overexpression is associated with increased levels of cell cycle-promoting proteins, particularly those that regulate the G1/S transition.[32,33] In lung cancer, WDR4's impact on cyclin D1 levels accelerates cell cycle progression by promoting the G1/S phase transition, enabling tumor cells to sustain high proliferation rates.[34] In addition, WDR4's influence on other cyclins and cyclin-dependent kinases may further reinforce its role in cell cycle regulation, contributing to continuous tumor growth.

2.2.2. Modulation of apoptosis

WDR4's role in apoptosis resistance is evident in its interactions with pro- and anti-apoptotic factors.[35,36] In head and neck squamous cell carcinoma, WDR4 downregulates or degrades p53, reducing cellular sensitivity to apoptosis-inducing signals.[20] Furthermore, WDR4 is associated with the upregulation of anti-apoptotic proteins, such as BCL-2, which inhibit apoptotic signaling pathways and protect cancer cells from programmed cell death.[36,37] This ability to modulate apoptosis is essential for cancer cell survival, particularly under stress conditions, such as nutrient deprivation or exposure to chemotherapy.[38,39] Figure 3 illustrates the molecular mechanisms underlying the inhibitory effects of WDR4 on the cell cycle and apoptosis of cancer cells.

3. WDR4 is associated with multiple oncogenic pathways

3.1. PI3K/AKT/mTOR pathway

The PI3K/AKT/mTOR signaling pathway is a crucial intracellular regulatory network that plays a key role in regulating fundamental biological processes such as cell growth, proliferation, survival, metabolism, and motility. Abnormal activation of this pathway is closely associated with the development of various diseases, particularly cancer, diabetes, and neurodegenerative diseases.[40-42] PI3K (phosphoinositide 3-kinase) is an enzyme that catalyzes the phosphorylation of phosphoinositides and their

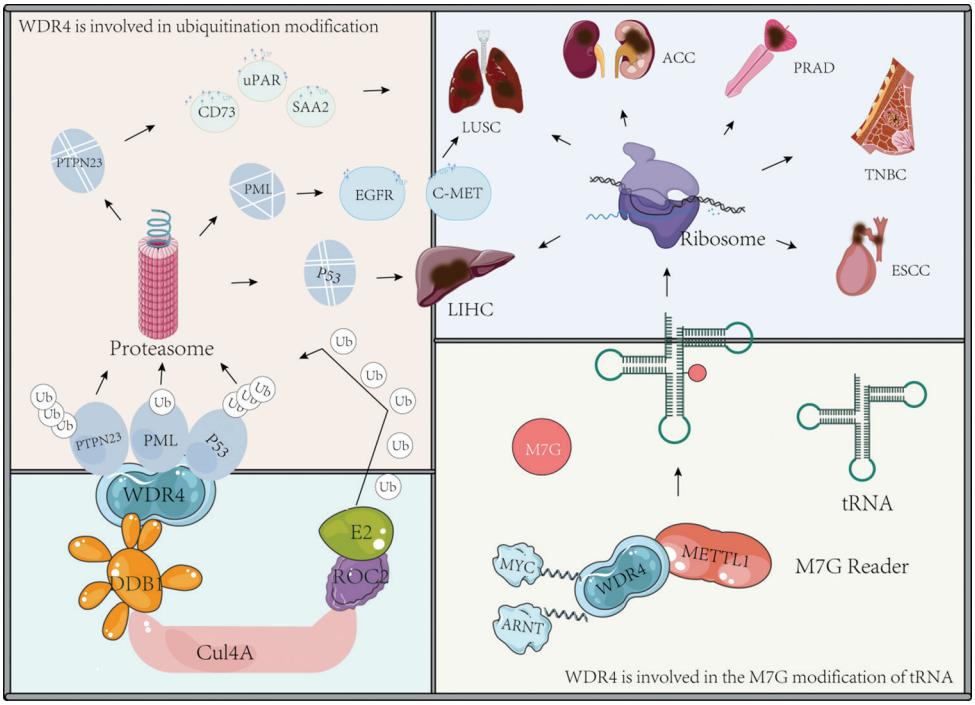


Figure 2. Molecular mechanisms of WDR4 in tumorigenesis. WDR4 can ubiquitinate and degrade multiple important proteins such as PML, PTPN23, and P53. It can also form a complex with METTL1 as a reader of M7G modification, promoting various types of cancers.
Abbreviations: ACC: Adrenocortical carcinoma; ARNT: Aryl hydrocarbon receptor nuclear translocator; EGFR: Epidermal growth factor receptor; ESCC: Esophageal squamous cell carcinoma; LIHC: Liver hepatocellular carcinoma; LUSC: Lung squamous cell carcinoma; METTL1: Methyltransferase like 1; PML: Promyelocytic leukemia; PRAD: Prostate adenocarcinoma; PTPN23: Protein tyrosine phosphatase non-receptor type 23; SAA2: Serum amyloid A2; TNBC: Triple-negative breast cancer; uPAR: Urokinase-type plasminogen activator receptor; WDR4: WD repeat domain 4.

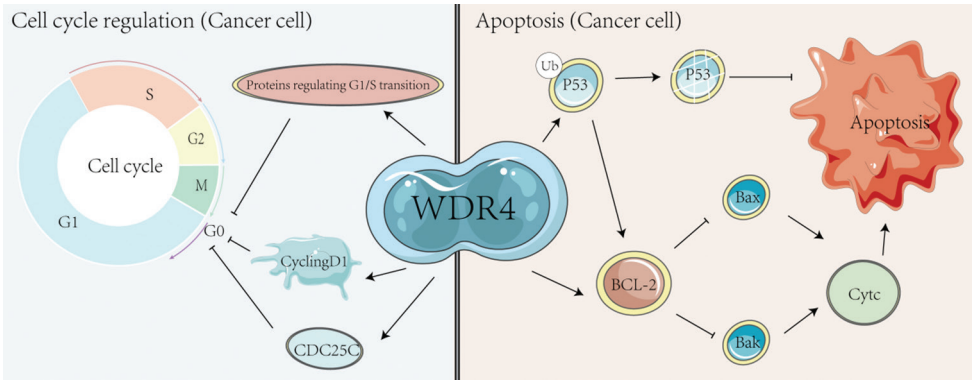


Figure 3. Molecular mechanisms underlying the inhibitory effects of WDR4 on the cell cycle and apoptosis of cancer cells.
Abbreviations: Bak: Bcl-2-associated x protein; Bax: Bcl-2-associated x protein; BCL-2: B-cell lymphoma 2; CDC25C: Cell division cycle 25C; WDR4: WD repeat domain 4.

derivatives, primarily initiating downstream signaling by generating phosphoinositide (3,4,5)-trisphosphate (PIP3) on the cell membrane.[43,44] PI3K activates this signaling pathway by interacting with receptor proteins on the cell membrane, such as growth factor receptors.

PI3K phosphorylates phosphoinositides on the cell membrane to produce PIP3, and the accumulation of PIP3 provides binding sites for downstream kinases like AKT, thus activating AKT.[45] This process is a core step in the PI3K/AKT/mTOR signaling pathway. Through the activation of AKT, this pathway regulates multiple cellular functions, including protein synthesis, metabolic regulation, cell cycle control, and anti-apoptotic actions. Moreover, the PI3K/AKT/mTOR pathway plays an essential role in the initiation and progression of various cancers by regulating cell proliferation and survival.[46]

In liver cancer, studies have shown that WDR4 may regulate the protein level of CCNB1, influencing the activation of the PI3K/AKT signaling pathway and promoting tumor progression.[12] In head and neck squamous cell carcinoma, it has been found that m7G tRNA modification mediates the interaction with the PI3K/AKT/mTOR pathway, regulating the mRNA expression profile and further promoting cancer progression.[20] This suggests the significant role of tRNA modifications in tumor metabolism and biological processes. In addition, in esophageal squamous cell carcinoma, WDR4 regulates m7G modification to affect tRNA expression, activating the RPTOR/ULK1/autophagy pathway and contributing to cancer development.[24] These findings indicate that WDR4, as a critical regulatory factor, plays a significant role in the onset and progression of various cancers through its regulation of the PI3K/AKT/mTOR signaling pathway.

3.2. MAPK pathway

The mitogen-activated protein kinase (MAPK) pathway is a critical intracellular signaling pathway involved in various physiological processes, including cell growth, differentiation, stress response, apoptosis, and metabolism.[47,48] The activation of the MAPK pathway is typically triggered by external stimuli such as growth factors, cytokines, and environmental stress.[49] On activation, this pathway regulates downstream transcription factors and other effector molecules, thereby influencing the function and fate of the cell.[50-52]

In pancreatic cancer, the MAPK pathway plays a significant role in regulating cell proliferation and survival.[53] The functional role of WDR4 in influencing protein stability may extend to the components of the MAPK pathway, thereby enhancing their stability and facilitating their activation. By modulating MAPK signaling, WDR4 supports tumor cell growth and metastasis, positioning it as a potential therapeutic target in MAPK-driven pancreatic cancer.

3.3. WNT/β-catenin pathway and epithelial-mesenchymal transition (EMT) pathway

The WNT/β-catenin pathway is a central signaling mechanism that regulates various physiological processes, including development, stem cell maintenance, and tissue homeostasis.[50,54] Dysregulation of this pathway is a key feature in the pathogenesis of many diseases, particularly cancer.[55,56]

The EMT is a biological process in which epithelial cells, which are normally tightly bound and organized in layers, lose their cell-cell adhesion properties and acquire mesenchymal characteristics.[57-59] These include increased motility, invasiveness, and the ability to degrade components of the extracellular matrix.[60] EMT is essential during embryogenesis, tissue development, and wound healing, and plays a significant role in cancer metastasis.[61,62]

In nasopharyngeal carcinoma, the expression of WDR4 is significantly elevated, leading to a notable increase in the translation efficiency of m7G-modified codon-containing mRNA. This enhanced translation efficiency activates the WNT/β-catenin signaling pathway, thereby influencing the EMT process.[63]

3.4. EGFR pathway

The EGFR pathway is a critical cellular signaling pathway that plays a fundamental role in regulating biological processes such as cell proliferation, survival, migration, and differentiation. EGFR is a transmembrane receptor belonging to the receptor tyrosine kinase family.[64-66]

In addition to its regulation through the E3 ubiquitin ligase-mediated degradation of PTPN23,[12] as previously discussed, WDR4 has been shown to influence tRNA modification by regulating the M7G cap in HCC.[14] This tRNA modification enhances resistance to lenvatinib, a first-line tyrosine kinase inhibitor used in the treatment of advanced liver cancer.[67] Specifically, WDR4 promotes the translation of genes involved in the EGFR signaling pathway, contributing to the development of drug resistance.

Furthermore, in bladder cancer, WDR4, in collaboration with METTL1, modulates tRNA modifications to regulate the translation of EGFR and EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1).[68] This process activates the EGFR signaling pathway, emphasizing the significant role of tRNA modifications and their interaction with key oncogenic signaling pathways in cancer progression and drug resistance. Figure 4 illustrates the key role of WDR4 in the pathway.

4. Clinical implications and therapeutic potential of WDR4

4.1. WDR4 as a prognostic and predictive biomarker

Elevated WDR4 expression across multiple cancers correlates with poor clinical outcomes, underscoring its potential as a prognostic and predictive biomarker. High levels of WDR4 expression in patient samples correlate with increased metastasis, reduced survival rates, and resistance to standard therapies, suggesting its use as a biomarker for assessing tumor aggressiveness and therapeutic resistance.

4.2. Therapeutic targeting of WDR4

Several approaches are applied to target WDR4's oncogenic activity, including small-molecule inhibitors, RNA interference, gene editing, and combination therapies.

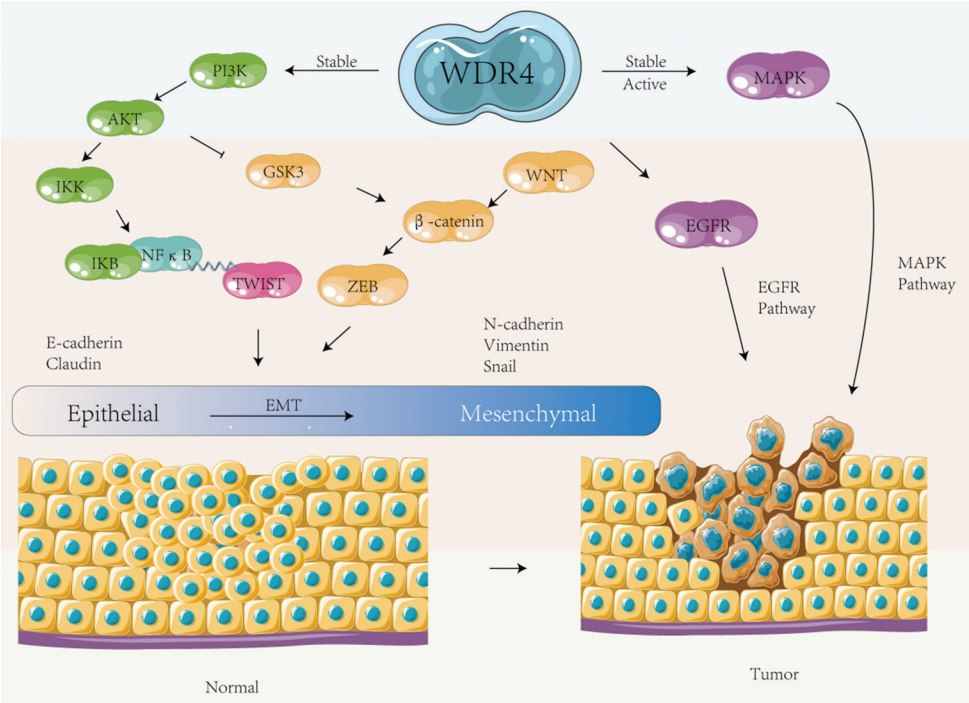


Figure 4. The key role of WDR4 in signaling pathway. WDR4 has the ability to modulate several signaling pathways, thereby contributing to the onset and progression of cancer.
Abbreviations: AKT: Protein kinase B; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; GSK3: Glycogen synthase kinase 3; IKB: Inhibitor of kappa B; IKK: IκB kinase; MAPK: Mitogen-activated protein kinase; NFκB: Nuclear factor kapp B; TWIST: Twist family BHLH transcription factor; WDR4: WD repeat domain 4; WNT: WD repeat domain 4; ZEB: Zinc finger E-box binding homeobox.

4.2.1. Small-molecule inhibitors

Developing small molecules that specifically inhibit WDR4's scaffold function or its involvement in RNA modification could hinder its tumor-promoting functions. However, achieving high specificity is challenging due to WDR4's role in normal cellular processes. Structure-based drug design and high-throughput screening could help identify compounds with optimal selectivity, minimizing off-target effects and preserving normal cellular functions.[69]

4.2.2. RNA interference and antisense oligonucleotides

RNA interference and antisense oligonucleotides targeting WDR4 mRNA offer a means to selectively reduce its expression in cancer cells, without affecting normal tissues. Pre-clinical studies have shown that silencing WDR4 in HCC and lung cancer models reduces tumor cell proliferation, and invasion, and promotes apoptosis.[14,17] Optimizing delivery systems, such as nanoparticle-based delivery, could improve these RNA-based therapies' tumor specificity and efficacy.[70]

4.2.3. Gene editing using CRISPR/Cas9

CRISPR/Cas9-mediated gene editing provides a precise approach to knocking out or reducing WDR4 expression in cancer cells. CRISPR-based WDR4 silencing in triple-negative breast cancer and HCC models has shown promise in reducing tumor growth and metastasis. Viral and non-viral vectors, such as lipid nanoparticles, are being explored to improve delivery efficiency, although managing off-target effects and ensuring specificity remain critical.[18]

4.2.4. Combination therapy approaches

Combining WDR4-targeted therapies with other treatments, such as cell cycle inhibitors, PI3K/mTOR pathway inhibitors, or immune checkpoint inhibitors, could enhance therapeutic efficacy. For example, in cancers where WDR4 stabilizes PI3K/Akt/mTOR pathway components, combination therapies with PI3K inhibitors may improve outcomes by inhibiting complementary survival pathways.

4.3. Challenges in clinical translation

Translating therapies targeting WDR4 into clinical practice faces several challenges. These include ensuring treatment selectivity to avoid toxicity in normal tissues, addressing tumor heterogeneity, and deepening our understanding of WDR4's role in normal physiology. To effectively overcome

these obstacles and fully realize the therapeutic potential of WDR4, advanced drug design, and innovative delivery systems will be critical. Specifically, developing highly selective inhibitors or modulators will help minimize side effects on non-tumor cells. In addition, personalized therapeutic strategies may be more effective in addressing the heterogeneity of different tumor types. Further research into the function of WDR4 in normal cells and tissues is warranted to explore strategies for avoiding unwanted side effects and for achieving precision treatment. Therefore, integrating basic research with clinical needs and fostering multidisciplinary collaboration in drug development are key steps toward the successful clinical translation of WDR4-targeted therapies.

5. Future directions for WDR4 research in cancer

To validate the therapeutic potential of WDR4-targeting strategy, future research should focus on mapping its interaction networks, developing precise preclinical models, exploring combination therapy approaches, and investigating its role in cancer stem cells and drug resistance. Understanding how WDR4 influences cancer biology and its interactions within the tumor microenvironment will be essential to unlock its potential as a therapeutic target.

6. Conclusion

Given its roles in RNA modification, protein stability, cell cycle regulation, and immune modulation, WDR4 represents a promising target in cancer therapy. Its overexpression and association with aggressive tumor phenotypes underscore its potential as both a biomarker and a therapeutic target. Advances in structural biology, preclinical modeling, and combination therapies could transform WDR4 into a cornerstone of cancer treatment, offering new hope for patients with aggressive and treatment-resistant cancers. Continued research into its molecular functions and interactions will be critical for translating WDR4-targeted therapies from bench to bedside.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Visualization: Xun Zou
Writing – original draft: All authors
Writing – review & editing: Bin Liu, Ling Tao

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Cheng W, Gao A, Lin H, Zhang W. Novel roles of METTL1/WDR4 in tumor via m^7G methylation. *Mol Ther Oncolytics*. 2022;26:27-34.

   doi: 10.1016/j.omto.2022.05.009

2. Michaud J, Kudoh J, Berry A, *et al*. Isolation and characterization of a human chromosome 21q22.3 gene (WDR4) and its mouse homologue that code for a WD-repeat protein. *Genomics*. 2000;68(1):71-79.

   doi: 10.1006/geno.2000.6258

3. Dedon PC, Begley TJ. Dysfunctional tRNA reprogramming and codon-biased translation in cancer. *Trends Mol Med*. 2022;28(11):964-978.

   doi: 10.1016/j.molmed.2022.09.007

4. Zhang X, Zhu WY, Shen SY, Shen JH, Chen XD. Biological roles of RNA m7G modification and its implications in cancer. *Biol Direct*. 2023;18(1):58.

   doi: 10.1186/s13062-023-00414-5

5. Tang Q, Li L, Wang Y, *et al*. RNA modifications in cancer. *Br J Cancer*. 2023;129(2):204-221.

   doi: 10.1038/s41416-023-02275-1

6. Zhang Y, Xu W, Peng C, *et al*. Exploring the role of m7G modification in Cancer: Mechanisms, regulatory proteins, and biomarker potential. *Cell Signal*. 2024;121:111288.

   doi: 10.1016/j.cellsig.2024.111288

7. Luo Y, Yao Y, Wu P, Zi X, Sun N, He J. The potential role of N^7-methylguanosine (m7G) in cancer. *J Hematol Oncol*.

2022;15(1):63.

doi: 10.1186/s13045-022-01285-5

8. Cai M, Yang C, Wang Z. N7-methylguanosine modification: From regulatory roles to therapeutic implications in cancer. *Am J Cancer Res*. 2023;13(5):1640-1655.

9. Du D, He J, Ju C, *et al*. When N^7-methyladenosine modification meets cancer: Emerging frontiers and promising therapeutic opportunities. *Cancer Lett*. 2023;562:216165.

doi: 10.1016/j.canlet.2023.216165

10. Wang YT, Chen RH. PML degradation fosters an immunosuppressive and pro-metastatic tumor microenvironment. *Mol Cell Oncol*. 2017;4(6):e1364212.

doi: 10.1080/23723556.2017.1364212

11. Singh S, Yeat NY, Wang YT, *et al*. PTPN23 ubiquitination by WDR4 suppresses EGFR and c-MET degradation to define a lung cancer therapeutic target. *Cell Death Dis*. 2023;14(10):671.

doi: 10.1038/s41419-023-06201-4

12. Xia P, Zhang H, Xu K, *et al*. MYC-targeted WDR4 promotes proliferation, metastasis, and sorafenib resistance by inducing CCNB1 translation in hepatocellular carcinoma. *Cell Death Dis*. 2021;12(7):691.

doi: 10.1038/s41419-021-03973-5

13. Wang YT, Chen J, Chang CW, *et al*. Ubiquitination of tumor suppressor PML regulates prometastatic and immunosuppressive tumor microenvironment. *J Clin Invest*. 2017;127(8):2982-2997.

doi: 10.1172/JCI89957

14. Huang M, Long J, Yao Z, *et al*. METTL1-Mediated m7G tRNA modification promotes lenvatinib resistance in hepatocellular carcinoma. *Cancer Res*. 2023;83(1):89-102.

doi: 10.1158/0008-5472.CAN-22-0963

15. Zhu S, Wu Y, Zhang X, *et al*. Targeting N^7-methylguanosine tRNA modification blocks hepatocellular carcinoma metastasis after insufficient radiofrequency ablation. *Mol Ther*. 2023;31(6):1596-1614.

doi: 10.1016/j.ymthe.2022.08.004

16. Dong R, Wang C, Tang B, *et al*. WDR4 promotes HCC pathogenesis through N^7-methylguanosine by regulating and interacting with METTL1. *Cell Signal*. 2024;118:111145.

doi: 10.1016/j.cellsig.2024.111145

17. Ma J, Han H, Huang Y, *et al*. METTL1/WDR4-mediated m(7)G tRNA modifications and m(7)G codon usage promote mRNA translation and lung cancer progression. *Mol Ther*. 2021;29(12):3422-3435.

doi: 10.1016/j.ymthe.2021.08.005

18. Liu Y, Jiang B, Lin C, *et al*. m7G-related gene NUDT4 as a novel biomarker promoting cancer cell proliferation in lung adenocarcinoma. *Front Oncol*. 2022;12:1055605.

doi: 10.3389/fonc.2022.1055605

19. Duan HP, Yan JH, Nie L, Wang Y, Xie H. A noval prognostic signature of the N7-methylguanosine (m7G)-related miRNA in lung adenocarcinoma. *BMC Pulm Med*. 2023;23(1):14.

doi: 10.1186/s12890-022-02290-7

20. Chen J, Li K, Chen J, *et al*. Aberrant translation regulated by METTL1/WDR4-mediated tRNA N7-methylguanosine modification drives head and neck squamous cell carcinoma progression. *Cancer Commun* (*Lond*). 2022;42(3):223-244.

doi: 10.1002/cac2.12273

21. Xu F, Cai D, Liu S, *et al*. N7-methylguanosine regulatory genes well represented by METTL1 define vastly different prognostic, immune and therapy landscapes in adrenocortical carcinoma. *Am J Cancer Res*. 2023;13(2):538-568.

22. Zhai Q, Hou Y, Ye Y, *et al*. Expression pattern and prognostic value of key regulators for N7-methylguanosine RNA modification in prostate cancer. *Acta Biochim Biophys Sin (Shanghai)*. 2023;55(4):561-573.

doi: 10.3724/abbs.2023017

23. Mei W, Jia X, Xin S, *et al*. A N^7-methylguanine-related gene signature applicable for the prognosis and microenvironment of prostate cancer. *J Oncol*. 2022;2022:8604216.

doi: 10.1155/2022/8604216

24. Han H, Yang C, Ma J, *et al*. N^7-methylguanosine tRNA modification promotes esophageal squamous cell carcinoma tumorigenesis via the RPTOR/ULK1/autophagy axis. *Nat Commun*. 2022;13(1):1478.

doi: 10.1038/s41467-022-29125-7

25. He S, Zhu J, Xiao Z, *et al*. WDR4 gene polymorphisms increase hepatoblastoma susceptibility in girls. *J Cancer*. 2022;13(12):3342-3347.

doi: 10.7150/jca.76255

26. Deng L, Hua RX, Deng C, *et al*. WDR4 gene polymorphisms and Wilms tumor susceptibility in Chinese children: A five-center case-control study. *J Cancer*. 2023;14(8):1293-1300.

doi: 10.7150/jca.83747

27. Jain BP, Pandey S. WD40 repeat proteins: Signalling scaffold with diverse functions. *Protein J*. 2018;37(5):391-406.

doi: 10.1007/s10930-018-9785-7

28. Alexandrov A, Martzen MR, Phizicky EM. Two proteins that form a complex are required for 7-methylguanosine modification of yeast tRNA. *RNA*. 2002;8(10):1253-1266.

doi: 10.1017/s1355838202024019

29. Li J, Wang L, Hahn Q, *et al*. Structural basis of regulated m^7G tRNA modification by METTL1-WDR4. *Nature*. 2023;613(7943):391-397.

doi: 10.1038/s41586-022-05566-4

30. Li R, Liu X, Deng K, Wang X. M^7G methylated core genes (METTL1 and WDR4) and associated RNA risk signatures are associated with prognosis and immune escape in HCC. *BMC Med Genomics*. 2023;16(1):179.

doi: 10.1186/s12920-023-01614-8

31. Wu PR, Chiang SY, Midence R, *et al*. Wdr4 promotes cerebellar development and locomotion through Arhgap17-mediated Rac1 activation. *Cell Death Dis*. 2023;14(1):52.

doi: 10.1038/s41419-022-05442-z

32. Patel DA, Patel SS, Patel HD. Advances in synthesis and biological evaluation of CDK2 inhibitors for cancer therapy. *Bioorg Chem*. 2024;143:107045.

doi: 10.1016/j.bioorg.2023.107045

33. Rubin SM, Sage J, Skotheim JM. Integrating old and new paradigms of G1/S control. *Mol Cell*. 2020;80(2):183-192.

doi: 10.1016/j.molcel.2020.08.020

34. Zhang H, Lin J, Yahaya BH. Comprehensive analysis of co-expressed genes with TDP-43: Prognostic and therapeutic potential in lung adenocarcinoma. *J Cancer Res Clin Oncol*. 2024;150(2):44.

doi: 10.1007/s00432-023-05554-9

35. Dong S, Alahari SK. Small molecule Mcl-1 inhibitor for triple negative breast cancer therapy. *Front Cell Dev Biol*. 2024;12:1408107.

doi: 10.3389/fcell.2024.1408107

36. Nguyen D, Osterlund E, Kale J, Andrews DW. The C-terminal sequences of Bcl-2 family proteins mediate interactions that regulate cell death. *Biochem J*. 2024;481(14):903-922.

doi: 10.1042/BCJ20210352

37. Cauwelier C, De Ridder I, Bultynck G. Recent advances in canonical versus non-canonical Ca^{2+}-signaling-related anti-apoptotic Bcl-2 functions and prospects for cancer treatment. *Biochim Biophys Acta Mol Cell Res*. 2024;1871(5):119713.

doi: 10.1016/j.bbamcr.2024.119713

38. Ummarino A, Cala N, Allavena P. Extrinsic and cell-intrinsic stress in the immune tumor micro-environment. *Int J Mol Sci*. 2024;25(22):12403.

doi: 10.3390/ijms252212403

39. Zhang Z, Su M, Jiang P, Wang X, Tong X, Wu G. Unlocking apoptotic pathways: Overcoming tumor resistance in CAR-T-cell therapy. *Cancer Med*. 2024;13(19):e70283.

doi: 10.1002/cam4.70283

40. Wang S, Liu C, Yang C, *et al*. PI3K/AKT/mTOR and PD1/CTLA4/CD28 pathways as key targets of cancer immunotherapy (review). *Oncol Lett*. 2024;28(6):567.

doi: 10.3892/ol.2024.14700

41. Peng Y, Wang Y, Zhou C, Mei W, Zeng C. PI3K/Akt/mTOR pathway and its role in cancer therapeutics: Are we making headway? *Front Oncol*. 2022;12:819128.

doi: 10.3389/fonc.2022.819128

42. Meuten TK, Dean GA, Thamm DH. Review: The PI3K-AKT-mTOR signal transduction pathway in canine cancer. *Vet Pathol*. 2024;61(3):339-356.

doi: 10.1177/03009858231207021

43. Zhang HP, Jiang RY, Zhu JY, *et al*. PI3K/AKT/mTOR signaling pathway: An important driver and therapeutic target in triple-negative breast cancer. *Breast Cancer*. 2024;31(4):539-551.

doi: 10.1007/s12282-024-01567-5

44. Leiphrakpam PD, Are C. PI3K/Akt/mTOR signaling pathway as a target for colorectal cancer treatment. *Int J Mol Sci*. 2024;25(6):3178.

doi: 10.3390/ijms25063178

45. Hao C, Wei Y, Meng W, Zhang J, Yang X. PI3K/AKT/mTOR inhibitors for hormone receptor-positive advanced breast cancer. *Cancer Treat Rev*. 2025;132:102861.

doi: 10.1016/j.ctrv.2024.102861

46. Browne IM, Okines AFC. Resistance to targeted inhibitors of the PI3K/AKT/mTOR pathway in advanced oestrogen-receptor-positive breast cancer. *Cancers* (*Basel*). 2024;16(12):2259.

doi: 10.3390/cancers16122259

47. Zhao P, Zhang X, Dong J, Li L, Meng X, Gao L. *In vitro* study of the pro-apoptotic mechanism of amino acid Schiff base copper complexes on anaplastic thyroid cancer. *Eur J Pharm Sci*. 2025;206:107005.

doi: 10.1016/j.ejps.2025.107005

48. Zhang F, Wu X, Jiao T, *et al*. Genomic characterization reveals distinct mutational landscape of acral melanoma in East Asian. *J Genet Genomics*. 2025.

doi: 10.1016/j.jgg.2024.12.018

49. You YL, Byun HJ, Chang Y, *et al*. *Euglena gracilis*-derived racilis, 24.12.018es particulate matter ($PM_{2.5}$)-induced airway inflammation by modulating nuclear factor kappa B, mitogen-activated protein kinase, and nuclear factor erythroid 2-related factor 2 signaling pathways in A549 cells and BALB/c mice. *Int J Biol Macromol*. 2025;296:139671.

doi: 10.1016/j.ijbiomac.2025.139671

50. Wu S, Nasser BSA, Ll NG, *et al*. The regulatory role of integrin in gastric cancer tumor microenvironment and drug resistance. *Prog Biophys Mol Biol*. 2025;195:130-136.

doi: 10.1016/j.pbiomolbio.2025.01.001

51. Lu Q, Tang X, Tao B, *et al*. Multifunctional hyaluronic acid microneedle patch enhances diabetic wound healing in

diabetic infections. *Int J Biol Macromol*. 2025;296:139685.

doi: 10.1016/j.ijbiomac.2025.139685

52. Liang C, Liu J, Jiang M, Zhu Y, Dong P. The advancement of targeted regulation of hepatic stellate cells using Traditional Chinese medicine for the treatment of liver fibrosis. *J Ethnopharmacol*. 2025;341:119298.

doi: 10.1016/j.jep.2024.119298

53. Wang Y, Xiong G, Cai W, Tao Q. METTL1 facilitates ameloblastoma invasive growth via MAPK signaling pathway. *Gene*. 2024;905:148234.

doi: 10.1016/j.gene.2024.148234

54. Wang M, Zheng Y, Hao Q, *et al*. Hypoxic BMSC-derived exosomal miR-210-3p promotes progression of triple-negative breast cancer cells via NFIX-Wnt/beta-catenin signaling axis. *J Transl Med*. 2025;23(1):39.

doi: 10.1186/s12967-024-05947-5

55. Utpal BK, Roy SC, Zehravi M, *et al*. Polyphenols as Wnt/M, i M, -5pathway modulators: A promising strategy in clinical neurodegeneration. *Anim Model Exp Med*. 2025.

doi: 10.1002/ame2.12525

56. Singhai H, Raikwar S, Rathee S, Jain SK. Emerging combinatorial drug delivery strategies for breast cancer: A comprehensive review. *Curr Drug Targets*. 2025.

doi: 10.2174/0113894501352081241211090911

57. Ye TT, Chen WH, Pei J, Jia YX, Wu HY. Expression and clinical significance of NEK2 and EMT related molecules in oral squamous cell carcinoma. *Shanghai Kou Qiang Yi Xue*. 2023;32(6):640-644.

doi: 10.19439/j.sjos.2023.06.014

58. Ye F, Xie L, Liang L, *et al*. Mechanisms and therapeutic strategies to combat the recurrence and progression of hepatocellular carcinoma after thermal ablation. *J Interv Med*. 2023;6(4):160-169.

doi: 10.1016/j.jimed.2023.10.004

59. Yang HW, Chun-Yu Ho D, Liao HY, *et al*. Resveratrol inhibits arecoline-induced fibrotic properties of buccal mucosal fibroblasts via miR-200a activation. *J Dent Sci*. 2024;19(2):1028-1035.

doi: 10.1016/j.jds.2023.06.027

60. Wang R, Zhu F, Gao G, *et al*. B-cell specific Moloney murine leukemia virus insertion site 1 contributes to invasion, metastasis, and poor prognosis in salivary adenoid cystic carcinoma. *J Dent Sci*. 2024;19(1):21-31.

doi: 10.1016/j.jds.2023.06.014

61. Poryazova E, Serteva D, Markov D, Chonov V, Markov G. Expression of snail and twist compared with clinical and pathological parameters in patients with gastric cancer. *Folia Med (Plovdiv)*. 2023;65(3):393-398.

doi: 10.3897/folmed.65.e84132

62. Pek JH, Quah LJJ, Teng KPD, Yeo YWM, Lee CYJ. Developing the disaster medical responderndecourse in Singapore. *Western Pac Surveill Response J*. 2023;14(6 Spec edition):1-6.

doi: 10.5365/wpsar.2023.14.6.1009

63. Chen B, Jiang W, Huang Y, *et al*. N^7-methylguanosine tRNA modification promotes tumorigenesis and chemoresistance through WNT/ters in patients with gastric cancer. noma. cin*Oncogene*. 2022;41(15):2239-2253.

doi: 10.1038/s41388-022-02250-9

64. Sabbah DA, Hajjo R, Sweidan K. Review on epidermal growth factor receptor (EGFR) structure, signaling pathways, interactions, and recent updates of EGFR inhibitors. *Curr Top Med Chem*. 2020;20(10):815-834.

doi: 10.2174/1568026620666200303123102

65. Talukdar S, Emdad L, Das SK, Fisher PB. EGFR: An essential receptor tyrosine kinase-regulator of cancer stem cells. *Adv Cancer Res*. 2020;147:161-188.

doi: 10.1016/bs.acr.2020.04.003

66. Singh D, Attri BK, Gill RK, Bariwal J. Review on EGFR inhibitors: Critical updates. *Mini Rev Med Chem*. 2016;16(14):1134-1166.

doi: 10.2174/1389557516666160321114917

67. Al-Salama ZT, Syed YY, Scott LJ. Lenvatinib: A review in hepatocellular carcinoma. *Drugs*. 2019;79(6):665-674.

doi: 10.1007/s40265-019-01116-x

68. Ying X, Liu B, Yuan Z, *et al*. METTL1-m^7 G-EGFR/EFEMP1 axis promotes the bladder cancer development. *Clin Transl Med*. 2021;11(12):e675.

doi: 10.1002/ctm2.675

69. Nai F, Flores Espinoza MP, Invernizzi A, *et al*. Small-Molecule Inhibitors of the m7G-RNA Writer METTL1. *ACS Bio Med Chem Au*. 2024;4(2):100-110.

doi: 10.1021/acsbiomedchemau.3c00030

70. Zhao W. Ling-Ling Chen: RNA has its own features; don't study it as a protein. *Natl Sci Rev*. 2024;11(2):nwad287.

doi: 10.1093/nsr/nwad287