Role of CHD4 in tumor progression, DNA damage response and treatment resistance (Review)

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Abstract. Chromodomain helicase DNA-binding protein 4 (CHD4) is a core adenosine triphosphate (ATP)-dependent chromatin-remodeling factor of the nucleosome-remodeling and deacetylase (NuRD) complex. It plays a crucial role in chromatin structure regulation, gene expression regulation, and DNA damage response. It has been demonstrated that CHD4 has context-dependent functions in tumor development and progression. It can influence tumor progression via such mechanisms as regulating tumor-related signaling pathways, maintaining the silencing of tumor suppressor genes, and promoting metabolic adaptation; it can also exert tumor-suppressive effects in specific transcriptional regulatory environments. Additionally, during DNA damage response, CHD4 participates in chromatin remodeling at damage sites, in cell cycle recovery, and in repair pathway selection. It is also involved in the development of tumor treatment resistance through mechanisms that include regulation of DNA repair, cell cycle progression, drug efflux, the tumor immune microenvironment, and replication fork stability. It has also been shown that various non-coding RNAs participate in the functional regulation of CHD4 by modulating its expression, localization, and protein stability. In summary, as a key node connecting chromatin regulation, genome stability, and tumor treatment response, CHD4 holds significant importance in tumor progression and treatment.

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Contents

1. Introduction

The occurrence and development of tumors are complex processes driven by multiple factors, including accumulation of gene mutations (1), imbalance in epigenetic regulation (2), and abnormalities in key signaling pathways (3). Although high-throughput sequencing technology has systematically depicted the mutation landscapes of different tumor types (4), gene mutations alone are insufficient to fully explain the high degree of plasticity and adaptability exhibited by tumor cells under different microenvironments and treatment pressures. By contrast, epigenetic regulation is dynamic and reversible, enabling tumor cells to rapidly reshape their transcriptional processes without altering the DNA sequence, which allows them to adapt to environmental changes and gain survival advantages (5). Therefore, chromatin-level regulation is an important mechanistic basis for understanding tumor progression and differences in treatment responses.

Of numerous chromatin-remodeling complexes, the nucleosome-remodeling and deacetylase (NuRD) complex holds a unique position due to its simultaneous adenosine triphosphate (ATP)-dependent chromatin-remodeling activity and histone deacetylase (HDAC) activity (6). Structural studies have revealed that the NuRD complex has a highly modular organizational form. The HDAC-metastasis-associated protein (MTA)-retinoblastoma-binding protein subunits form a relatively stable deacetylase core, while chromodomain helicase DNA-binding protein 3 or 4 (CHD3, CHD4) constitutes the ATP-dependent chromatin-remodeling module. The selective assembly of different subunits determines the functional characteristics of different NuRD subtypes (7) (Fig. 1).

CHD4 belongs to the CHD family of chromatin-remodeling proteins and contains multiple conserved functional domains. Its N-terminus has two tandem plant homeodomain (PHD) finger domains that can recognize histone H3 tail modifications, thereby promoting localization of the NuRD complex to chromatin regions associated with gene silencing (8). Following the PHD finger domains, CHD4 has two tandem chromodomains that can interact with nucleosomal DNA and participate in regulation of ATPase activity. Its central region encompasses a highly conserved sucrose non-fermentable 2 (SNF2) family ATPase/helicase domain, which provides energy via ATP hydrolysis to drive nucleosome sliding (9). In addition to the ATPase core domain, multiple auxiliary regions of CHD4 are also involved in its functional regulation. For example, the N-terminal disordered region can enhance chromatin-remodeling activity, while the C-terminal region has a certain self-inhibitory effect, thereby limiting the catalytic ability of the ATPase. When the SWItch 3-adenosine deaminase 2-nuclear receptor corepressor 1-transcription factor IIIB/SANT-like Imitation SWItch domain (SANT/SLIDE) DNA-binding domain binds to DNA, this self-inhibitory state can be relieved, thereby activating the nucleosome-remodeling function of CHD4 (10). Through the synergistic action of these domains, CHD4 plays important roles in gene expression regulation (11), DNA damage response (DDR) (12), and chromatin structure regulation (13,14). Therefore, abnormal expression or gene mutations of *Chd4* are closely associated with various human diseases, including congenital developmental defects and neurological disorders (6). Meanwhile, an increasing number of studies have shown that CHD4 also plays a key role in tumor initiation, tumor evolution, and the development of treatment resistance (15).

2. Context-dependent roles of CHD4 in tumor progression

CHD4 is a typical context-dependent epigenetic regulator. In different cell types, chromatin environments, and signaling pathways, CHD4 can either promote tumorigenesis or exhibit tumor-suppressive functions (16).

Molecular mechanisms by which CHD4 promotes tumor progression. In various solid tumors, high expression of CHD4 is often associated with increased tumor aggressiveness, enhanced metastatic potential, and poor prognosis, suggesting that its role in tumor progression is crucial (17). Recent studies have shown that CHD4 does not function through a single molecular pathway but is more likely to influence tumor cell behavior by regulating multiple interconnected transcriptional processes (18-20).

Of these transcriptional regulatory networks (TRNs), oncogenic signaling pathways form an important basis for CHD4's involvement in tumor migration and invasion. Wingless/Integrated (Wnt)/β-catenin is a typical signaling pathway through which CHD4 regulates tumor metastasis. In gastric cancer (GC), CHD4 interacts with myosin heavy chain 9, thereby inhibiting the activity of glycogen synthase kinase-3β and stabilizing β-catenin, which activates the Wnt/epithelial-mesenchymal transition (EMT) signaling pathway, thereby promoting tumor invasion and metastasis (18). Similar regulatory patterns can also be observed in ovarian cancer, where CHD4 enhances nuclear accumulation and transcriptional activity of β-catenin through the enhancer of zeste homolog 2 (EZH2)/β-catenin signaling axis (19). These studies suggest that CHD4 may repeatedly participate in the regulation of β-catenin-related transcriptional processes in different tumor types, thereby promoting EMT and tumor metastasis. In addition to the Wnt/β-catenin pathway, CHD4's influence on tumor cell migration is also closely related to cytoskeleton-related signaling pathways. In non-small cell lung cancer, CHD4 activates the *Ras* homolog gene family, member A (RhoA)/ρ-associated protein kinase signaling pathway by regulating PHD finger protein 5A, thereby enhancing the proliferation and migratory ability of tumor cells (20). This mechanism suggests that CHD4 might help regulate tumor cell movement by affecting cytoskeletal dynamics and act as a bridge between different signaling networks.

The regulatory role of CHD4 is not limited to cell migration but also extends to regulation of tumor cell proliferation. For example, in breast cancer (BC), CHD4 upregulates the transcriptional levels of estrogen receptor-α (ERα) and inhibits its ubiquitination degradation, thereby continuously enhancing the transcriptional activity of the ERα signaling pathway (21). This phenomenon indicates that CHD4 can not only regulate classical signaling pathways but might also further amplify oncogenic signals by stabilizing key transcription factors (TFs).

A hypoxic state in the tumor microenvironment (TME) further expands the functions of CHD4, which can co-activate hypoxia-inducible factors 1α and 2α (HIF-1α, HIF-2α), synergistically promoting the transcription of hypoxia-responsive genes with the HIF complex. Under normoxic conditions, CHD4 is already enriched in the promoter regions of HIF target genes and promotes the loading of RNA polymerase II via p300, while HIF activation under hypoxic conditions further enhances the recruitment of CHD4 to chromatin, forming a positive-feedback regulatory loop and amplifying the hypoxia response signal (22). This process suggests that the chromatin-binding and transcriptional regulatory activity of CHD4 may be further enhanced under hypoxic conditions. Such changes may further affect the downstream TRN of CHD4. For example, CHD4 can promote citrullination of the key glycolytic enzyme pyruvate kinase muscle isozyme 2 (PKM2) by regulating the expression of peptidyl arginine deiminases 1 and 3 (PADI1, PADI3), thereby altering PKM2's metabolic regulatory mode and enhancing glycolytic activity (23). Given that enhanced glycolysis is an important means by which tumor cells adapt to hypoxic environments, this CHD4-PADI1/3-PKM2 regulatory axis may be a mechanism by which CHD4 participates in tumor metabolic adaptation under hypoxic conditions.

In addition to signaling and metabolic regulation, CHD4 also participates in tumorigenesis by maintaining the silencing of tumor suppressor genes. In colorectal cancer (CRC), CHD4 is recruited to DNA damage sites and further recruits DNA methyltransferases (DNMTs) to establish abnormal DNA methylation and maintain suppressive chromatin structures at the promoter regions of multiple tumor suppressor genes (24). Moreover, CHD4 can synergize with DNMT1 and DNMT3B to jointly maintain the stable silencing of tumor suppressor genes through multiple epigenetic mechanisms, including DNA methylation, histone deacetylation, and nucleosome remodeling (25).

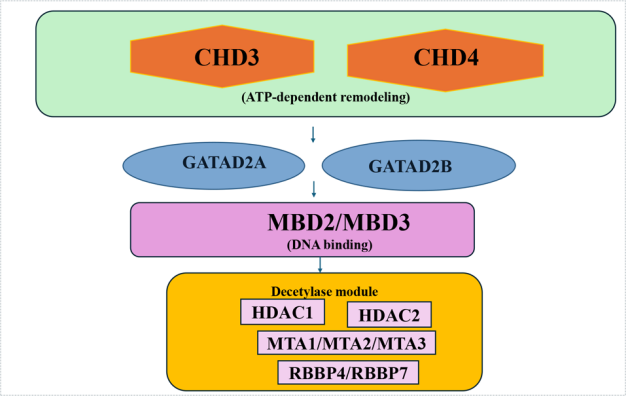

Figure 1. Modular organization of the NuRD Complex. CHD3 and CHD4 constitute the ATP-dependent chromatin-remodeling module, which interacts with GATAD2A/B and MBD2/3. The deacetylase module contains HDAC1/2, MTA1/2/3 and RBBP4/7. NuRD, nucleosome remodeling and deacetylase; CHD3, chromodomain helicase DNA-binding protein 3; CHD4, chromodomain helicase DNA-binding protein 4; GATAD2A, GATA zinc finger domain containing 2A; GATAD2B, GATA zinc finger domain containing 2B; MBD2, methyl-CpG-binding domain protein 2; MBD3, methyl-CpG-binding domain protein 3; HDAC1, histone deacetylase 1; HDAC2, histone deacetylase 2; MTA1/2/3, metastasis-associated proteins 1/2/3; RBBP4, retinoblastoma-binding protein 4; RBBP7, retinoblastoma-binding protein 7.

It is worth noting that in certain tumor types, CHD4 also helps maintain chromatin structural homeostasis. For example, in Ewing sarcoma, CHD4 deletion leads to chromatin structural disorders and induces spontaneous DNA damage accumulation, thereby significantly inhibiting tumor cell proliferation (13). This phenomenon suggests that the role of CHD4 may be highly dependent on the context of the specific tumor environment.

Taken together, these studies paint an increasingly clearer picture: CHD4 reshapes tumor cell behavior through multiple mechanisms, including regulation of signaling pathways, microenvironment adaptation, metabolic reprogramming, and epigenetic regulation, thereby promoting tumor progression.

Tumor-suppressive role of CHD4 in specific transcriptional environments. Although numerous studies have shown that CHD4 has oncogenic effects in various tumors, under specific transcriptional regulatory conditions, it may also exhibit tumor-suppressive functions. For example, in luminal-type BC, the TF transcriptional repressor GATA binding 1 (TRPS1) can recruit the CHD4/NuRD (MTA2) complex to the promoter region of tp63, inhibiting tp63 expression via chromatin remodeling and thereby limiting tumor cell migration and invasion (26). Further research has found that TRPS1 can also recruit CHD4 to the regulatory region of sex-determining region Y (SRY)-related high-mobility group (HMG) box 2 (SOX2), inhibiting SOX2 transcription by altering local chromatin structure (27). Since SOX2 is an important factor for maintaining cancer stem cell characteristics, the TRPS1-CHD4-SOX2 regulatory axis can exert tumor-suppressive effects by limiting tumor stemness. In addition, CHD4 can help inhibit tumor progression by regulating enhancer activity. Studies have shown that AT-rich interactive domain-containing protein 1A (ARID1A) promotes the binding of the CHD4-zinc finger myeloid, Nervy, and deformed epidermal autoregulatory factor 1 homolog, or MYND, type containing 8 (ZMYND8) complex to super-enhancers by maintaining the distribution of the histone variant H3.3 on chromatin, thereby exerting transcriptional inhibitory effects on genes related to EMT and cell migration. When ARID1A function is lost, the transcriptional inhibition mediated by CHD4-ZMYND8 is disrupted, leading to excessive activation of super-enhancers and promoting tumor cell migration and invasion (16).

The results of the aforementioned studies indicate that when CHD4 synergizes with specific TFs or chromatin regulators, it can limit the activation of abnormal transcriptional processes by maintaining suppressive chromatin structures, thereby exerting tumor-suppressive effects under specific contexts.

Effect of Chd4 mutations on tumor progression. In addition to changes in expression levels, mutations to the *Chd4* gene can also reshape the TRN related to tumor progression. It has been shown that *Chd4* mutations do not necessarily lead to complete loss of its function but may reshape the cell's transcriptional process by altering its chromatin-remodeling activity or target gene selectivity. This view was first supported by functional studies. Researchers used the *Drosophila* homolog dMi-2 as a model to systematically analyze various missense mutations of *Chd4* obtained from patients with tumors. The results revealed that these mutations could alter the ATPase activity, nucleosome-binding ability, and nucleosome-sliding efficiency of *Chd4* in a mutation-specific manner. Some mutations reduce ATP hydrolysis ability or weaken chromatin-remodeling efficiency, while others may enhance related activities (28). Similar mutation effects have also been observed in human tumors. For example, in endometrial cancer, the common mutations R975H and R1162W can reduce CHD4 protein stability and weaken its function, thereby activating the transforming growth factor-β signaling pathway and enhancing cancer cell stemness characteristics (29). Another study also found that the R975H mutation could activate multiple oncogenic signaling pathways, such as tumor necrosis factor-α/nuclear factor κ-light-chain-enhancer of activated B cells, Kirsten *Ras* oncogene homolog, mammalian target of rapamycin, and myelocytomatosis oncogene; and promote polarization of tumor-associated macrophages toward an immunosuppressive M2 phenotype, thereby enhancing tumor immune escape ability (15). In addition to missense mutations, some truncating mutations located in the SNF2 domain (such as p.Trp736Ter) may also disrupt the integrity of the NuRD complex and lead to abnormal chromatin remodeling, thereby promoting tumorigenesis and metastasis (30). In conclusion, the effects of *Chd4* mutations on tumor progression show significant heterogeneity.

3. CHD4 in DDR and tumor treatment resistance

Regulatory role of CHD4 in DDR. DDR, the core defense system allowing cells to maintain genomic integrity, encompasses multiple stages such as damage recognition, signal transduction, chromatin remodeling and DNA repair (31). It has been shown that dynamic changes in chromatin structure are an indispensable regulatory link in the DDR chain. As an

important chromatin-remodeling factor, CHD4 plays a crucial role in this process (32).

After the occurrence of DNA double-strand breaks (DSBs), cells first rapidly recognize the damaged sites through poly [adenosine diphosphate (ADP)-ribose] polymerase 1/2 (PARP1/2)-mediated poly-ADP-ribosylation reactions. Poly [adenosine diphosphate (ADP)-ribose] (PAR) chains not only serve as a scaffold for recruiting DNA repair factors but they can also induce local chromatin relaxation, thereby promoting recruitment of repair factors (33). Studies have demonstrated that at this stage, CHD4 can be rapidly recruited to DNA damage sites in a PAR-dependent manner and participate in early chromatin remodeling (32). In the early stages of DDR, CHD4 usually works in concert with the acetyltransferase p300. P300 reduces chromatin compaction through histone acetylation, while CHD4 relies on its ATPase activity to regulate nucleosome positions. This maintains a relatively open and dynamic chromatin state in the damaged region, thereby providing optimal conditions for the entry of DNA repair factors (34).

As DDR signals are further amplified, ataxia telangiectasia mutated protein (ATM) kinase is activated and initiates a series of signal cascades. Really Interesting New Gene finger protein 8 (RNF8)-mediated histone ubiquitination is considered an important step in signal amplification. RNF8 can catalyze the ubiquitination modification of H2A and H2A histone family member X, providing a molecular platform for the stable binding of DNA repair complexes such as breast cancer type 1 (BRCA1) (35). During this catalytic process, CHD4 enhances the spatial accessibility between RNF8 and its substrates by regulating the chromatin structure around the damaged sites, thereby promoting formation of ubiquitin chains. Meanwhile, RNF8 can also promote recruitment of additional CHD4 to the damaged region via a non-catalytic mechanism, forming a positive-feedback regulatory loop at damaged sites and further stabilizing the assembly of DNA repair complexes (36).

Regulation of DDR also relies on the synergistic action of multiple chromatin regulatory factors. For example, the silent mating type information regulation 2 homolog 6 (SIRT6)/CHD4 pathway is considered an important regulatory branch for DSB repair. SIRT6 can act as a damage sensor and promote early signal amplification by activating PARP1 (37); under ATM-dependent conditions, interaction between SIRT6 and CHD4 is significantly enhanced, and they jointly promote chromatin remodeling at the damaged sites and homologous recombination repair (HRR). When ATM activity is inhibited or absent, this synergistic effect is significantly weakened, leading to a decrease in HRR efficiency (38). In addition, it has been demonstrated that CHD4-mediated chromatin remodeling may also affect the choice of DNA repair pathways via regulation of R-loop-related mechanisms. When DSBs occur in transcriptionally active chromatin regions, the bromodomain and extra-terminal domain family protein bromodomain-containing protein 3 can recruit CHD4 and work in concert with the Tat interacting protein, 60 kDa complex to initiate chromatin remodeling, promoting histone H4-lysine 16 acetylation and expelling heterochromatin protein 1. This inhibits the binding of p53 binding protein 1 at damaged sites and promotes the recruitment of BRCA1 and R-loop-related repair factors (39), a process that ultimately promotes R-loop-mediated HRR. Taken together, these findings suggest that CHD4 can affect DNA repair pathway selection by regulating R-loop-related chromatin remodeling, thereby maintaining genomic stability.

As DNA damage is gradually repaired, cells must terminate DDR signals in a timely manner and restore normal cell cycle progression. The ATM-checkpoint kinase 2-p53 signaling axis plays a central role in this process: p53 can induce p21 expression to mediate G1/S checkpoint arrest, thereby providing a window of time for DNA repair (40). It has been revealed that as a core subunit of the NuRD complex, CHD4 can mediate p53 deacetylation and inhibit its transcriptional activity (41). This suggests that CHD4 may be involved in terminating DDR signals and restoring cell cycle after DNA repair is completed.

In the more complex chromatin regulatory network (CRN), the overall synergistic action of the NuRD complex is also crucial for DDR. For example, the R-loop structure formed on DNA damage can promote the establishment of chromatin boundaries via the GATA zinc finger domain containing 2B/NuRD complex in the damaged region, thereby limiting excessive DNA end resection and maintaining the stability of the repair process (42). In addition, in the PARP-dependent repair pathway, chromatin regulatory factors such as lysine (K)-specific demethylase 5A and ZMYND8 can further stabilize the enrichment of CHD4 at damaged sites by interacting with NuRD complex subunits (43). The aforementioned CRNs jointly participate in the dynamic remodeling of chromatin structure in the damaged region, thereby affecting the localization of DNA repair factors and choice of repair pathways (Fig. 2).

CHD4 and tumor treatment resistance. Abnormal CHD4 expression is closely related to insensitivity of tumors to radiotherapy (44) and chemotherapy (CT) (45), suggesting that it plays an important role in the development of tumor treatment resistance. In the context of DNA-damaging treatment, CHD4 can regulate chromatin structure to keep DDR-related genes ready to be rapidly activated, thereby enhancing tumor cells' ability to repair treatment-induced DNA damage. This effect is relatively typical in glioblastoma, where CHD4 maintains the expression of key HRR factors such as RAD51, thereby increasing tumor cell resistance to radiotherapy and DNA-damaging CT drugs (46). This phenomenon suggests that the treatment resistance mediated by CHD4 is not merely due to changes in a single repair factor but rather reflects CHD4's regulation of the DNA repair transcriptional process's overall accessibility.

In addition to enhanced DNA repair ability, CHD4 can also participate in CT resistance by regulating pro-survival signaling pathways and drug efflux mechanisms. In GC, high CHD4 expression is closely related to tumor progression and CT resistance. CHD4 promotes the interaction between mitogen-activated protein kinase (MEK1/2) and extracellular signal-regulated kinase 1/2 (ERK1/2) and activates the MEK/ERK signaling pathway, thereby maintaining continuous phosphorylation of ERK and enhancing the proliferation and survival ability of tumor cells. Meanwhile, this pathway can also upregulate major vault protein expression, promote drug efflux, and reduce the intracellular concentration of CT drugs (for example, cisplatin), ultimately leading to CT resistance

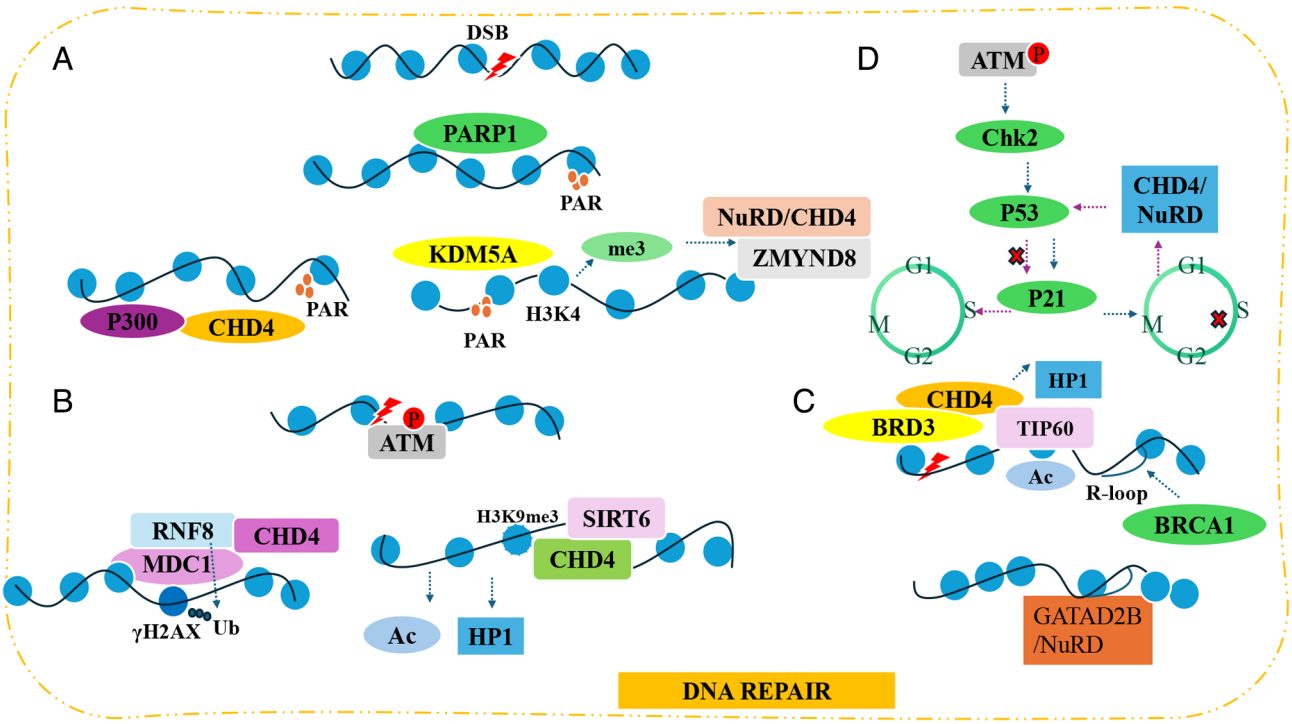

Figure 2. CHD4's involvement in DDR. (A) After DNA damage occurs, PARP is activated and recruits the CHD4/p300 complex or the ZMYND8/NuRD complex, thereby promoting DNA repair. (B) ATM drives chromatin remodeling mediated by RNF8-CHD4 or SIRT6-CHD4. (C) CHD4 is involved in R-loop-mediated DNA repair. (D) After DNA repair is completed, CHD4/NuRD inhibits p53 activity via deacetylation, thereby terminating DDR signals. DSB, DNA double-strand break; PARP1, poly(ADP-ribose) polymerase 1; PAR, poly(ADP-ribose); P300, E1A binding protein p300; CHD4, chromodomain helicase DNA-binding protein 4; KDM5A, lysine-specific demethylase 5A; H3K4, histone H3 lysine 4; me3, trimethylation; NuRD, nucleosome remodeling and deacetylase complex; ZMYND8, zinc finger MYND-type containing 8; ATM, ataxia telangiectasia mutated; RNF8, RING finger protein 8; MDC1, mediator of DNA damage checkpoint 1; γH2AX, phosphorylated H2A histone family member X; Ub, ubiquitin; SIRT6, sirtuin 6; HP1, heterochromatin protein 1; Ac, acetylation; BRD3, bromodomain-containing protein 3; TIP60, Tat interacting protein, 60 kDa; R-loop, RNA-DNA hybrid structure; BRCA1, breast cancer type 1 susceptibility protein; GATAD2B, GATA zinc finger domain containing 2B; Chk2, checkpoint kinase 2; p53, tumor protein p53; p21, cyclin-dependent kinase inhibitor 1A.

in GC cells (47). Similar drug efflux mechanisms can also be observed in ovarian cancer, where high CHD4 expression can upregulate that of multidrug resistance mutation 1 and enhance drug efflux ability, thereby reducing the accumulation of cisplatin in cells and leading to platinum-based CT resistance (48). These findings collectively indicate that CHD4 not only affects the DNA repair ability of tumor cells but may also expand drug resistance by remodeling the intracellular-drug disposition and survival signaling networks.

The effect of CHD4 on treatment response also extends to the level of cell cycle regulation. In BC, CHD4 forms the NuRD complex with HDAC1 and acts on the p21 promoter region, inhibiting the transcription and expression of p21 via chromatin remodeling and histone deacetylation (49). Since p21 is an important cell cycle inhibitor, such a decrease in its expression can promote cell cycle progression, making tumor cells more likely to bypass cell cycle checkpoints after DNA damage and thereby enhancing their resistance to CT drugs. This shows that CHD4-mediated treatment resistance not only depends on 'repairing more damage' but also involves the reshaping of cell cycle timing, enabling tumor cells to maintain a proliferative advantage under treatment pressure.

In addition to the intrinsic mechanisms of tumor cells, CHD4 can also affect the response to immunotherapy by regulating the tumor immune microenvironment. In microsatellite-stable CRC, CHD4 can recruit the histone methyltransferase euchromatic histone lysine methyltransferase 2 (EHMT2) to form a co-transcriptional inhibitory complex, thereby inhibiting the expression of galectin-7 (GAL7) and maintaining an immunosuppressive 'cold-tumor' microenvironment. Inhibition of EHMT2 can restore GAL7 expression and enhance Cluster of Differentiation 8^+ ($CD8^+$) T-cell-mediated antitumor immune responses, thereby increasing sensitivity to programmed cell death protein 1 inhibitor therapy (50). Pan-cancer data analysis further supports the important role of CHD4 in tumor treatment resistance. CHD4 promotes the development of genomic-instability characteristics via epigenetic regulation while shaping an immunosuppressive TME characterized by reduced $CD8^+$ T-cell infiltration and increased immune escape (51). This suggests that the role of CHD4 extends beyond tumor cells themselves to the tumor immune system interactions on which treatment responses depend.

Notably, CHD4's effect on treatment resistance does not always manifest in the same way but is shaped by specific genetic backgrounds. In BRCA1/2-deficient tumors, CHD4 deletion does not restore HRR ability but instead enhances replication fork stability by inhibiting meiotic recombination 11 homolog 1-mediated replication fork degradation, thereby increasing the resistance of tumor cells to cisplatin and PARP inhibitors (52). This phenomenon shows that the role of CHD4 cannot be simply summarized as 'promoting repair'

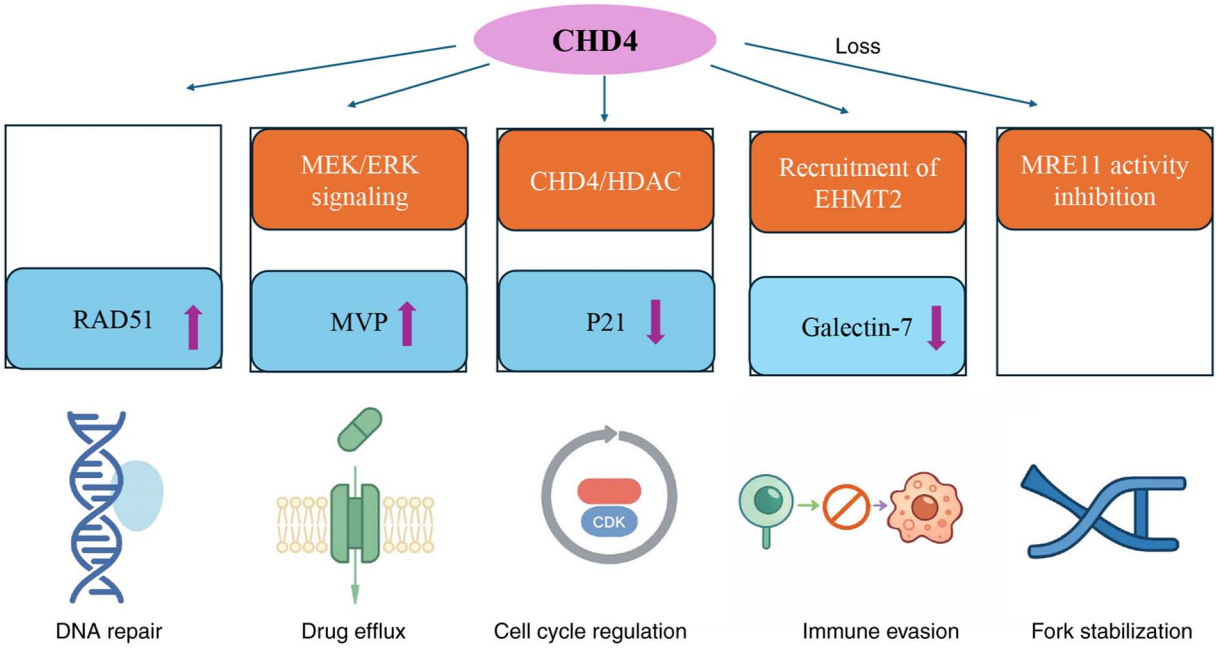

Figure 3. Role of CHD4 in tumor therapy resistance. CHD4 mediates tumor therapy resistance via regulation of DNA repair, drug efflux, cell cycle progression, immune evasion and replication fork stability. CHD4, chromodomain helicase DNA-binding protein 4; RAD51, RAD51 recombinase; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MVP, major vault protein; HDAC, histone deacetylase; EHMT2, euchromatic histone lysine methyltransferase 2; MRE11, MRE11 homolog double-strand break repair nuclease; p21, cyclin-dependent kinase inhibitor 1A.

or 'inhibiting repair'; its deeper function may lie in regulating how tumor cells respond to replication and treatment stresses. Therefore, its role in tumor treatment resistance is obviously context dependent, and its biological consequences depend on the specifics of the genetic background, repair pathway state, and TME characteristics (Fig. 3).

4. Non-coding RNA (ncRNA)-mediated regulatory network of CHD4

Although CHD4 plays a crucial role in chromatin remodeling, DDR, and tumor therapy resistance, its function is not solely determined by the protein complex itself. In recent years, ncRNAs have increasingly been recognized as significant regulators of CHD4, a key epigenetic hub (53). In transcriptionally active regions, RNA molecules can directly bind to CHD4, thereby influencing its chromatin-binding capacity and nucleosome-remodeling activity. Studies have shown that CHD4 exhibits a high affinity for RNA molecules rich in guanine (G) and that RNA binding inhibits CHD4's interaction with chromatin and weakens its nucleosome-remodeling ability. Mechanistically, RNA and CHD4 have a competitive binding relationship, which hinders CHD4 from establishing repressive chromatin structures in transcriptional regions and maintains a relatively open chromatin state (54). Under DNA damage conditions, long ncRNAs can also participate in functional regulation of CHD4. For example, nuclear paraspeckle assembly transcript 1 (*Neat1*) undergoes spatial relocation via N6-methyladenosine modification after DNA damage and acts as a 'molecular scaffold' at the damage site, thereby redistributing the subnuclear localization of CHD4. This process not only helps amplify the damage signal but also promotes assembly of DNA repair complexes (53). Another class of ncRNAs with active regulatory roles is developmental pluripotency associated 2 upstream binding RNA (*Dubr*). Research has found that *Dubr* can directly interact with the NuRD complex and inhibit the expression of genes related to cell differentiation and morphogenesis by regulating chromatin accessibility at activator protein 1 enhancer regions (55).

In addition to directly regulating CHD4 activity, various microRNAs (miRNAs or miRs) and circular RNAs (circRNAs) can modulate CHD4 expression levels by affecting its transcription, mRNA stability, or protein degradation. In GC, *circFBXL4* acts as a competing endogenous RNA for miR-146a-5p, relieving its inhibition of signal transducer and activator of transcription 1 and thereby indirectly promoting CHD4 transcription (56). Meanwhile, hsa-circ-0007396 can 'adsorb' miR-767-3p, weakening its targeting effect on CHD4 mRNA and thus upregulating CHD4 expression (57). In oral squamous-cell carcinoma, hsa-miR-194-5p can directly target CHD4 and regulate the phosphoinositide 3-kinase/protein kinase B signaling pathway, thereby enhancing cell anti-apoptotic ability and promoting drug resistance (58). Furthermore, some circRNAs can participate in tumor progression by regulating CHD4 protein stability. For example, in CRC, *circWBSCR22* can inhibit up-frameshift mutation 1 homolog (UPF1)-mediated CHD4 ubiquitination and degradation by binding to UPF1, thereby stabilizing CHD4 protein and promoting EMT, cell invasion and tumor metastasis (59) (Fig. 4).

In summary, these ncRNAs construct a multi-layered regulatory network by modulating CHD4 localization, activity, transcriptional level and protein stability. This network plays a crucial role in shaping the context-dependent functions of CHD4 and provides new insights into understanding the high plasticity exhibited by tumor cells

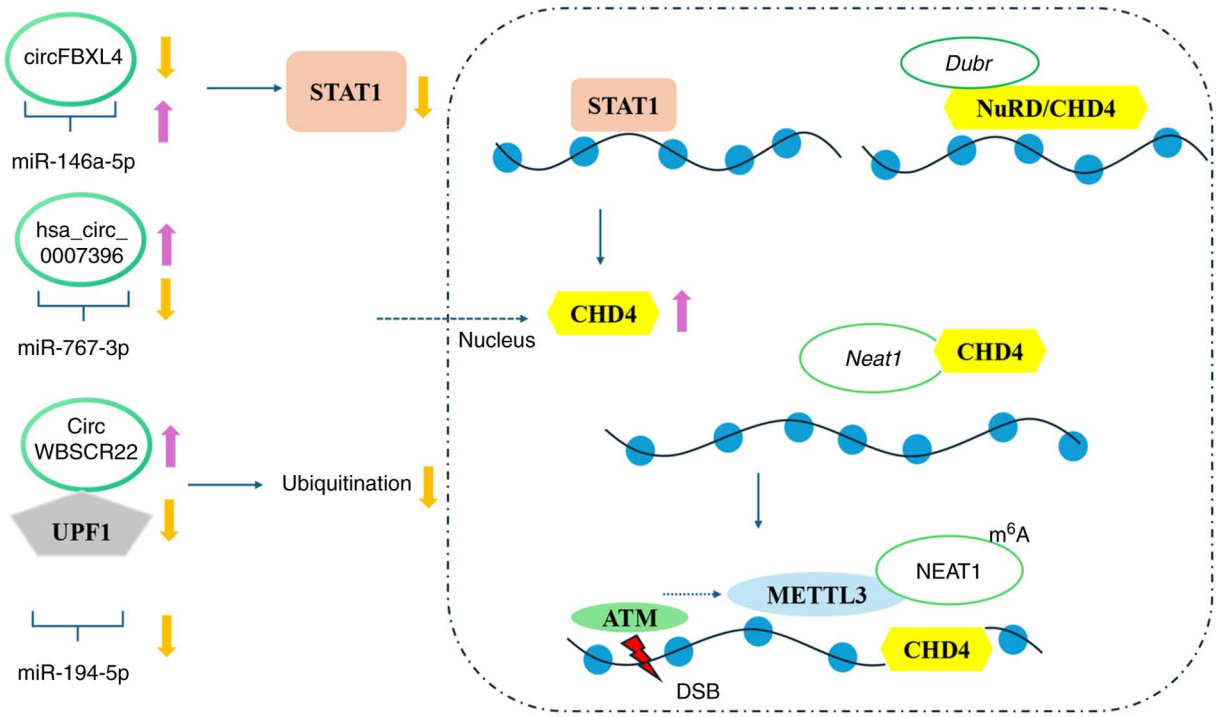

Figure 4. Non-coding RNA regulation of CHD4. lncRNAs (such as *Neat1* and *Dubr*) can influence chromatin remodeling or DNA repair signals by regulating CHD4 localization or NuRD complex activity. Meanwhile, miRNAs and circRNAs mainly regulate CHD4 expression levels via competing endogenous RNA mechanisms, transcriptional regulation, or protein stability regulation. *circFBXL4*, circular RNA FBXL4; miRNA or miR, microRNA; hsa_circ_0007396, human circular RNA 0007396; *circWBSCR22*, circular RNA WBSCR22; UPF1, up-frameshift mutation 1 homolog; STAT1, signal transducer and activator of transcription 1; CHD4, chromodomain helicase DNA-binding protein 4; NuRD, nucleosome remodeling and deacetylase complex; *Neat1*, nuclear paraspeckle assembly transcript 1; *Dubr*, developmental pluripotency associated 2 upstream binding RNA; METTL3, methyltransferase-like 3; ATM, ataxia telangiectasia mutated; DSB, DNA double-strand break; m^6A, N6-methyladenosine.

under therapeutic pressure. Moreover, the interaction between RNA and CHD4 may also serve as a potential therapeutic-intervention target, particularly in tumor therapy resistance and DDR regulation.

5. Discussion

Recent studies have revealed the high functional plasticity of CHD4 in different biological contexts, a characteristic that has been demonstrated with relative clarity in developmental systems. For example, during cardiac development, CHD4 can form specific regulatory complexes with different TFs, resulting in different transcriptional regulatory outcomes. Studies have shown that the TF T-box transcription factor 5 can recruit CHD4 to the regulatory regions of atrial-related genes, promoting atrial-specific gene expression and maintaining cardiac-rhythm homeostasis in a specific chromatin environment (60). In other developmental contexts, CHD4 can synergize with TFs such as SET and MYND domain containing 1 (61) or GATA4/natural killer 2 homeobox 5 (62) to inhibit non-myocardial-gene expression through the NuRD complex, thereby maintaining the specific transcriptional process of myocardial cells. These studies suggest that the biological function of CHD4 largely depends on its binding TF partners and the local chromatin environment.

Similar context-dependent regulation is also greatly significant in tumors. Current research indicates that CHD4 function shows obvious context dependence by tumor type, which is mainly reflected in tumor progression and therapy resistance. During tumor progression, CHD4-mediated chromatin remodeling (11) and transcriptional regulation (13) promote tumor cell proliferation, migration and invasion. However, in specific TRNs, CHD4 may also limit tumor progression by inhibiting abnormal transcriptional processes. In terms of therapy resistance, high expression of CHD4 is usually associated with enhanced DDR capacity (46) and CT resistance (47), while against certain genetic backgrounds, CHD4 functional loss may generate alternative drug resistance mechanisms by altering DDR modes or replication fork stability. Therefore, the role of CHD4 in tumors is not unidirectional but is instead influenced by multiple factors such as genetic background, TRNs and chromatin environment.

From the perspective of epigenetic regulation, CHD4 can integrate multiple chromatin modification mechanisms to shape transcriptional states. For example, CHD4 can synergize with HDAC1/2 to regulate chromatin compaction, thereby inhibiting gene transcription. Meanwhile, it can also work with histone methyltransferases [for example, SET domain bifurcated histone lysine methyltransferase 1 (SETDB1) (63) or EHMT2] to further reinforce gene silencing by maintaining repressive chromatin marks like histone H3-lysine 9 (H3K9) methylation. In addition, in some tumors, CHD4 can synergize with DNA methyltransferases DNMT1 and DNMT3B to maintain abnormal DNA methylation states at the promoter regions of tumor suppressor genes, thereby strengthening transcriptional repression. These different levels of epigenetic modifications jointly determine the transcriptional regulatory effects of CHD4.

Table I. CHD4 abnormalities and mechanisms in different tumor types.

First author/s, year	Tumor type	Expression/mutation status	Outcome	Main mechanism	(Refs.)
Wu *et al*, 2023	Gastric cancer	High expression	Oncogenic	Enhances the interaction between MEK1/2 and ERK1/2, leading to higher ERK phosphorylation levels and sustained pathway activation	(47)
Shi *et al*, 2025		High expression	Oncogenic	Binds MYH9 via the ATPase domain and promotes its nuclear export; cytoplasmic MYH9 then inhibits GSK3β, resulting in β-catenin stabilization	(18)
Kim *et al*, 2011		Gene mutation; loss of function	Oncogenic	Alters gene expression by affecting chromatin structure	(66)
Li *et al*, 2018	Endometrial cancer	R975H and R1162W mutations	Oncogenic	Activates transforming growth factor beta signaling	(29)
Zhang *et al*, 2022	Breast cancer	Not specified	Tumor suppressor	Is recruited to the SOX2 promoter region by TRPS1, repressing transcription	(27)
Wang *et al*, 2020		High expression	Oncogenic	Under hypoxic conditions, its interaction with HIF is enhanced, promoting the transcription of HIF target genes	(22)
Sattout *et al*, 2024		High expression	Oncogenic	Enhances ERα transcriptional activity	(21)
Luo *et al*, 2018		High expression	Oncogenic	Binds to the promoter region of the E-cadherin gene and represses its transcription	(67)
Ou-Yang *et al*, 2019		High expression	Oncogenic	Promotes the transcription of β1-integrin	(68)
Xia *et al*, 2017	Colorectal cancer	High expression	Oncogenic	After its localization to oxidative-damage sites via OGG1, it recruits DNA methyltransferase and suppresses multiple tumor suppressor genes	(24)
Kim *et al*, 2011		Gene mutation; loss of function	Oncogenic	Alters gene expression by affecting chromatin structure	(66)
Sun *et al*, 2024		Not specified	Oncogenic	Recruits EHMT2 to form a co-transcriptional silencing complex, repressing GAL7 expression	(50)
Pratheeshkumar *et al*, 2021	Thyroid cancer	High expression	Oncogenic	Regulates the expression of EMT-related genes	(69)
Wang *et al*, 2023	Ovarian cancer	High expression	Oncogenic	Interacts with EZH2, promoting nuclear accumulation of β-catenin	(19)
Nio *et al*, 2015	Liver cancer	High expression	Oncogenic	Regulates the epigenetic state of cells through the NuRD complex	(70)
Xu *et al*, 2020	non-small cell lung cancer	High expression	Oncogenic	Interacts with PHF5A and activates the RhoA/ROCK pathway	(20)

CHD4, chromodomain helicase DNA-binding protein 4; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MYH9, myosin heavy chain 9; GSK3β, glycogen synthase kinase-3 beta; β-catenin, beta-catenin; SOX2, sex-determining region Y-related high-mobility group box 2; TRPS1, transcriptional repressor GATA binding 1; HIF, hypoxia-inducible factor; ERα, estrogen receptor alpha; E-cadherin, epithelial cadherin; OGG1, 8-oxoguanine DNA glycosylase 1; EHMT2, euchromatic histone lysine methyltransferase 2; GAL7, galectin-7; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; NuRD, nucleosome remodeling and deacetylase complex; PHF5A, PHD finger protein 5A; RhoA, Ras homolog gene family member A; ROCK, Rho-associated protein kinase.

In addition to the aforementioned epigenetic modifications, the local chromatin environment may also affect recruitment and function of CHD4. For example, some cancer-associated histone mutations (such as H3.3 G34R) can alter the conformation and dynamic behavior of the histone tail, thereby affecting the interactions between chromatin regulatory proteins such as CHD4 and nucleosomes (64). Furthermore, studies on SelectID technology have found that the CHD4/NuRD complex can be significantly enriched in methylated DNA regions (65), suggesting that DNA methylation may help regulate gene expression by recruiting chromatin-remodeling complexes.

At the therapeutic level, the CRN mediated by CHD4 may provide new interventional ideas for epigenetic targeted therapy. For example, the HDAC subunits in the NuRD complex are already important targets of various antitumor drugs, indicating that interfering with CHD4/NuRD complex function may affect tumor-related transcriptional processes. In addition, it has been identified that synthetic-lethality relationships may exist between CHD4 and other epigenetic regulatory factors. For example, dual inactivation of CHD4 and the H3K9 methyltransferase SETDB1 can significantly reduce tumor cell viability (63). These findings suggest that exploiting the dependencies within the epigenetic regulatory network may provide an important theoretical basis for new combination therapy strategies. The abnormalities of *Chd4* in different tumor types and their corresponding mechanisms are summarized in Table I.

In conclusion, the research value of CHD4 lies not only in whether it can be directly targeted but also in how it, as an integration node of the CRN, reshapes the stress response trajectory of tumor cells in different contexts. Future research should analyze the context-dependent regulatory mechanisms of CHD4 at the system level by, for example, systematically analyzing its chromatin-binding profile, NuRD complex assembly mode, and DNA repair pathway selection and combining emerging technologies such as single-cell multi-omics and spatial transcriptomics to provide new theoretical bases for CRN-based intervention strategies in precision tumor therapy.

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Authors' contributions

SL contributed to the conception and design of the review, performed comprehensive literature analysis and interpretation, and drafted the manuscript. QM contributed to literature acquisition, analysis and interpretation, and participated in manuscript drafting and revision. KL contributed to literature analysis and organization, figure and table preparation, and manuscript revision. ZJ contributed to critical analysis and interpretation of the literature and revised the manuscript critically for important intellectual content. YM conceived and supervised the study, contributed to interpretation of the literature, critically revised the manuscript, and gave final approval of the version to be published. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work. Data authentication is not applicable.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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