Molecules and Cells

Minireview

Biological functions and molecular mechanisms of MORC2 in human diseases

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ABSTRACT

Microrchidia family CW-type zinc finger 2 (MORC2) is a nuclear protein that has been highly conserved throughout evolution. MORC2 consists of an ATPase domain at the N-terminus, a CW-type zinc finger domain in the middle, and coiled-coil domains at the C-terminus. MORC2 is involved in various important biological processes such as transcriptional regulation, chromatin remodeling, DNA damage repair, and metabolism. Recent studies suggest that MORC2 may serve as a potential biomarker and therapeutic target for hereditary neurological diseases and cancers. However, the exact molecular functions and pathogenic mechanisms of MORC2 in human diseases remain to be explored. In this review, we provide an overview of recent advancements in understanding the molecular functions of MORC2, as well as the characteristics and mechanisms of MORC2-related diseases, which will be valuable for future studies.

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INTRODUCTION

xMicrorchidia family CW-type zinc finger 2 (MORC2) is a highly conserved protein that plays an important role in human health and diseases. MORC2 belongs to the MORC protein family and shares structural domains, including a GHKL-type ATPase domain at the N-terminus, a CW-type zinc finger (CW-ZF) motif, and coiled-coil (CC) domains at the C-terminus (Perry and Zhao, 2003; Wang et al., 2010). The GHKL-ATPase domain is involved in chromatin remodeling by binding and hydrolyzing ATP, and is found in both prokaryotic and eukaryotic chromatin-related proteins (Iyer et al., 2008; Li et al., 2016; Wang et al., 2010). The CW-ZF domain plays a crucial role in interacting with nucleic acid templates and promoting protein-protein and protein-small-molecule interactions (Perry and Zhao, 2003; Wang et al., 2010). The CW-ZF is involved in various biological functions such as replication, transcription, and epigenetic regulation (He et al., 2010; Wang et al., 2010). The CC domains consist of consecutive heptad repeats that are recognized by the presence of hydrophobic residues (Hu et al., 2017; Wang et al., 2010). They are present in approximately 10% of proteins and are involved in a wide range of biological functions, including protein-protein interaction, protein-DNA interaction, protein stability, protein functional activation, transcriptional regulation, DNA damage response, subcellular localization, and signaling transduction (Hu et al., 2017).

MORC2 is widely distributed in various human tissues, with the highest levels found in the testes, followed by the brain and ovary (Wang et al., 2010; Sevilla et al., 2016). Moderate expression is also found in the lungs, kidneys, liver, and heart, while lower expression is detected in skeletal muscle, pancreas, and spleen (Wang et al., 2010; Sevilla et al., 2016). Extensive research using biochemistry, genomics, transcriptomics, proteomics, and other methodologies has elucidated the role of MORC2 in tumor development and neurological diseases (Wang et al., 2018; Sevilla et al., 2016). Furthermore, MORC2 is involved in regulating numerous cellular processes, including gene transcription, chromatin remodeling, DNA damage repair (DDR), and metabolism.

Post-translational modifications (PTMs) are pivotal in the etiology and progression of neurological disorders and cancer. These modifications are essential for regulating cellular signaling pathways, facilitating molecular transport, and preserving cellular homeostasis (Tao et al., 2024). The MORC2 protein, which participates in a range of PTMs, is implicated in the initiation and advancement of both cancer and neurological diseases. These findings offer new possibilities for the treatment of various diseases. This review provides an overview of the latest advances in our understanding of the regulatory functions of MORC2 in various
cellular processes. Additionally, we explore the relationship between MORC2 expression and the pathogenesis of neurological diseases and cancer. The review also provides a comprehensive summary of the PTMs involving MORC2, including PARylation, phosphorylation, SUMOylation, acetylation, methylation, alternative polyadenylation (APA), and O-GlcNAcylation. These PTMs have been shown to influence pathological physiological processes in tumorigenesis and neurological development.

**ROLE OF MORC2 IN HUMAN HEALTH**

**Tumor**

MORC2 is upregulated in various human cancers and plays a role in different stages of tumor development (Fig. 1) (Yang et al., 2022; Liu et al., 2022). It affects processes such as angiogenesis, proliferation, tumorigenesis, invasion, and metastasis through various mechanisms, including the regulation of immune infiltrates, cell cycle checkpoints, DDR, resistance to anticancer therapies, epithelial-mesenchymal transition (EMT), and expression of glycolytic enzymes (Fig. 1) (Hu et al., 2023; Tan et al., 2023; Wang et al., 2018; Yang et al., 2020, 2022; Zhang et al., 2018, 2021, 2023; Liu et al., 2019, 2019, 2020).

MORC2 undergoes acetylation in response to DNA-damaging substances and ionizing radiation, resulting in the inhibition of cyclin and cyclin-dependent protein kinase (CDK), which are crucial regulators of cell cycle checkpoints. In addition, acetylated MORC2 activates the G2 checkpoint in breast cancer cells. Knockdown of MORC2 in breast cancer cells leads to compromised proliferation and reduced growth-stimulating effects of E2, while increasing cellular sensitivity to antiestrogens in a phosphorylation-dependent manner. The CDK1-mediated phosphorylation of MORC2 enhances its interaction with HSPA8 and LAMP2A, leading to autophagic degradation. Degradation of MORC2 activates the spindle assembly checkpoint, resulting in mitotic arrest and resistance of cancer cells to microtubule-targeting agents. SUMOylation of MORC2 is involved in the regulation of chromatin structure and DNA repair, and its levels change dynamically during the different stages of DNA damage (Zhang et al., 2023). The expression of SUMOylation-deficient mutant MORC2 increases the sensitivity of...
breast cancer cells to DNA-damaging chemotherapeutic drugs (Zhang et al., 2023). Furthermore, p21-activated kinase 1 (PAK)-mediated MORC2 phosphorylation promotes proliferation and tumorigenicity of gastric cancer cells (Wang et al., 2015). MORC2 inhibits Hippo tumor suppressor signaling by promoting hypermethylation and transcriptional repression of the upstream Hippo regulators NF2 and KIBRA (Wang et al., 2018). This ultimately promoted stemness and tumorigenesis in hepatocellular carcinoma cells (Wang et al., 2018). Additionally, MORC2 interacts with SIRT1 to inhibit NDRG1 promoter activity and downregulate the expression of NDRG1, a metastatic suppressor and prognostic biomarker for colorectal cancer. Both in vitro and in vivo studies, MORC2 has been shown that enhances colorectal cancer cell migration, invasion, and lung metastasis. High MORC2 expression significantly correlates with lymph node metastasis, poor pTNM stage, and poor prognosis in patients with colon cancer. Furthermore, MORC2 regulates the expression of several glycolytic enzymes, including hexokinase 1, lactate dehydrogenase A (LDHA), and phosphofructokinase platelets, which contribute to breast cancer cell proliferation and migration processes that require high energy (Guddeti et al., 2023). MORC2 also plays a role in the migration and invasion of cancer cells by regulating the expression of EMT-associated protein markers (E-cadherin, N-cadherin, and vimentin) and the EMT-inducing transcription factor, Slug. The MORC2 mutation M276I enhances its binding to heterogeneous nuclear ribonucleoprotein M, leading to the heterogeneous nuclear ribonucleoprotein M–mediated splicing switch of CD44. This splicing switch is essential for EMT and breast cancer metastasis, ultimately affecting migratory, invasive, and lung metastatic potential. Additionally, using the TIMER database, researchers found a significant association between MORC2 expression in colon adenocarcinoma and the levels of immune cell infiltration, including B cells, CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells (Zhao et al., 2023). Moreover, MORC2 plays a crucial role in cancer development by regulating tumor regulators, such as Arg kinase–binding protein 2 (ArgBP2), heat shock factor 1, and carbonic anhydrase IX (CAIX) (Shao et al., 2010; Tong et al., 2018).

These findings indicate the significant role of MORC2 protein in tumorigenesis and progression, and have potential implications in the diagnosis, prognosis, and treatment of cancers. The expression level of MORC2 in tumor tissues may serve as a pivotal prognostic and diagnostic biomarker for cancer. Targeted therapies against MORC2 exhibit immense promise due to their diverse and crucial functions in cancer progression. For instance, the development of MORC2-specific inhibitors could aid in modulating the tumor microenvironment, bolstering the immune system’s antitumor response, and potentially disrupting the energy supply of cancer cells, thereby hampering their proliferation and invasive abilities (Li et al., 2023). Future research can focus on the discovery and optimization of small-molecule inhibitors that may inhibit the activity of MORC2 by affecting its ATPase activity and chromatin remodeling functions. Additionally, targeting the epigenetic regulation of MORC2, such as inhibitors against NAT10, could potentially impact the function of MORC2 and may serve as an effective therapeutic strategy. Inhibitors against O-GlcNAc transferase (OGT), like OSMI-1, may suppress the function of MORC2, offering new avenues for cancer treatment. Interventions targeting the GPER1-PRKACA-chaperone-mediated autophagy (CMA) pathway may help overcome resistance to endocrine therapy. However, targeted therapeutic strategies against MORC2 may encounter numerous challenges. One such challenge involves ensuring that MORC2-specific inhibitors do not inadvertently interfere with other crucial biological pathways. Additionally, given MORC2’s ubiquitous expression in normal tissues, targeted treatments may induce adverse side effects. These side effects must be rigorously evaluated and monitored to ensure the safety and efficacy of the treatment. Future studies can also explore the interactions between MORC2 and other signaling pathways (such as the transforming growth factor-β [TGF-β] and Hippo signaling pathways), as well as the roles of these cross-talks in cancer development.

Neurological Diseases
Heterozygous missense mutations in MORC2 were first identified in patients with Charcot-Marie-Tooth disease type 2Z (CMT2Z) and a spinal muscular atrophy (SMA)-like phenotype (Fig. 1) (Ando et al., 2017; Hyun et al., 2016; Zhao et al., 2016; Albulym et al., 2016; Sevilla et al., 2016). CMT2Z is characterized by a childhood or early adulthood onset of weakness and muscle atrophy in the distal extremities, which spreads proximally (Albulym et al., 2016; Sevilla et al., 2016). On the other hand, SMA presents with congenital or infantile onset of extensive weakness and atrophy (Albulym et al., 2016; Sevilla et al., 2016). Patients with MORC2-mutated CMT show high clinical variability (Semplicini et al., 2017). In addition to the prominent clinical features mentioned above, patients carrying MORC2 mutations can also exhibit pyramidal features, mental retardation, white matter abnormalities, cerebellar ataxia, nocturnal hypoventilation, and other symptoms (Albulym et al., 2016; Sevilla et al., 2016). To date, more than 50 families have been reported with MORC2-related neuropathy worldwide. The most common hot spot mutations are MORC2 R252W and S87L (Hyun et al., 2016; Zhao et al., 2016; Albulym et al., 2016; Sevilla et al., 2016). Most neuropathy-related MORC2 mutations are localized to the N-terminal ATPase module. The CMT-related mutation R252W mildly decreases the rate of ATP hydrolysis in MORC2, whereas the SMA mutation T424R significantly increases ATPase activity (Douse et al., 2018). The S87L variant, which has both CMT- and SMA-like features, displays low ATPase activity (Douse et al., 2018). R252W MORC2 variant hyperactivates human silencing hub (HUSH)-mediated epigenetic silencing (Douse et al., 2018). Further research confirmed that the S87L variant forms constitutive N-terminal dimers without the exogenous addition of nucleotides, whereas the T424R variant forms a mixture of monomers and dimers in the presence of 2 mM AMPPNP (Douse et al., 2018). These findings indicated that disease-associated variants are capable of ATP binding, dimerization, and hydrolysis. Structural analyses have shown that the S87L mutant leads to more stable ATP-bound dimers than the wild-type, whereas the T424R mutant increases the rate of dimer assembly and disassembly (Douse et al., 2018). While the aforementioned studies have
delved into the pathogenesis of CMT stemming from MORC2 gene mutations, the precise underlying mechanism still awaits further scrutiny. For instance, while MORC2 mutations are known to suppress the expression of HUSH target genes, the precise mechanisms that link this suppression to peripheral nerve axon degeneration remain unclear. Moreover, the limited scope of these studies, focusing on just 3 MORC2 mutations (S87L, R252W, and T424R), may not provide a comprehensive understanding of MORC2’s role in neuropathy. It remains uncertain whether other MORC2 mutations exhibit a similar inhibitory effect, and whether other modifier genes contribute to the disease phenotype. Additionally, given that biochemical and cellular experiments often fail to replicate the intricate complexity of in vivo environments, the findings from these studies may require validation in more complex in vivo settings to ensure their physiological and pathological relevance. Developing small-molecule drugs to modulate the ATPase activity of MORC2 or its interaction with the HUSH complex may aid in treating related diseases. Repairing MORC2 gene mutations through gene-editing techniques, such as CRISPR-Cas9, may restore its normal function. By studying the role of MORC2 in epigenetic regulation, it is expected that new therapeutic strategies can be developed, such as utilizing histone deacetylase (HDAC) inhibitors. For the protein stability and folding issues of MORC2 mutants, molecular chaperones or chemical molecules can be developed to stabilize the protein structure.

De novo variants in the ATPase module of MORC2 were recently reported in a cohort of 20 individuals (Guillen Sacoto et al., 2020). These individuals presented developmental delays, intellectual disabilities, growth delay, microcephaly, and variable craniofacial dysmorphisms (Fig. 1). In addition, they also showed weakness and hyporeflexia. Through gene complementation experiments in HELA cell lines, researchers found that MORC2 mutations significantly activated HUSH-mediated silencing (Guillen Sacoto et al., 2020). Notably, the specific variants c.79G > A (p.Glu27Lys) and c.394C > T (p.Arg132Cys) have been shown to have the most pronounced hyperactivation effect on this silencing mechanism (Guillen Sacoto et al., 2020). Further investigation is imperative to elucidate the precise mechanisms by which MORC2 mutations precipitate neurodevelopmental disorders. For instance, it remains to be determined whether mutations within the ATPase domain modulate the ATP hydrolysis activity of the MORC2 protein. Additionally, the influence of HUSH target genes on the intricate processes of neural development warrants in-depth exploration.

**BIOLOGICAL FUNCTIONS AND MOLECULAR MECHANISMS OF MORC2**

**Role of MORC2 in Gene Transcription**

During the development of an organism, specific genes are activated or suppressed to establish different cell types (Knauer et al., 2019). This precise regulation occurs during transcription and has been a major focus of molecular biology research. Transcription factors are key players in almost all biological processes, particularly in gene expression (Medvedev et al., 2018). They recognize target genes and form transcription initiation complexes or coregulator DNA complexes, thereby regulating the activation or inhibition of various biological processes (Ge et al., 2024). Transcription initiation in the promoter region is critical for regulating gene expression (Haberle and Stark, 2018). Epigenetic modifications, such as DNA methylation in the promoter region, can alter chromatin structure and gene accessibility, allowing transcription initiation complexes to assemble in the promoter regions (Bind et al., 2022). Through complex transcriptional regulatory signals, cells achieve differential gene expression, which determines their identity and influences numerous physiological and pathological processes.

The role of MORC2 in gene transcription is well-established. Wang et al. (2010) conducted a study that investigated the transcriptional function of MORC2 using reporter gene assays. They compared truncated MORC2 with full-length MORC2 and found that MORC2 exerts transcriptional inhibition in cancer cells through DNA binding mediated by its proline-rich domain (Wang et al., 2010). In addition, MORC2 regulates the expression of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), 2 key enzymes involved in lipogenesis (Fig. 2) (Sanchez-Solana et al., 2014). When MORC2 expression was down-regulated using a specific siRNA, the level of the adipocyte marker protein aP2 decreased (Fig. 2) (Sanchez-Solana et al., 2014). Conversely, MORC2 overexpression has the opposite effect (Sanchez-Solana et al., 2014). MORC2 also regulates the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), which is involved in the mevalonate pathway and converts acetyl-CoA into mevalonate (Fig. 2) (Sanchez-Solana et al., 2014). Depletion of endogenous MORC2 using specific siRNAs results in decreased HMGCR mRNA expression (Sanchez-Solana et al., 2014). These findings suggest that MORC2 plays a key role in the synthesis of fatty acids and the mevalonate pathway through transcriptional regulation.

Tchasovnikarova et al. (2017) conducted genome-wide forward genetic screening using CRISPR/Cas9 technology and found that MORC2 was required for transgene silencing of the HUSH complex. MORC2 interacts with the HUSH complex subunits TASOR and MPP8. The HUSH complex recruits MORC2 to heterochromatic sites marked by H3K9me3 and modulates the expression of MORC2. Genetic complementation experiments in a MORC2 knockout HeLa clone demonstrated that exogenous expression of MORC2 variants in the key residues of the ATPase domain, essential for ATP binding (N39A) or hydrolysis (D68A), could not restore HUSH function and failed to inhibit the GFP reporter construct. In contrast, the introduction of wild-type MORC2 successfully restored these functions. This suggests that the ATP binding and hydrolytic capabilities of MORC2 may be critical for the transcriptional repression mediated by the HUSH complex (Fig. 2) (Tchasovnikarova et al., 2017). Another study by Douse et al. (2018) found that MORC2 and MORC3 resemble prototypical GHKL ATPases with low ATP-binding affinity and slow ATP hydrolysis. Due to their low enzymatic turnover, GHKL ATPases do not function as motors but rather use ATP binding and hydrolysis as conformational switches to trigger dimer formation and dissociation (Douse et al., 2018). A recent study investigated the collaboration between HUSH, MORC2, and DNA methylation in regulating the transcription of LINE-1 retrotransposons (L1s) and other genomic repeats. The study reveals a mechanism that DNA methylation primarily
silences the transcription of young L1s in human neural progenitor cells (Pandiloski et al., 2024). The loss of MORC2 or the HUSH subunit TASOR does not lead to widespread misexpression of L1s, as these elements are maintained in a transcriptionally silent state by robust promoter DNA methylation. However, upon genome demethylation and activation of evolutionarily young L1s, MORC2 binding is attracted, and the simultaneous depletion of DNMT1 (DNA methyltransferase 1) and MORC2 results in a massive accumulation of L1 transcripts. This indicates that DNA methylation status controls the sensitivity of L1s to HUSH-MORC2 restriction. Furthermore, the study identifies a similar mechanistic hierarchy at pericentromeric alpha-satellite repeats and clustered protocadherin genes, which are important for chromosome structure and neurodevelopment, respectively. While these findings underscore the pivotal role of MORC2 in cellular transcriptional regulation, the extent to which MORC2 interfaces with other transcription factors to collaboratively modulate gene expression warrants additional investigation. Furthermore, the impact of PTMs on MORC2’s transcriptional regulatory capabilities is an area that demands deeper exploration.

**Role of MORC2 in Chromatin Remodeling**

Eukaryotic genomes can be divided into 2 types: euchromatin and heterochromatin. Euchromatin is less condensed and transcriptionally active and has a low degree of compaction, whereas heterochromatin is relatively highly condensed and transcriptionally inactive and has a high degree of compaction (Hilbert et al., 2021; Saksouk et al., 2015). Chromatin remodeling refers to the dynamic change in chromatin structure between the condensed and decondensed states (Bayona-Feliu et al., 2021). Chromatin regulates the accessibility of transcription factors to genomic DNA, alters the position and structure of nucleosomes, and regulates gene expression. This process is important for the regulation of physiological functions and maintenance of cell homeostasis. The chromatin structure
can be altered through covalent modification of chromatin components (e.g., histones and DNA) or noncovalent modification of ATP-dependent chromatin remodeling factors (e.g., SWI/SNF, INO80, ISWI, and CHD complexes) (Bayona-Feliu et al., 2021). ATP-dependent chromatin remodeling complexes regulate the structure of chromatin and nucleosomes by utilizing ATP hydrolysis energy, thereby controlling the accessibility of transcription factors for binding (Bayona-Feliu et al., 2021).

Similar to other chromatin remodeling complexes, MORC2 is involved in various aspects of chromatin remodeling, including the promotion of histone exchange and nucleosome remodeling. A recent study demonstrated that human MORC2 is phosphorylated and activated by PKA1 in response to DNA damage (Fig. 3) (Li et al., 2012). Phosphorylated MORC2 facilitates chromatin remodeling and DNA repair after DNA damage by utilizing its ATPase activity to bind and hydrolyze ATP (Fig. 3) (Li et al., 2012). MORC2 dynamically associates with chromatin in a PKA1 phosphorylation-dependent manner and induces the phosphorylation of H2AX, leading to the production of gamma-H2AX (Li et al., 2012). This process influences chromatin structure and plays a crucial role in the DNA damage response and chromatin remodeling by recruiting downstream DDR proteins and chromatin remodeling complexes. Further investigations have confirmed that MORC2 can alter the nucleosome structure in a PKA1 phosphorylation- and ATPase-dependent manner (Li et al., 2012). Xie et al. compared the effects of MORC2 depletion and wild-type MORC2 on the interactions between histones and DNA, revealing that MORC2 regulates the association between histones and chromatin (Xie et al., 2019). Additionally, they discovered that MORC2 can form dimers through its C-terminal coil domain and that the dimer structure of MORC2 is essential for nucleosome stability (Fig. 3) (Xie et al., 2019). These findings confirm the crucial role of MORC2 in chromatin compaction.

Role of MORC2 in DNA Damage Repair
The correct and timely repair of DNA damage caused by internal and external factors is crucial for maintaining the stability of the cell genome (Huang and Zhou, 2021). The accumulation of DNA damage can lead to gene mutations and tumor development. DDR refers to the process of restoring the structure of DNA molecules in biological cells following damage. This repair process involves various enzymes and signaling pathways, as well as PTMs such as phosphorylation and ubiquitination/deubiquitination (Huang and Zhou, 2021). Proteins such as BRCA1, 53BP1, and Rad51 play important roles in initiating signaling cascades for DNA repair in mammalian cells. Chromatin dynamics also contribute to DNA repair.

Poly(ADP-ribose) polymerase 1 (PARP1) is a DNA damage sensor responsible for 80% to 90% of PARylation of DDR (Zhang and Li, 2019). Through mass spectrometry proteomics,
western blotting, immunofluorescence, and immunoprecipitation, PARP1 has been shown to directly interact with MORC2 and catalyze MORC2 PARylation at 2 residues within its conserved CW-ZF domain. MORC2, in turn, stabilizes PARP1 by enhancing NAT10-mediated acetylation of PARP1 (Fig. 3). When DNA damage occurs, PARP1 recruits MORC2 to the DNA damage sites, stimulating ATPase and chromatin remodeling activities. The depletion of MORC2 impairs the production of PAR in response to DNA damage and the recruitment of DNA repair proteins to DNA lesions, resulting in increased sensitivity to genotoxic stress. The expression of mutant MORC2 leads to reduced cell survival after DNA damage (Zhang and Li, 2019). Phosphorylation is an important PTM of MORC2 in response to DNA damage. Following DNA damage, MORC2 is phosphorylated by PKA, and the phosphorylated MORC2 associates with chromatin and facilitates chromatin remodeling by regulating ATPase activity (Fig. 3). Furthermore, MORC2 promotes the phosphorylation of H2AX, which is necessary for the recruitment of DNA repair proteins to damaged chromatin (Li et al., 2012). Dimerization of MORC2 through its C-terminal CC domain destabilizes nucleosomes and enhances chromatin dynamics after DNA damage by weakening histone-DNA interactions. Expression of the CC domain-defective MORC2 mutant impairs the recruitment of DDR proteins to sites of damaged chromatin. MORC2, a DDR protein, is considered a candidate biomarker and potential therapeutic target for multiple cancer types. After DNA damage, MORC2 weakens the interaction between histones and DNA, promoting the dissociation of core histones from the chromatin (Xie et al., 2019).

**Role of MORC2 in Metabolism**

In addition to its expression in the nucleus and role in transcriptional regulation and chromatin remodeling, MORC2 is also expressed in the cytoplasm and is involved in lipid metabolism pathways (Sanchez-Solana et al., 2014). MORC2 interacts with ATP-citrate lyase (ACL) and promotes its activity in the cytosol of lipogenic breast cancer cells (Fig. 4). ACL catalyzes the formation of acetyl-CoA and plays critical roles in glucose catabolism, fatty acid anabolism, and the mevalonate pathway. Depletion of endogenous MORC2 in breast cancer cells leads to decreased mRNA expression of HMGCR. HMGCR converts acetyl-CoA into mevalonate and regulates the first rate-limiting step of the mevalonate pathway. MORC2 also controls the expression of ACC and FAS, which are essential enzymes in lipogenesis. Furthermore, MORC2 alters the expression of aP2, a marker of adipocytes (Sanchez-Solana et al., 2014). These findings suggest that MORC2 is involved in intracellular lipid accumulation and the fatty acid and mevalonate pathways by regulating the activity and expression of these lipogenic enzymes. During differentiation of 3T3-L1 mouse preadipocytic...
adipocyte, MORC2 mRNA and protein expression levels were significantly increased. Conversely, knockdown of endogenous MORC2 in 3T3-L1 cells decreases the expression levels of several adipocyte-specific genes (aP2, PPARγ, CCAAT/enhancer-binding protein a [CREB-Pa], and C/EBPβ) and various lipogenic genes (such as ACYL, ACC, and FAS), and compromises the adipogenic conversion of 3T3-L1 cells (Sanchez-Solana et al., 2014). These results indicate that MORC2 plays an essential role in the adipogenic process. Further investigation is warranted to elucidate the role of MORC2 across various cell types, including hepatocytes and adipocytes, and to determine if its regulatory function in lipid metabolism exhibits cell-specific characteristics. Additionally, it is imperative to delve into the mechanisms by which MORC2 participates in the pathology of nonalcoholic fatty liver disease, cardiovascular disease, and other conditions associated with lipid metabolism dysregulation.

Abnormal glucose metabolism is a significant indicator of tumor energy metabolism and is characterized by increased glycolysis and glucose uptake and consumption. By analyzing data from the GEO and PRIDE databases, MORC2 has been identified to regulate glucose metabolism. It significantly influences the cellular glucose metabolic pathways by modulating the expression of key glycolytic enzymes, including hexokinase 1, phosphofructokinase liver, phosphofructokinase platelets, and LDH (Guddeti et al., 2021). In the MCF-7 and BT-549 cell lines, MORC2 has been validated to positively regulate the expression of LDHA and the enzyme activity of LDH, a key enzyme in both glycolysis and pentose phosphate pathways. Furthermore, in silico and coimmunoprecipitation studies have demonstrated that MORC2 interacts with c-MYC, an oncogene-encoded protein, and collaboratively regulates the expression and function of LDHA by binding to the LDHA promoter (Guddeti et al., 2021). This study illuminates a novel function for MORC2 in the realm of glucose metabolism; however, the findings necessitate additional corroboration through primary tumor sample analysis to confirm their clinical relevance.

POST-TRANSLATIONAL MODIFICATIONS IN MORC2

PTMs are pivotal in regulating cellular signal transduction, facilitating molecular transport, and preserving cellular homeostasis. The spectrum of PTMs is vast, with prevalent examples being phosphorylation, acetylation, methylation, glycosylation, and ubiquitination. The PTMs are not only integral to cellular biology but also serve as significant risk factors in the development and progression of many diseases, including Alzheimer’s, Parkinson’s, and stroke. PTMs have become very promising therapeutic targets with a significant amount of attention. Currently, there are various experimental and established treatment strategies targeting harmful PTMs that may improve clinical outcomes. An increasing number of studies indicate that the MORC2 protein is involved in multiple PTMs and plays a crucial role in various life processes (Table 1). Given the potential of PTMs as therapeutic targets, research on MORC2’s PTMs is of great importance.

PARylation

PARylation, catalyzed by PARP1, is a dynamic PTM that modulates the activity and interactions of proteins involved in DDR. MORC2 interacts with PARP1 and is PARylated by PARP1 at 2 specific residues within its conserved CW-ZF domain (Zhang and Li, 2019). This modification enhances MORC2’s ATPase activity and chromatin remodeling capabilities. Moreover, MORC2 stabilizes PARP1 by facilitating NAT10-mediated acetylation at lysine 949. This acetylation event prevents the ubiquitination of PARP1 by the E3 ubiquitin ligase CHFR, thereby blocking its degradation and ensuring the sustained availability of PARP1 for DNA damage signaling and repair (Zhang and Li, 2019). In summary, MORC2 emerges as a critical node in the PARylation-mediated DDR pathway, where it undergoes PARylation to modulate its chromatin remodeling activities, and contributes to the stabilization of PARP1 through a cross-talk with other PTMs.

Phosphorylation

Phosphorylation of MORC2 on specific residues, such as Ser677/739, has been shown to be mediated by PAK1, which is crucial for cell cycle progression and tumorigenesis (Li et al., 2012). This modification enhances MORC2’s ability to regulate chromatin remodeling during DNA damage response, thereby affecting genomic stability. The phosphorylation status of MORC2 is positively correlated with PAK1 expression in gastric cancer, and high levels of phosphorylated MORC2 are associated with poor prognosis, suggesting a critical role in cancer development and progression. The acetylation of MORC2 by NAT10 at lysine 767 (K767Ac) is counteracted by the deacetylase SIRT2 (Liu et al., 2020). DNA-damaging agents and ionizing radiation stimulate MORC2 K767Ac, enhancing its interaction with histone H3 phosphorylated at threonine 11 (H3T11P). This acetylation is essential for the DNA damage-induced reduction of H3T11P and the transcriptional repression of downstream target genes CDK1 and Cyclin B1, contributing to the activation of the G2 checkpoint. The interplay between acetylation and phosphorylation underscores the complex regulatory network governing MORC2’s function in response to genotoxic stress. In the context of breast cancer, MORC2’s phosphorylation at T582 by PRKACA, activated by GPER1, has been shown to block its lysosomal degradation via CMA, thereby stabilizing MORC2 and promoting oncogenic activities (Yang et al., 2020). This stabilization enhances estrogen-induced proliferation and contributes to endocrine resistance in breast cancer cells. The clinical relevance is further emphasized by the elevated levels of phosphorylated MORC2 at T582 in breast tumors from patients experiencing recurrence after tamoxifen treatment. In summary, MORC2 is a key node in the regulatory network of PTMs, with phosphorylation playing a central role in its function. Understanding the intricate mechanisms of MORC2 modification is crucial for developing targeted therapies that could potentially sensitize cancer cells to DNA-damaging treatments.

SUMOylation

MORC2 is modified by SUMO1 and SUMO2/3 at lysine 767 (K767) in a SUMO-interacting motif–dependent manner. Upon DNA damage, MORC2 sumoylation is initially decreased, which is associated with a transient relaxation of chromatin to facilitate DNA repair. At later stages of DNA damage, MORC2 interacts with PARP1 and is PARylated by PARP1 at 2 specific residues within its conserved CW-ZF domain (Zhang and Li, 2019). This modification enhances MORC2’s ATPase activity and chromatin remodeling capabilities. Moreover, MORC2 stabilizes PARP1 by facilitating NAT10-mediated acetylation at lysine 949. This acetylation event prevents the ubiquitination of PARP1 by the E3 ubiquitin ligase CHFR, thereby blocking its degradation and ensuring the sustained availability of PARP1 for DNA damage signaling and repair (Zhang and Li, 2019). In summary, MORC2 emerges as a critical node in the PARylation-mediated DDR pathway, where it undergoes PARylation to modulate its chromatin remodeling activities, and contributes to the stabilization of PARP1 through a cross-talk with other PTMs.
| Modification | Related enzymes | Modified residue and location | Mechanisms | Biological process | Diseases | References |
|--------------|-----------------|-----------------------------|------------|--------------------|----------|------------|
| PARylation   | PARP1           | Glutamate (E) 516, lysine (K) 517 | MORC2 interacts with PARP1 and is PARylated by PARP1. MORC2 stabilizes PARP1 by facilitating the acetylation of PARP1 at lysine 949 by the acetyltransferase NAT10 | DNA damage response | Breast cancer | Zhang and Li (2019) |
|              | PARP1, NAT10    | —                           | PARylated NAT10 colocalizes and interacts with MORC2, resulting in DNA damage–induced MORC2 acetylation at lysine 767 | DNA damage | — | Liu et al. (2020) |
| Phosphorylation | PAK1             | Serine (S) 739, threonine (T) 582 | MORC2 is phosphorylated in a PAK1-dependent manner, and phosphorylated MORC2 regulates its DNA-dependent ATPase activity to facilitate chromatin remodeling | Chromatin remodeling, DNA damage repair | Gastric cancer, breast cancer | Li et al. (2012) |
|              | PAK1            | S677                        | PAK1-mediated MORC2 phosphorylation promotes gastric tumorigenesis | Proliferation, tumorigenesis | Gastric tumor | Wang et al. (2015) |
|              | Cyclin-dependent kinase 1 | T717, T733 | Destabilization of MORC2 via the cyclin-dependent kinase 1-chaperone-mediated autophagy pathway promotes mitotic arrest and enhances cancer cellular sensitivity to microtubule-targeting agents | Mitotic progression and resistance of cancer cells to MTAs | Cancer | Hu et al. (2023) |
|              | GPER1-PRKACA-CMA | T582                       | MORC2 is phosphorylated through GPER1-PRKACA pathway, and is protected from lysosomal degradation by chaperone-mediated autophagy | Estrogen-induced proliferation and endocrine resistance | Breast tumors | Yang et al. (2020) |
| SUMOylation  | SUMO1, SUMO2/3  | K767                        | MORC2 is modified by SUMO1 and SUMO2/3 | DNA damage repair, chemoresistance | Breast cancer | Zhang et al. (2023) |
|              | C/EBPα          | —                           | MORC2 regulates C/EBPα-mediated axis of differentiation/proliferation via sumoylation modification, and affects its protein stability | Cell proliferation and tumorigenesis | Gastric cancer | Liu et al. (2019) |

(continued on next page)
| Modification     | Related enzymes | Modified residue and location | Mechanisms                                                                 | Biological process                | Diseases                    | References       |
|------------------|-----------------|------------------------------|----------------------------------------------------------------------------|-----------------------------------|-----------------------------|-------------------|
| Acetylation      | NAT10           | K767                         | Acetylation of MORC2 by NAT10 regulates cell cycle checkpoint control and resistance to DNA-damaging chemotherapy and radiotherapy | Cell cycle checkpoint            | Breast tumor           | Liu et al. (2020) |
| NAT10-PARP1      | —               | —                            | MORC2 stabilizes PARP1 through enhancing acetyltransferase NAT10-mediated acetylation of PARP1. PARP1 recruits DNA repair proteins in a PAR-dependent manner | DNA damage response              | —                           | Zhang et al. (2019) |
| PARP1-NAT10      | K767            | —                            | PARP1 catalyzes PARylation of NAT10, which acetylates MORC2 in response to DNA damage | DNA damage                       | —                           | Liu et al. (2022)  |
| CAIX             | —               | —                            | MORC2 downregulates CAIX by decreasing the acetylation level of histone H3 at the CAIX promoter | Transcriptional regulation        | —                           | Shao et al. (2010) |
| Histone methylation | ArgBP2       | —                            | MORC2 enhances the recruitment of EZH2, which promotes the trimethylation of H3K27, leading to the transcriptional repression of ArgBP2 | Transcriptional repression        | Gastric cancer         | Tong et al. (2015) |
| Alternative polyadenylation | DNMT3B/NUDT21/APA/MORC2/DAPK1 | 3′UTR | Loss of APA regulator NUDT21 induces APA reprogramming of MORC2 | Gene expression regulation, carcinogenesis | Kidney renal clear cell carcinoma | Tan et al. (2023) |
| O-GlcNAcylation  | OGT, TGF-β     | T556                         | O-GlcNAcylation of MORC2 at threonine 556 by OGT couples TGF-β signaling to breast cancer progression | Migration and invasion           | Breast cancer           | Liu et al. (2022)  |

3′UTR, 3′ untranslated region; ArgBP2, Arg kinase–binding protein 2; CAIX, carbonic anhydrase IX; DNMT3B, CMA, chaperone-mediated autophagy; DNA methyltransferase 3B; MORC2, microorchidia family CW-type zinc finger 2; MTA, microtubule-targeting agents; PAK1, p21-activated kinase 1; PARP1, poly(ADP-ribose) polymerase 1; TGF-β1, transforming growth factor-β1.
sumoylation is restored, and SUMOylated MORC2 interacts with protein kinase CSK21, leading to the phosphorylation of DNA-dependent protein kinase catalytic subunit and the promotion of DNA repair. This dynamic regulation of MORC2 sumoylation is crucial for proper DDR and contributes to the development of chemoresistance in breast cancer. Furthermore, the sumoylation status of MORC2 has been linked to the regulation of C/EBPα, a transcription factor involved in cell differentiation and proliferation (Liu et al., 2019). MORC2 overexpression promotes the sumoylation and subsequent degradation of wild-type C/EBPα, but not the sumoylation-deficient mutant C/EBPα-K161R. This finding suggests that MORC2-mediated sumoylation of C/EBPα plays a role in determining the cellular fate between differentiation and proliferation. In summary, MORC2 is a key player in the sumoylation pathway, with its modification by SUMO proteins influencing chromatin structure, DNA repair mechanisms, and cellular differentiation. The interplay between MORC2 sumoylation and other PTMs, such as acetylation and phosphorylation, adds another layer of complexity to the regulation of MORC2’s function. Understanding the intricate dynamics of MORC2 sumoylation offers new insights into the development of therapeutic strategies for cancer treatment, particularly in targeting chemoresistant tumors.

Acetylation

Acetylation of MORC2 has been implicated in the regulation of cell cycle checkpoint control and resistance to DNA-damaging chemotherapy and radiotherapy in breast cancer. Specifically, MORC2 is acetylated by the acetyltransferase NAT10 at lysine 767 (K767Ac), a process that is counteracted by the deacetylase SIRT2 under normal conditions. Upon DNA damage, MORC2 K767Ac is stimulated through enhanced interaction between MORC2 and NAT10 (Liu et al., 2020, 2022). Acetylated MORC2 binds to histone H3T11P and is essential for the DNA damage–induced reduction of H3T11P and transcriptional repression of downstream target genes CDK1 and Cyclin B1, contributing to the activation of the G2 checkpoint. The inhibition or depletion of NAT10 or expression of an acetylation-defective MORC2 mutant (K767R) results in hyperacetylistivity to DNA-damaging agents, highlighting the significance of MORC2 acetylation in DDR and therapeutic resistance. In addition to its role in DDR, MORC2 has been shown to downregulate the expression of CAIX through histone deacetylation (Shao et al., 2010). MORC2 decreases the acetylation level of histone H3 at the CAIX promoter, and this process is associated with HDAC4. MORC2 and HDAC4 are found to be assembled on the same region of the CAIX promoter, suggesting a combinatorial action in the transcriptional repression of CAIX. Collectively, these findings underscore the importance of MORC2 acetylation in the regulation of chromatin structure and cellular responses to DNA damage. The interplay between acetylation and other PTMs reveals a complex regulatory network that governs the function of MORC2 in maintaining genomic stability and cellular homeostasis.

Methylation

In gastric cancer cells, MORC2 binds to the promoter of the cytoskeleton adapter protein, ArgBP2, and enhances the recruitment of EZH2 (Tong et al., 2015). This interaction results in an increase in H3K27 trimethylation, which in turn leads to the transcriptional repression of ArgBP2. The downregulation of ArgBP2, a protein involved in cell adhesion and migration, is associated with the promotion of gastric cancer cell proliferation, migration, and invasion. These findings suggest that MORC2-mediated histone methylation plays a significant role in the epigenetic regulation of genes that control cellular processes critical for cancer progression. Recent studies have demonstrated that MORC2 interacts with the HUSH complex, which is crucial for the transcriptional repression of LINE-1 retrotransposons and other repetitive sequences (Pandiloski et al., 2024). In human neural progenitor cells, the loss of MORC2 does not lead to widespread transcriptional activation of LINE-1s, indicating that DNA methylation plays a dominant role in silencing these elements. However, when DNA methylation is disrupted, MORC2 binding to activated young LINE-1s increases, resulting in significant transcriptional upregulation. This suggests that MORC2’s role is context-dependent, where it functions to restrict transcription only when DNA methylation is compromised. Understanding the precise mechanisms by which MORC2 influences DNA methylation and chromatin dynamics will provide valuable insights into its functional roles in cellular contexts. By targeting MORC2 or its associated histone methylation machinery, it may be possible to modulate the expression of genes involved in cancer cell behavior, offering a new avenue for cancer treatment strategies.

Alternative Polyadenylation

APA is a modification that dictates the length of the 3’ untranslated region (3’UTR) of mRNA. APA has been increasingly recognized for its role in carcinogenesis, particularly in kidney renal clear cell carcinoma (KIRC), where MORC2’s oncogenic potential is significantly enhanced by 3’UTR shortening (Tan et al., 2023). MORC2 functions in KIRC by epigenetically silencing the tumor suppressor DAPK1 via DNA methylation. MORC2 recruits DNMT3A to facilitate hypermethylation of the DAPK1 promoter, a process that is enhanced by the 3’UTR shortening of MORC2. The loss of APA regulator NUDT21, induced by DNMT3B-mediated promoter methylation, is identified as responsible for the 3’UTR shortening of MORC2 in KIRC. This finding uncovers a novel role of DNA methylation in APA regulation and establishes a regulatory axis involving DNMT3B, NUDT21, APA, MORC2, and DAPK1 in KIRC. This knowledge provides insights into the molecular mechanisms underlying KIRC and may pave the way for novel therapeutic strategies targeting the MORC2-mediated epigenetic regulation in KIRC.

O-GlcNAcylation

O-GlcNAcylation is a critical PTM that plays a significant role in regulating protein function and cellular signaling. MORC2 is modified at a conserved threonine residue, T556, by the OGT, with the process being reversible and regulated by O-GlcNAcase (Liu et al., 2022). Mutation of T556 or pharmacological inhibition of the OGT impairs MORC2-mediated breast cancer cell migration and invasion in vitro and lung colonization in vivo. This modification is induced by TGF-β1 through enhancing the stability of glutamine-fructose-6-phosphate aminotransferase, the rate-limiting enzyme for producing the sugar donor for OGT. O-GlcNAcylated MORC2 is required for
the transcriptional activation of TGF-β1 target genes, such as connective tissue growth factor and snail family transcriptional repressor 1, which are crucial for breast cancer progression. Clinically, high expression of OGT, MORC2, snail family transcriptional repressor 1, and connective tissue growth factor in breast tumors correlates with poor patient prognosis, emphasizing the significance of MORC2 O-GlcNAcylation in cancer development and metastasis. The discovery of MORC2 as an O-GlcNAcylated protein provides new insights into the regulatory mechanisms of chromatin-associated enzymes in cancer and suggests that targeting MORC2 O-GlcNAcylation could be a potential therapeutic strategy for breast cancer treatment.

CONCLUSIONS

Evidence shows that MORC2 plays a role in various biological processes, including transcriptional regulation, chromatin remodeling, DDR, and lipid metabolism (Sanchez-Solana et al., 2014). MORC2 has been implicated in the development and progression of cancer by affecting proliferation, tumorigenesis, invasion, metastasis, immune infiltration, cell cycle checkpoints, DDR, anticancer therapy resistance, and EMT (Zhang et al., 2018). Next-generation sequencing techniques have identified MORC2 mutations responsible for CMT2Z, SMA-like phenotypes, and neurodevelopmental diseases (Guillen Sacoto et al., 2020; Albulym et al., 2016; Sevilla et al., 2016). Detailed descriptions of MORC2-related phenotypes can aid in accurate disease identification and diagnosis. Biochemical and structural studies have elucidated the underlying mechanisms of these diseases. However, further studies are required to understand how MORC2 influences cancer progression. Considering the expression of MORC2 in tumor tissues and its involvement in immune infiltration, targeting MORC2 in tumor tissues may hold promise for enhancing immune cell function and improving the effectiveness of tumor immunotherapy. Further investigation is needed to gain mechanistic insights into how MORC2 mutations lead to peripheral neuropathy. A future challenge is the development of therapeutics that specifically target MORC2 mutations.

This review clarifies the diseases associated with MORC2 and their pathogenic mechanisms, including neurological disorders and tumors. It also introduces the biological functions of MORC2 and its PTMs. In summary, MORC2 is involved in several important biological processes and is crucial for human health and disease. Nonetheless, there are ample opportunities for further exploration of the mechanistic fundamentals of MORC2 in human diseases. Further research is needed to understand the exact role of MORC2 in hereditary neuropathy and cancers, which would also help to confirm the therapeutic potential of MORC2 in different pathological conditions. As our understanding of MORC2’s role in various biological processes and diseases deepens, it is becoming increasingly clear that this protein represents a promising target for therapeutic intervention.

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Xin Zhao: Writing—review and editing, writing—original draft, funding acquisition, formal analysis, and conceptualization. Jinfeng Miao: Writing—original draft, visualization, and data curation.

DECLARATION OF COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

There is nothing to disclose.

DATA AVAILABILITY STATEMENT

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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