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Database issue

M6AREG 2.0: the landscape of m^{6}A-centered crosstalk with diverse epigenetic regulation

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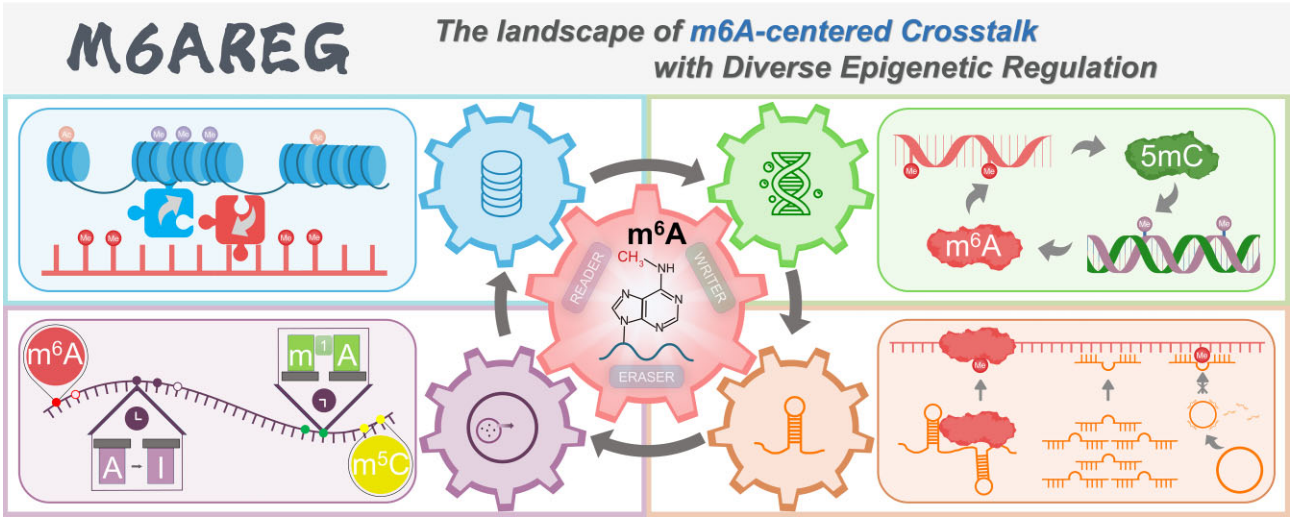
Abstract

m^{6}A-centered crosstalk with epigenetic regulation (m6A-CT) is essential for understanding disease development and drug response. Based on different layers of epigenetic regulation, m6A-CT can be classified into four categories: m^{6}A-centered crosstalk with histone modification (m6A-HistMod), m^{6}A-centered crosstalk with DNA methylation (m6A-DNAMeth), m^{6}A-centered crosstalk with RNA modification (m6A-RNAMod), and m^{6}A-centered crosstalk with non-coding RNA (m6A-ncRNA). However, none of the existing databases has comprehensively provided the crucial data regarding m6A-CT. Therefore, a significant update was made to the M6AREG database. This updated version includes 713 entries for m6A-HistMod, 300 entries for m6A-DNAMeth, 483 entries for m6A-RNAMod, and 939 entries for m6A-ncRNA. These types of crosstalk can alter cellular pathways and processes, ultimately leading to the development of 271 categories of diseases and the response data of 205 drugs, which are regulated by 585 epigenetic regulators (including 138 regulatory proteins and 447 non-coding RNAs). Given that these data are critical for identifying diagnostic biomarkers and therapeutic targets, discovering drugs that target m^{6}A modification, and developing combinatorial therapies to overcome drug resistance or immune evasion, this update will greatly enhance the impact of M6AREG and hold significant importance for m^{6}A-relevant studies. The database is currently accessible to all users at: https://idrblab.org/m6areg/.

Graphical abstract



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Introduction

N^6-Methyladenosine (m^6A), one of the most prevalent RNA modifications, plays critical roles in regulating disease progress and drug response [1–3]. The M6AREG database has therefore been developed to systematically depict data of m^6A regulation [4]. Recently, extensive research has focused on the study of "m^6A-centered crosstalk with epigenetic regulation (m6A-CT)", which is frequently reported to be involved in critical biological processes (such as embryonic development, immune regulation, and cell proliferation), providing new insight on regulation of disease progress and drug response by m^6A [5, 6]. Consequently, with continuous attention paid to m6A-CT, the relationships between m^6A modification and epigenetic regulation are reported to be crucial for guiding (i) disease diagnosis and treatment [7], (ii) drug design and optimization [8], and (iii) combinatorial therapeutic strategies to overcome chemotherapy resistance [9]. Therefore, it is necessary to establish a database that provides the key data of m6A-CT and its effect on disease development and drug response.

Due to the diversity of epigenetic regulations, m6A-CT has been classified into four categories (as shown in Fig. 1): (i) m^6A-centered crosstalk with histone modification (m6A-HistMod) that triggers epigenetic remodeling and is essential for revealing the mechanisms of disease progression [10]; (ii) m^6A-centered crosstalk with DNA methylation (m6A-DNAMeth) that is key for discovering therapeutic targets which are specifically directed at m^6A modification [11]. (iii) m^6A-centered crosstalk with RNA modification (m6A-RNAMod) that is crucial for developing RNA modification-based therapeutics and regulating immune responses [12]; and (iv) m^6A-centered crosstalk with non-coding RNA (m6A-ncRNA) that plays an essential role in the optimization of clinical treatment strategies and drug development [13]. Therefore, recent reports have emphasized the need for m6A-CT data to facilitate m^6A research, including pathology and pathophysiology [14], clinical laboratory diagnostics [15], and medicinal biochemistry [16].

So far, a variety of famous databases related to m^6A modification have been constructed. Some of them, such as RMDisease [17], WHISTLE [18], SRAMP [19], MeT-DB [20], and RM2Target [21], collectively compile extensive information on m^6A-related sites, targets, and functional annotations across various biological contexts. Some others, such as RMBase [22], RMVar [23], and m^6A-Atlas [24], provide potential associations between m^6A targets and histones or ncRNAs. These resources have greatly facilitated study on m^6A biology and provided a valuable foundation for understanding its regulatory role across multiple biological/pathological contexts. However, none of the existing databases (including the original version of our M6AREG) has comprehensively provided the crucial data concerning m^6A-centered crosstalk with epigenetic regulation. Therefore, there is an urgent need for a database that systematically provides the key data of m6A-CT and its effect on disease development and drug response.

In this study, M6AREG has been significantly updated to version 2.0, with a systematic collection and provision of m6A-CT data, including m6A-HistMod, m6A-DNAMeth, m6A-RNAMod, and m6A-ncRNA. In particular, 713 pieces of m6A-HistMod data that involve five types of histone modifications (histone methylation, acetylation, ubiquitination, propionylation, and lactylation) regulated by 60 histone-modifying enzymes (such as SETDB1, CREBBP, and KDM6B) were systematically described, and the biological effects of histone modifications on the expression of 78 downstream genes were also manually curated from the literature; 300 pieces of m6A-DNAMeth data involving six DNA methylation regulators (e.g. TET1, DNMT1, and DNMT3A) were systematically collected; 483 pieces of m6A-RNAMod data which encompass nine types of RNA modification (5-methylcytosine, N^1-methyladenosine, adenosine-to-inosine, etc.) regulated by 27 RNA modification regulators (including NSUN2, TRMT6, and ADARB1) were provided, and a total of 115 460 RNA modification sites (such as m^6A sites, A-to-I sites, and m^5C sites) across 1494 targets were compiled; and 938 pieces of m6A-ncRNA data involving 446 distinct ncRNAs (such as CircMEG3, FTO-IT1, and miR-515-5p) were described. Furthermore, m^6A regulators and m^6A targets were significantly enriched compared with M6AREG 1.0, resulting in the inclusion of 50 m^6A regulators and 1555 experimentally validated m^6A targets in this update. As a result, a total of 271 diseases (such as liver cancer, inflammatory responses, and diabetes) and the corresponding response data of 205 drugs (including cisplatin, sorafenib, and tamoxifen) regulated by 585 epigenetic regulators (138 regulatory proteins and 446 ncRNAs) were included. Moreover, 15 070 small molecules (6517 approved/clinical trial and 8553 investigational) were collected from DrugBank [25], TTD [26], PubChem [27], and MolBiC [28], which regulate disease progression and drug response through the mediation of specific m^6A-centered epigenetic regulators and targets. Overall, m6A-CT data will provide new insights into m^6A-mediated regulation of pathological processes and treatment outcomes. All in all, due to the application of m6A-CT data in diverse directions, M6AREG 2.0 is expected to attract a lot of attention from relevant research communities. Users can freely access M6AREG 2.0 without registration via the following URL: https://idrblab.org/m6areg/.

Factual content and data retrieval

Data collection for m^6A-centered crosstalk with epigenetic regulation

The data on m6A-CT are systematically collected through the following steps. Firstly, the data of m6A-CT (m6A-HistMod, m6A-DNAMeth, m6A-RNAMod, and m6A-ncRNA) were comprehensively collected by searching the peer-reviewed literature in PubMed using keyword combinations such as "m^6A + histone modification", "m^6A + DNA modification", "m^6A + RNA modification", "m^6A + ncRNA", "m^6A regulator name + epigenetic regulator name", etc. The key components involved in m6A-CT have been identified, such as m^6A regulators, m^6A targets, histone-modifying enzymes, DNA methylation regulators, RNA modification regulators, ncRNAs, associated diseases, and drug responses. Secondly, detailed information on m6A-CT was manually collected, including crosstalk relationship (inhibition/enhancement), crosstalk mechanism, cellular pathway, cellular processes, and *in vitro*/*vivo* model. Based on the m6A-CT mechanism, illustrative diagrams clearly depicting the crosstalk between m^6A and other types of epigenetic regulation were also provided. Thirdly, a substantial number of RNA modification sites were collected via retrieving data from RM2Target [21], RMBase [22], and m^6A-Atlas [24]. They are well-established

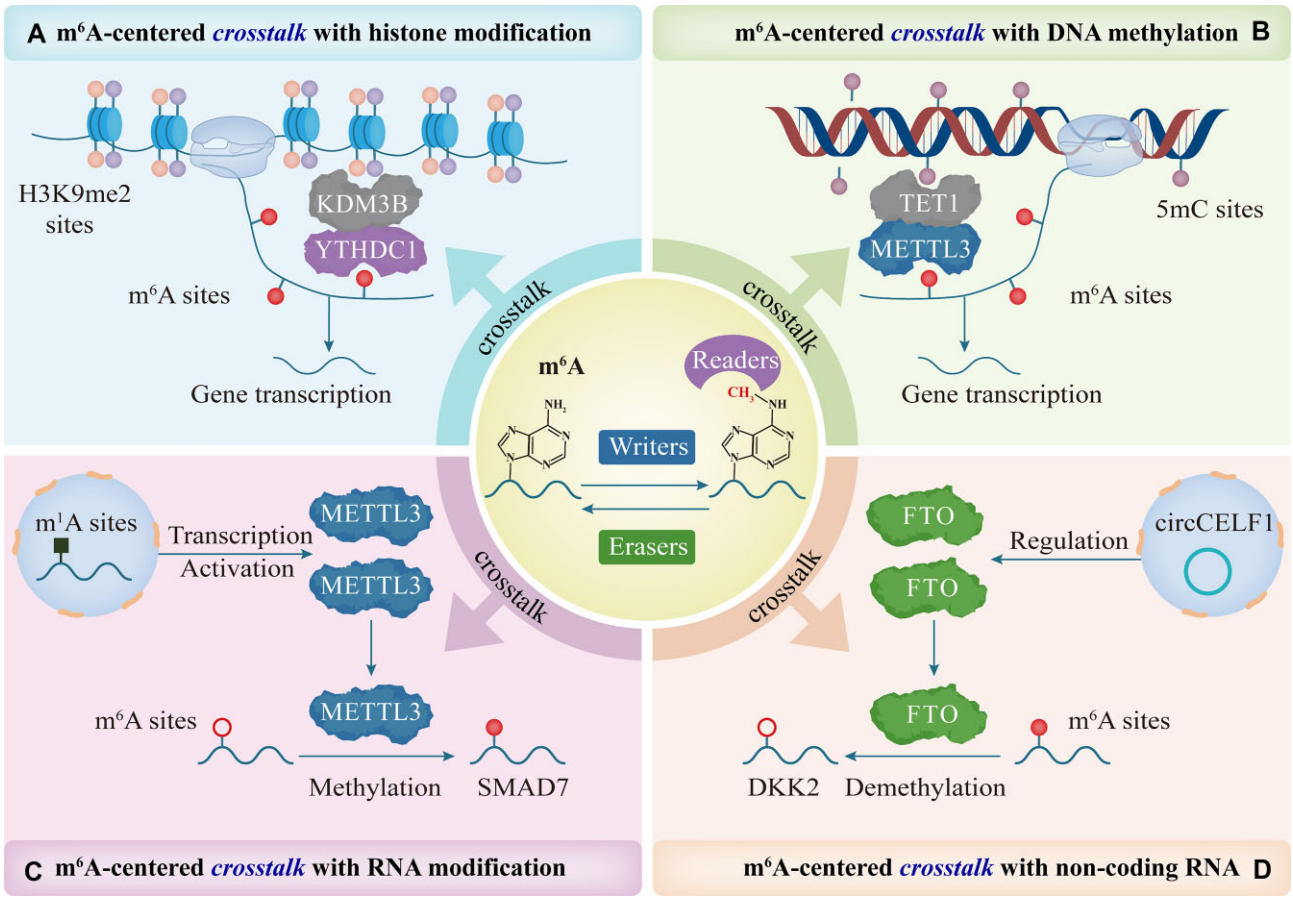


Figure 1. The data of m^{6}A-centered crosstalk with epigenetic regulation (m6A-CT) updated to M6AREG 2.0. (**A**) m^{6}A-centered crosstalk with histone modification (m6A-HistMod); (**B**) m^{6}A-centered crosstalk with DNA methylation (m6A-DNAMeth); (**C**) m^{6}A-centered crosstalk with RNA modification (m6A-RNAMod); (**D**) m^{6}A-centered crosstalk with non-coding RNA (m6A-ncRNA).

databases that provide high-confidence, experimentally validated RNA modification site data, offering critical resources for understanding RNA modification landscapes and their biological significance [29]. Fourthly, some small molecules have been reported to regulate disease progression and drug response by targeting key regulators and targets within m6A-CT [30]. Therefore, many potential compounds impacting m6A-CT were collected from the DrugBank [25], TTD [26], and PubChem [27], providing valuable guidance for m^{6}A-related research.

The crosstalk between m^{6}A and epigenetic regulation

m^{6}A, one of the most pivotal epigenetic modifications in RNA, regulates gene expression by influencing RNA splicing, degradation, stability, translation, and nuclear export, thereby impacting physiological and pathological processes [31]. However, in addition to m^{6}A modification, other extensively investigated types of epigenetic regulation include histone modification [32], DNA methylation [33], RNA modification [34], and the functional roles of ncRNAs [35]. As described in Fig. 2, these types of epigenetic regulation participate in gene expression regulation at distinct epigenetic layers without altering the DNA sequence, each through unique molecular pathways [36–38], and orchestrate a highly coordinated and dynamic regulatory network, the disruption of which can impair normal cellular functions and precipitate the onset of various diseases [39]. However, accumulating evidence has revealed intricate crosstalk between m^{6}A modification and the above types of epigenetic regulation which form complicated feedback circuits or cooperative networks to drive epigenetic reprogramming [40]. Their crosstalk contributes to diverse physiological and pathological processes, offering novel insights into m^{6}A-centered regulation in disease pathogenesis and therapeutic responses [41, 42].

m^{6}A-centered crosstalk with histone modification (m6A-HistMod)

m6A-HistMod is essential for revealing the mechanism of disease progression and can lead to epigenetic remodeling [43]. Firstly, m^{6}A modifications and histone modifications reciprocally regulate each other by modulating the expression of their respective regulatory proteins [44, 45]. As shown in Fig. 3, histone deacetylase HDAC1 inhibits the m^{6}A demethylation of FSP1 mRNA by down-regulating H3K27ac at the promoters of FTO, while the inhibition of HDAC1 effectively overcomes ferroptosis resistance in colorectal cancer [46]. These findings underscore that exploring the molecular mechanisms of m6A-HistMod underlying disease progression can provide novel insights for developing therapeutic strategies, particularly in cancer [47]. Secondly, the m^{6}A regulators recruit histone-modifying enzymes to m^{6}A-associated chromatin regions and influence histone modification and gene expression, which is essential for maintaining physiological development

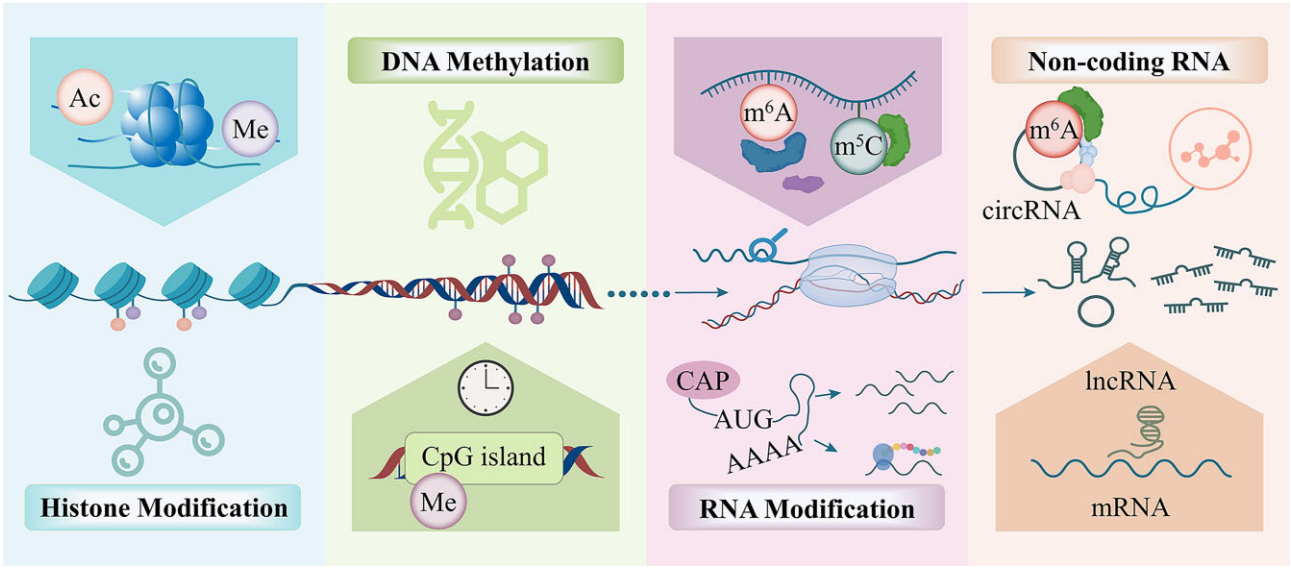


Figure 2. Molecular mechanisms of the four types of epigenetic regulation. (**A**) Histone modification, mediated by histone-modifying enzymes, involves post-translational modifications of specific amino acids on histones, which facilitate the dynamic transition between euchromatin and heterochromatin states, thereby fine-tuning gene expression. (**B**) DNA methylation, catalyzed by DNA methyltransferases or demethylases, typically occurs at the 5′ position of cytosine (5-methylcytosine, 5mC), influencing genomic stability, chromatin architecture, and transcriptional activity. (**C**) RNA modification, operating at the transcriptomic level, regulates RNA metabolism—including stability, splicing, and translation—through diverse RNA-modifying enzymes. (**D**) Non-coding RNA primarily function at the post-transcriptional level by interacting with mRNA, chromatin, or regulatory proteins to modulate gene expression.

and health [48, 49]. Therefore, a comprehensive understanding of how m6A-HistMod influences epigenetic remodeling is crucial for both the treatment of diseases and the maintenance of physiological development and health.

All in all, M6AREG 2.0 integrates 713 pieces of m6A-HistMod data including 19 m^6A regulators and 309 m^6A targets for the m^6A modifications. The histone modifications involve five types (histone methylation, acetylation, ubiquitination, propionylation, and lactylation) regulated by 60 histone-modifying enzymes (including SETDB1, CREBBP, and KDM6B), as well as 78 downstream genes affected by chromatin conformational changes. In addition, due to differences in their sites of modification and underlying functional mechanisms, the biological effects of histone modifications, known to exert diverse influences on downstream gene expression (activation/repression), were systematically collected [50, 51]. As shown in Fig. 3, some modifications such as histone H4 lysine 5 lactylation (H4K5la) at promoter regions are associated with transcriptional activation, whereas others such as histone H3 lysine 9 trimethylation (H3K9me3) are linked to transcriptional repression. These modifications regulate gene expression by altering chromatin structure or by recruiting specific effector proteins. Overall, M6AREG 2.0 clearly delineates the specific mechanisms of m6A-HistMod and its impact on disease progression and drug response.

m^6A-centered crosstalk with DNA methylation (m6A-DNAMeth)

m6A-DNAMeth is crucial for expanding the discovery of therapeutic targets directed at m^6A modification [52]. As shown in Fig. 4, 5mC-mediated suppression of SOCS3 by DNMT3A leads to STAT3 activation, which subsequently transactivates YTHDF1 through HIF-1α. The crosstalk between m^6A and 5mC contributes to progression of hepatic fibrosis, thereby offering novel epigenetic therapeutic targets for the treatment of hepatic fibrosis [53]. In addition, the dynamic interplay between m^6A regulators and 5mC regulators facilitates the identification of potential therapeutic compounds and druggable targets, and enables precise prediction of clinical outcomes in hepatocellular carcinoma (HCC) patients [54]. All in all, by systematically profiling m6A-DNAMeth data, researchers can elucidate the dynamic regulatory mechanisms underlying disease development [55, 56], which in turn lead to the discovery of novel therapeutic targets and precise prediction of clinical outcomes, as well as providing novel strategies for preventing and treating diseases [57].

M6AREG 2.0 integrates a total of 300 pieces of m6A-DNAMeth data including 20 m^6A regulators and 95 m^6A targets for the m^6A modifications. Within the collected data, DNA methylation modifications are predominantly represented by 5mC, with 40 target genes regulated by DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B), DNA demethylases (TET1 and TET2), and the DNA recognition protein methyl-CpG-binding protein 2 (MECP2). In Fig. 4, the key elements involved in m6A-DNAMeth are provided, including the m^6A regulator, m^6A target, DNA methylation regulator, and regulated target gene. By clicking the "Regulator Info", "Target Gene", or "View Details" buttons, users can access detailed basic information for each element, including synonyms, gene name, sequence, family, function, gene ID, UniProt ID, HGNC ID, miRBase ID, and chromosomal location. Furthermore, detailed information on m6A-DNAMeth is also provided, including crosstalk relationship (enhancement/inhibition), crosstalk mechanism, literature description, cellular pathway, associated diseases, drug response, and an *in vivo*/*in vitro* model. In summary, M6AREG 2.0 provides a comprehensive resource that not only captures the intricate interactions between m^6A modifications and DNA methylation but also supports a deeper understanding of

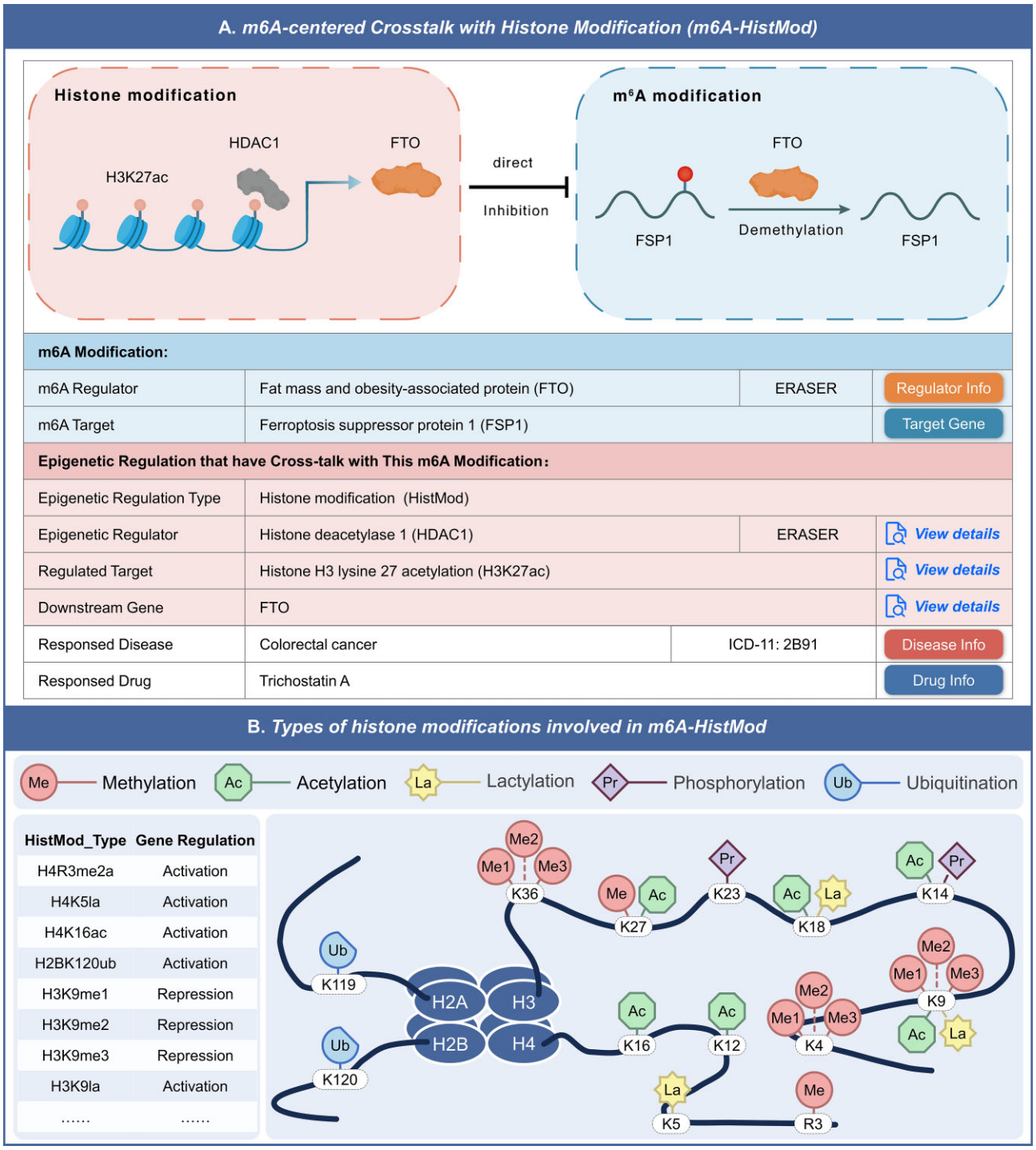
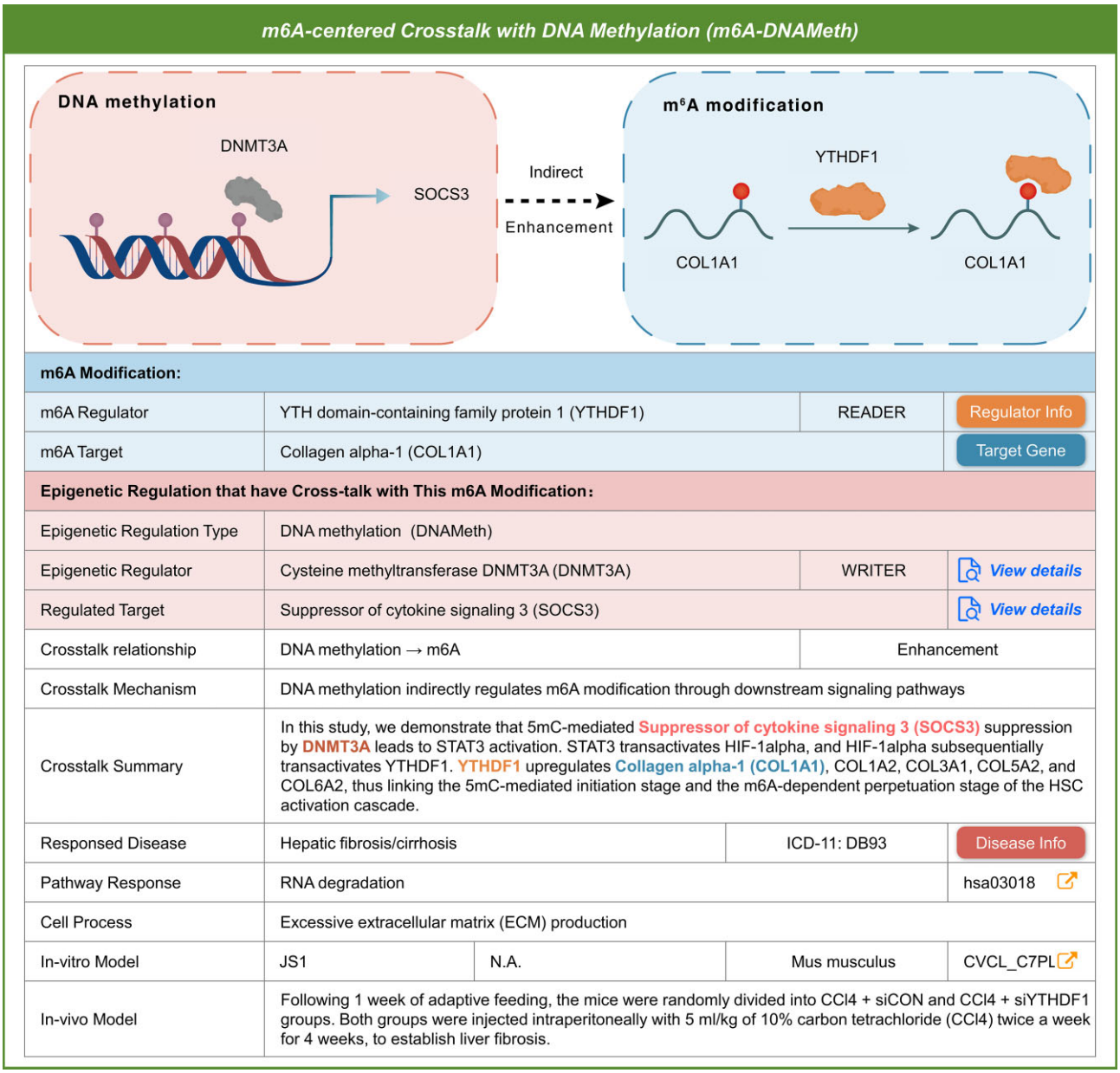


Figure 3. A typical page providing information on m^{6}A-centered crosstalk with histone modification (m6A-HistMod). (**A**) General information of m6A-HistMod. The graphic illustrating the relationship between m^{6}A modification and histone modification is provided at the top. The detailed information of each m6A-HistMod, including m^{6}A regulator, m^{6}A target, histone-modifying enzyme, histone substrate, downstream gene, crosstalk mechanism, and the disease and drug responding, is given. (**B**) List of types of histone modifications involved in m6A-HistMod. Due to differences in their sites of modification and underlying functional mechanisms, distinct types of histone modifications exert diverse effects on downstream gene expression, which can generally be categorized into transcriptional activation or transcriptional repression.



m6A Modification:			
m6A Regulator	YTH domain-containing family protein 1 (YTHDF1)	READER	Regulator Info
m6A Target	Collagen alpha-1 (COL1A1)		Target Gene
Epigenetic Regulation that have Cross-talk with This m6A Modification:			
Epigenetic Regulation Type	DNA methylation (DNAMeth)		
Epigenetic Regulator	Cysteine methyltransferase DNMT3A (DNMT3A)	WRITER	View details
Regulated Target	Suppressor of cytokine signaling 3 (SOCS3)		View details
Crosstalk relationship	DNA methylation → m6A	Enhancement	
Crosstalk Mechanism	DNA methylation indirectly regulates m6A modification through downstream signaling pathways		
Crosstalk Summary	In this study, we demonstrate that 5mC-mediated Suppressor of cytokine signaling 3 (SOCS3) suppression by DNMT3A leads to STAT3 activation. STAT3 transactivates HIF-1alpha, and HIF-1alpha subsequentially transactivates YTHDF1. YTHDF1 upregulates Collagen alpha-1 (COL1A1), COL1A2, COL3A1, COL5A2, and COL6A2, thus linking the 5mC-mediated initiation stage and the m6A-dependent perpetuation stage of the HSC activation cascade.		
Responsed Disease	Hepatic fibrosis/cirrhosis	ICD-11: DB93	Disease Info
Pathway Response	RNA degradation		hsa03018
Cell Process	Excessive extracellular matrix (ECM) production		
In-vitro Model	JS1	N.A.	Mus musculus	CVCL_C7PL
In-vivo Model	Following 1 week of adaptive feeding, the mice were randomly divided into CCl4 + siCON and CCl4 + siYTHDF1 groups. Both groups were injected intraperitoneally with 5 ml/kg of 10% carbon tetrachloride (CCl4) twice a week for 4 weeks, to establish liver fibrosis.		

Figure 4. A typical page providing information of m^{6}A-centered crosstalk with DNA methylation (m6A-DNAMeth). The graphic illustrating the relationship between m^{6}A modification and DNA methylation is provided at the top. The detailed information of each m6A-DNAMeth, including m^{6}A regulator, m^{6}A target, DNA methylation regulator, regulated target, crosstalk mechanism, disease, drug, pathway, cell process, and *in vitro*/*vivo* model is given.

their regulatory mechanisms and potential therapeutic applications, backed by experimental evidence.

m^{6}A-centered crosstalk with RNA modification (m6A-RNAMod)

The dynamic crosstalk between m^{6}A and other RNA modifications at the transcript level reveals the complexity and precision of gene expression regulation, where these modifications cooperatively influence RNA stability, splicing, translation, and decay, thereby governing pivotal physiological and pathological processes [58]. Therefore, targeting m6A-RNAMod provides a foundation for the development of RNA modification-based therapeutics [59]. In particular, RBM15B-mediated m^{6}A modification and NSUN5-mediated m^{5}C modification on GPX4 collectively enhance anticancer immunity by activating the cGAS–STING signaling pathway in colorectal adenocarcinoma (COAD), which highlights the role of m6A-RNAMod in immunometabolism and further influences immune responses [60]. Moreover, GPX4 has been shown to possess significant prognostic value and therapeutic potential [61]. These studies suggest that m6A-RNAMod plays an essential role in immune responses [62] and holds significant implications for therapeutic efficacy and prognostic evaluation in various diseases [63]. Therefore, a comprehensive understanding of the mechanisms underlying m6A-RNAMod can lead to the development of RNA modification-based therapeutics [64] and the identification of potential biomarkers for immune responses and disease prognosis [65].

M6AREG 2.0 integrates 483 pieces of m6A-RNAMod data, capturing crosstalk between m^{6}A regulation and other RNA modifications (excluding m^{6}A). Specifically, the m^{6}A modifications involve 20 m^{6}A regulators and 94 m^{6}A targets,

while the RNA modifications encompass nine types (m^5C; A-to-I RNA editing; m^1A; m^1G; 2′-*O*-methylation; ac^4C; m^6Am; pseudouridine; and m^7G) regulated by 27 RNA modification regulators (including NSUN2, TRMT6, and ADARB1). These RNA modification regulators are classified into writers, erasers, and readers based on their functional roles in the dynamic regulation of RNA modifications: (i) writers catalyze the addition of chemical modifications to RNA molecules; (ii) erasers remove RNA modifications, making the process reversible; and (iii) readers recognize and bind to specific RNA modifications, thereby translating the modification signals into functional outcomes. In addition, RNA modification sequence and site information of all targets was compiled, encompassing a total of 115 460 RNA modification sites across 1494 targets, including 91 123 m^6A sites, 11 058 A-to-I sites, 5254 m^5C sites, and 8025 other RNA modification sites. As shown in Fig. 5, users can access detailed RNA modification sequence and site information of target genes by clicking either the "Target gene" button or the "View details" button on the webpage, which includes the type of RNA modification (e.g. m^6A, m^5C, and A-to-I), precise modification sites, surrounding sequence context, motif scores, experimental cell lines/tissues, and detection methods (such as m6A-seq, MeRIP-seq, and DART-seq). Together, M6AREG 2.0 provides a valuable framework for understanding the coordinated regulatory landscape of diverse RNA modifications beyond m^6A.

m^6A-centered crosstalk with non-coding RNA (m6A-ncRNA)

m6A-ncRNA is crucial for clinical treatment optimization and drug development by modulating biological functions in pathology [66]. The m^6A modification of ncRNAs regulates their biogenesis and functionality through impacts on splicing, transport, stability, degradation, and even translation [67]. For instance, METTL14-mediated m^6A modification of circ_ORC5 suppresses gastric cancer progression by regulating the miR-30c-2-3p/AKT1S1 axis, which is of importance to the early diagnosis and treatment of gastric cancer [68]. Conversely, ncRNAs can dynamically influence m^6A modification through influencing the function or expression of m^6A regulators [69, 70]. Targeting m6A-ncRNA may serve as a feasible therapeutic strategy for disease treatment [71, 72]. In addition, there is mounting evidence indicating that m6A-ncRNA modulates immune responses and contributes to therapeutic resistance [73–75], thereby presenting novel opportunities for clinical treatment optimization. Meanwhile, additional RNA-binding domains have been identified within RNA-binding proteins (RBPs) involved in m6A-ncRNA, providing a theoretical basis for the development of more drugs targeting these domains [76]. Therefore, a comprehensive understanding of the mechanistic roles of m6A-ncRNA may offer novel insights into clinical treatment optimization and drug development.

M6AREG 2.0 integrates 938 pieces of m6A-ncRNA data which involve 35 m^6A regulators and 467 m^6A targets, with 446 ncRNAs engaged in m6A-ncRNA including 179 microRNAs (miRNAs; e.g. miR-200c-3p, miR-665, and let-7b-5p), 71 circular RNAs (circRNAs; e.g. circZBTB44, circORC5, and circMAP3K4), and 84 long non-coding RNAs (lncRNAs; e.g. ABHD11-AS1, PACERR, and STEAP3-AS1). In addition, M6AREG 2.0 encompasses information on 110 disease classes (e.g. liver cancer, inflammatory response, and diabetes) and the response profiles of 65 therapeutic drugs (e.g. cisplatin, sorafenib, and tamoxifen), all regulated by these ncRNAs. As shown in Fig. 6, these ncRNAs exert diverse regulatory effects on m^6A modifications through distinct mechanisms, such as translational repression of m^6A regulators through direct targeting by miRNAs, competitive inhibition via circRNA-mediated miRNA sponging, and modulation of m^6A regulators through direct interactions with lncRNAs. The downstream impacts of m6A-ncRNA involve alterations in key cellular phenotypes (e.g. DNA damage repair, proliferation, metastasis, tumor microenvironment, epithelial–mesenchymal transition, and ubiquitination-mediated degradation), which further influence multiple diseases including tumors, neurological disorders, cardiovascular diseases, and respiratory diseases. Additionally, M6AREG 2.0 links m6A-ncRNA crosstalk to drug responses and biomedical applications, such as mechanistic studies, biomarker identification, drug discovery, and resistance reversal, providing a valuable resource for exploring epigenetic regulatory mechanisms and their therapeutic potential.

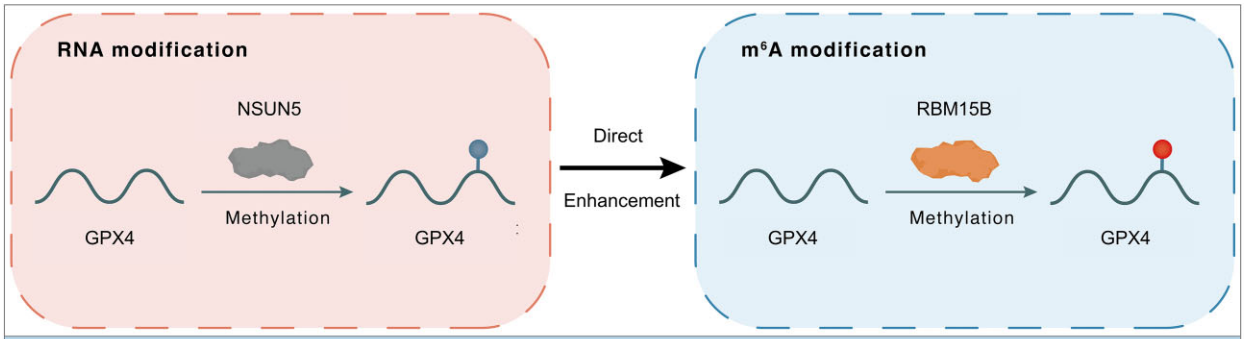
Standardization, access, and retrieval of data

To enhance user accessibility and facilitate comprehensive analysis of the M6AREG 2.0 dataset, all raw data underwent rigorous curation and systematic standardization. These procedures included: (i) the normalization and cross-referencing of all genes, RNAs, proteins, signaling pathways, and *in vitro* models involved in crosstalk events with authoritative databases such as NCBI Gene [77], HGNC [78], miRbase [79], Ensembl [80], UniProt [81], KEGG [82], and Cellosaurus [83]; (ii) the standardization of all disease terms according to the latest edition of the International Classification of Diseases (ICD-11); and (iii) the cross-linking of drug-related data to leading pharmaceutical databases, including DrugBank [25], TTD [26], and PubChem [27]. All curated content in the M6AREG 2.0 database is freely accessible, searchable, and downloadable without login restrictions at: https://idrblab.org/m6areg/.

Conclusion

In recent years, research on m^6A modification has shifted from focusing on its isolated functions to exploring its complex interactions with other epigenetic regulation. m6A-CT remodels target gene expression without altering the genetic sequence, thereby regulating cellular pathways and phenotypes. As a result, it plays a crucial role in both normal physiological processes and pathological changes. Furthermore, the co-regulatory networks between m^6A regulators and other epigenetic factors have provided deeper insights into how m^6A influences disease progression and drug responses. Therefore, this update introduces a novel module capturing crosstalk between m^6A and four epigenetic regulatory systems (m6A-HistMod, m6A-DNAMeth, m6A-RNAMod, and m6A-ncRNA), while also incorporating information of RNA modification sites and enriching the original data (m^6A regulators, m^6A targets, associated diseases, and drug responses). The expanded resource provides valuable guidance for the design and optimization of m^6A-targeted therapeutics, disease diagnosis/treatment/prognosis, and combinatorial strategies to overcome drug resistance. Consequently, M6AREG 2.0 is anticipated to exert substantial influence on future research into m^6A-based regulation.

A. *m6A-centered Crosstalk with RNA Modification (m6A-RNAMod)*



m6A Modification:			
m6A Regulator	RNA-binding motif protein 15B (RBM15B)	WRITER	Regulator Info
m6A Target	Phospholipid hydroperoxide glutathione peroxidase GPX4 (GPX4)		Target Gene
Epigenetic Regulation that have Cross-talk with This m6A Modification:			
Epigenetic Regulation Type	RNA modification (RNAMod)		
Epigenetic Regulator	28S rRNA (cytosine-C(5))-methyltransferase (NSUN5)	WRITER	View details
Regulated Target	Phospholipid hydroperoxide glutathione peroxidase GPX4 (GPX4)		View details
Responsed Disease	Colon cancer	ICD-11: 2B90	Disease Info

B. *RNA Modification Sequencing Data Associated with the Target*

▼ **Phospholipid hydroperoxide glutathione peroxidase GPX4 (GPX4)**

N6-Methyladenosin (m6A): **In total 25 m6A sequence/site(s) in this target gene**		
mod ID	*M6ASITE000001*	Click to Show/Hide the Full List
mod Site	chr19:1106440-1106441:+	
Sequence	TGCGTGGTGAAGCGCTACGGACCCATGGAGGAGCCCCTGGT	
Motif Score	3.62240476190476	
Cell/Tissue List	HepG2; MT4; MM6; Huh7; endometrial	
Seq Type List	m6A-seq; MeRIP-seq	
Transcript ID List	ENST00000592940.2; ENST00000587648.5; ENST00000588919.5; ENST00000589115.5	
External Link	RMBase: m6A_site_407149	
mod ID	*M6ASITE000002*	Click to Show/Hide the Full List
mod ID	*M6ASITE000003*	Click to Show/Hide the Full List
5-Methylcytosine (m5C): **In total 6 m5C sequence/site(s) in this target gene**		
mod ID	*M5CSITE000001*	Click to Show/Hide the Full List
mod ID	*M5CSITE000002*	Click to Show/Hide the Full List
2'-O-Methylation (2'-O-Me): **In total 1 2'-O-Me sequence/site(s) in this target gene**		

Figure 5. A typical page providing information of m^{6}A-centered crosstalk with RNA modification (m6A-RNAMod). (**A**) General information of m6A-RNAMod. The graphic illustrating the relationship between m^{6}A modification and RNA modification is provided at the top. The detailed information of each m6A-RNAMod, including m^{6}A regulator, m^{6}A target, RNA modification regulator, regulated target, crosstalk mechanism, responding disease, and responding drug. (**B**) List of types of RNA modification sequencing data associated with the target. RNA modification sequence and site information for all targets are provided, including detailed annotations such as the type of RNA modification (e.g. m^{6}A, m^{5}C, and A-to-I), exact modification sites, surrounding sequence context, motif score, experimental cell lines or tissues, and detection methods.

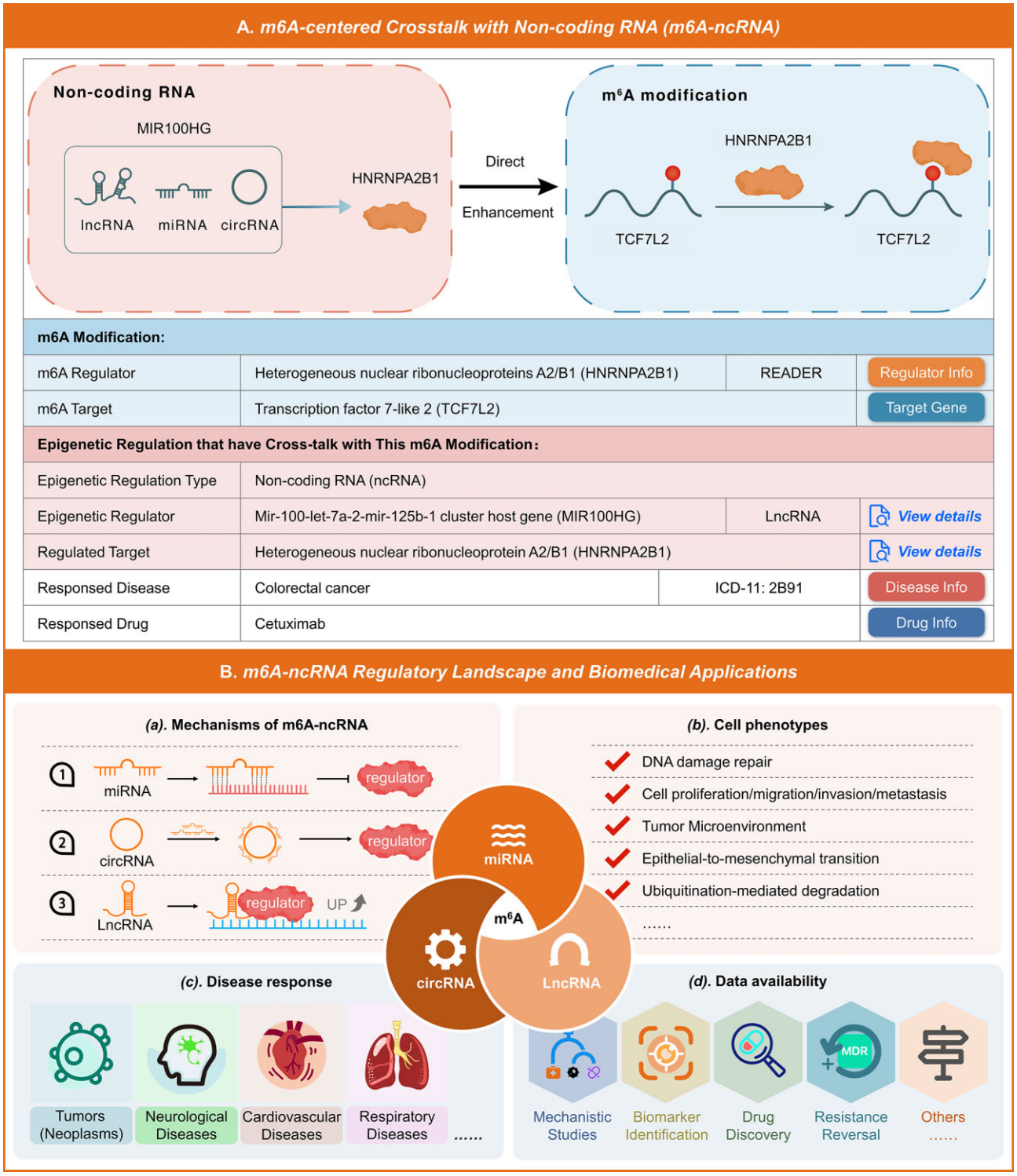


Figure 6. A typical page providing information of m^{6}A-centered crosstalk with non-coding RNA (m6A-ncRNA). (**A**) General information of m6A-ncRNA. The graphic illustrating the relationship between m^{6}A modification and non-coding RNA is provided at the top. The detailed information of each m6A-ncRNA, including m^{6}A regulator, m^{6}A target, ncRNA name, regulated target, crosstalk mechanism, responding disease, and responding drug, is given. (**B**) m6A-ncRNA regulatory landscape and biomedical applications. (a) Mechanisms of m6A-ncRNA. ncRNAs regulate m^{6}A modification through distinct mechanisms depending on their type: (1) miRNAs target the transcripts of m^{6}A regulators, thereby suppressing their expression; (2) circRNAs sequester miRNAs, thereby relieving their inhibitory effect on m^{6}A regulators and leading to the up-regulation of these regulators; (3) lncRNAs can physically associate with m^{6}A regulators, influencing their catalytic activity and consequently altering the methylation status of specific m^{6}A targets. (b) Cell phenotypes induced by m6A-ncRNA include DNA damage repair, tumor microenvironment, cell proliferation, and cell migration. (c) Diseases affected by m6A-ncRNA are provided, such as tumors, neurological diseases, cardiovascular diseases, and respiratory diseases. (d) Data availability and biomedical applications enabled by m6A-ncRNA research, including mechanistic studies, biomarker identification, drug discovery, resistance reversal, and additional emerging applications.

In addition to experimentally validated data mentioned above, the accurate identification of RNA modification sites is essential for elucidating the specific roles of m6A-CT in various biological processes [84]. So far, several computational models have been developed to predict potential RNA modification sites, such as DeepBIO [84], m5C-pred [85], and BERMP [86]. These models, leveraging machine learning and deep learning approaches, provide a crucial complement to experimental data, thereby broadening our understanding of m6A-CT research. As the database expands, the enhanced resource will offer more precise tools for researchers to explore the crosstalk between m^{6}A and other epigenetic mechanisms, ultimately driving the development of targeted therapies. In the future, we will refine existing computational models and continue to explore relevant data, with the goal of further improving and expanding the database.

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Conflict of interest

None declared.

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Data availability

The data underlying this article are available in the article and in its online supplementary data. The latest version of M6AREG is freely accessible at: https://idrblab.org/m6areg/.

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