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M6AREG: m^{6}A-centered regulation of disease development and drug response

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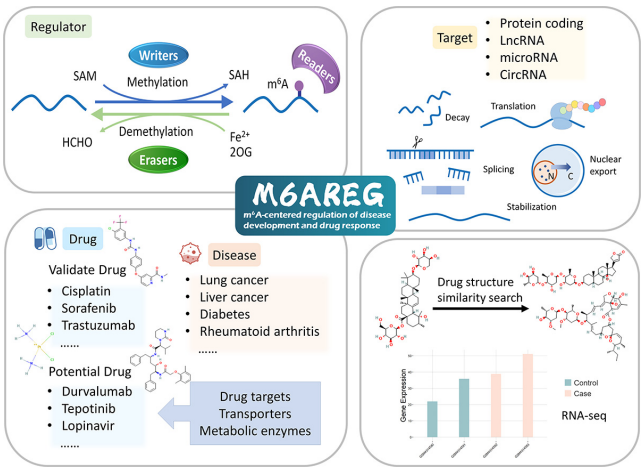
ABSTRACT

As the most prevalent internal modification in eukaryotic RNAs, *N*^{6}-methyladenosine (m^{6}A) has been discovered to play an essential role in cellular proliferation, metabolic homeostasis, embryonic development, etc. With the rapid accumulation of research interest in m^{6}A, its crucial roles in the regulations of disease development and drug response are gaining more and more attention. Thus, a database offering such valuable data on m^{6}A-centered regulation is greatly needed; however, no such database is as yet available. Herein, a new database named 'M6AREG' is developed to (i) systematically cover, for the first time, data on the effects of m^{6}A-centered regulation on both disease development and drug response, (ii) explicitly describe the molecular mechanism underlying each type of regulation and (iii) fully reference the collected data by cross-linking to existing databases. Since the accumulated data are valuable for researchers in diverse disciplines (such as pathology and pathophysiology, clinical laboratory diagnostics, medicinal biochemistry and drug design), M6AREG is expected to have many implications for the future conduct of m^{6}A-based regulation studies. It is currently accessible by all users at: https://idrblab.org/m6areg/

GRAPHICAL ABSTRACT



INTRODUCTION

As the most prevalent internal modification in eukaryotic RNAs, *N*^{6}-methyladenosine (m^{6}A) is widely known to play essential roles in cellular proliferation, metabolic homeostasis, embryonic development, and so on (1–6). With the rapid

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increase in research interest in m^{6}A, its crucial roles in the occurrence and progression of various diseases, including cardiovascular disease (7), influenza (8), gastroenteritis (9), liver fibrosis (10), diabetes (11) and cancer (12), are gaining more and more attention. Moreover, various types of m^{6}A regulation are found to affect the responses of a drug in its corresponding disease via mediating the expression of target genes (13–15). In other words, the regulation of disease development and drug response by m^{6}A has emerged as one of the most promising directions in recent years (7–19), and various studies have been conducted to uncover the molecular mechanism underlying regulation (mediated by the regulators of methyltransferase (writers), demethylase (erasers) and m^{6}A-binding proteins (readers) (20–22).

The above-mentioned studies have accumulated valuable data for researchers in the diverse directions of (i) pathology and pathophysiology clarifying the essential role of m^{6}A modifications in the occurrence/progression of disease (23–26), (ii) clinical laboratory diagnostics promoting the discovery of new therapeutic targets (27–31) and diagnostic/prognostic biomarkers (32–37) and (iii) medicinal biochemistry and drug design facilitating the discovery of m^{6}A's mechanisms in determining drug sensitivity and the design of new drug and drug combinations (38–42). Therefore, it is essential to have a database that provides data on the effect of m^{6}A-centered regulation on disease development and drug response, together with the molecular mechanisms underlying each type of regulation.

So far, a variety of popular m^{6}A-related databases have been developed (43–52). Some focus on describing the genome-wide landscape of RNA modification, variants and a variant's effect on post-transcriptional regulation [such as RMDisease (43), RMBase (44) and RMVar (45)]. Some others aim to show the m^{6}A modification sites of RNAs based on sequencing experiments and transcriptome-wide prediction [such as m6A-Atlas (46), WHISTLE (47), m6Avar (48) and SRAMP (49)]. The remaining databases provide the validated or predicted targets of m^{6}A regulators based on low-/high-throughput studies [such as MeT-DB (50) and M6A2Target (51)]. The majority of these existing databases have been frequently accessed and highly cited due to their considerable contributions to the needs of research communities (44–50). However, to date, there is no database available to provide data of m^{6}A-centered regulation of disease development and drug response. Moreover, such a database is needed to systematically describe the molecular mechanisms underlying each type of regulation.

Herein, a database named 'm^{6}A-centered regulations of disease development and drug response (M6AREG)' is therefore introduced. First, a systematic literature review on m^{6}A's regulation of disease development and drug response was conducted. The development of various diseases and the response data of drugs that were reported to be regulated by the corresponding m^{6}A were systematically collected into the M6AREG database. Second, the molecular mechanisms underlying each type of regulation discussed above were then retrieved from the literature. The target RNAs regulated by the identified m^{6}A regulators and their corresponding pathways were systematically collected. In particular, their regulation profiles (including m^{6}A modification pattern, up-/down-regulation of expression and the cell processes regulated) were provided. Finally, because some xenobiotics were reported to interact with and mediate a particular m^{6}A regulator (53–55), a number of xenobiotics regulating disease development and drug response through the mediation of certain m^{6}A regulators were also provided. M6AREG data were also fully cross-linked to available databases. Since the data provided in M6AREG (https://idrblab.org/m6areg/) are valuable for diverse directions, it is expected to have great implications for the future conduct of m^{6}A-based regulation studies.

FACTUAL CONTENT AND DATA RETRIEVAL

Data collection for m^{6}A-centered regulation

Data on m^{6}A-centered regulation of disease developments and drug responses were collected based on the following procedure. First, a large number of diseases, drugs and the m^{6}A regulators were retrieved from ICD-11 (56), DrugBank (57), TTD (58), NCBI Gene (59), UniProt (60) and HGNC (61). Second, the data about m6A-centered regulations of disease development and drug response were collected by a comprehensive literature review in PubMed (59) using the keywords: 'm^{6}A + disease', 'm^{6}A + drug', 'm^{6}A Regulator Name + disease', 'm^{6}A Regulator Name + drug', 'm^{6}A + Disease Name', 'm^{6}A + Drug Name', 'Regulator Name + Disease Name', 'Regulator Name + Drug Name', etc. As a result, the development of 165 classes of diseases (such as diabetes, lung cancer and rheumatoid arthritis) and the response data of 70 drugs (such as cisplatin, sorafenib and tamoxifen) which were regulated by 31 regulators (such as FTO, METTL3 and ALKBH5) were collected in M6AREG. Third, all identified publications were reviewed and their detailed regulation information was manually collected, which included cell lines, animal models, targets and pathways. In addition, a total of 93 xenobiotics that regulated disease development and drug response via affecting m^{6}A regulators were also collected.

The m^{6}A regulators and their biological function

The m^{6}A modification is an important RNA methylation without affecting the nucleotide sequence, which is achieved by m^{6}A regulators (14). Such regulators include writers (e.g. METTL3, METTL14 and METTL16), erasers (e.g. FTO and ALKBH5) and readers (e.g. YTHDC1-2, IGF2BP1-3 and SND1), which have been reported to play key biological roles in many epigenetic directions, such as the mRNA life cycle and the cellular/developmental/disease process (62).

The biological function of writers, erasers and readers. As shown in Figure 1, m^{6}A methyltransferase complexes are composed of the catalytic core METTL3, the RNA support element METTL14, the stabilizer WTAP and various adaptors [e.g. RBM1515B, ZC3H13, GBLL1 and VIRMA (63,64)]. m^{6}A modifications are reversible and dynamic, since they can be removed by erasers, such as FTO and ALKBH5. Both writers and erasers regulating the level of

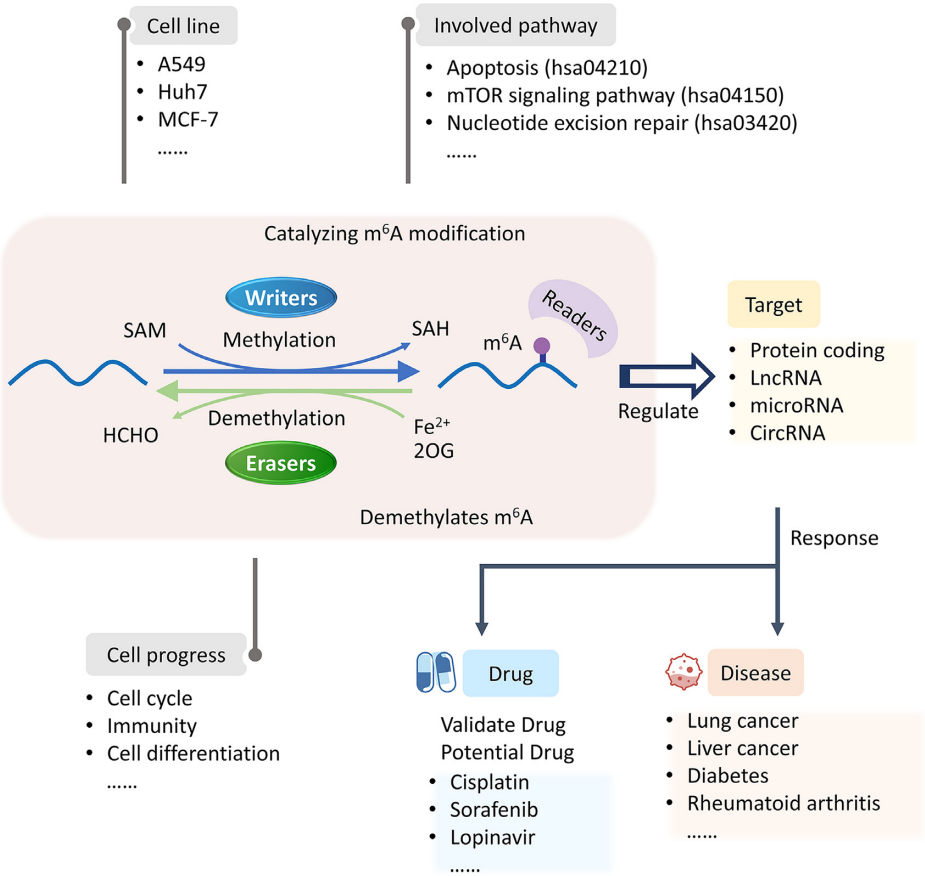

Figure 1. Function and corresponding mechanism of m^{6}A writers and erasers in various cellular processes. The m^{6}A modification is reversible and dynamic, which can not only be introduced into various target RNAs using the core methyltransferase complex (METTL3/METTL14/WTAP) and other adaptors, but can also be removed by the demethylases. These m^{6}A-regulated RNAs which are involved in disease occurrence/progression and drug response were collected in M6AREG.

a target's m^{6}A modification by methylation or demethylation play a critical role in the development of different classes of diseases (such as cancer, diabetes and rheumatoid arthritis) and drug response by targeting both coding and non-coding RNA (65–68). Taking the oscillatory shear stress-induced proatherogenic process as an example (shown in Figure 2), the expression of a writer METTL3 is up-regulated, which induces METTL3-dependent m^{6}A hypermethylation of two targets (NLRP1 and KLF4), and then results in the elicitation of atherogenic responses, such as inflammation and cell adhesion (69). Another example of a writer is METTL14, which is reported to be remarkably down-regulated in trastuzumab-resistant cancer cells compared with their parental HER2-positive breast cancer cells. Some mechanistic studies reveal that it decreases the expression of FGFR4 by m^{6}A modification (as shown in Figure 2), and FGFR4 could phosphorylate GSK-3β and stimulate β-catenin/TCF4 signaling to drive anti-HER2 resistance (70,71). Moreover, the first identified m^{6}A demethylase (eraser), FTO, is found to play critical roles in leukemogenesis and drug response. It promotes leukemic oncogene-mediated cell transformation and leukemogenesis, and inhibits all-*trans*-retinoic acid-induced leukemia cell differentiation. Mechanistic studies show that FTO performs its oncogenic role by reducing the m^{6}A level in mRNA transcripts of ASB2 and RARA, and then decreasing their expression (72).

Once RNA has been m^{6}A methylated, the m^{6}A writers (including YTHDFs, YTHDCs, IGF2BPs, eIF3, HNRNPs and FMRPs) could bind to the methylation site and play a specific role in RNA nuclear export, stabilization, splicing, translation and decay (73,74). As shown in Figure 3, due to such characteristics, great diversity in the m^{6}A modification pattern and expression regulation (up-/down-) toward target RNAs was exhibited, which resulted in different regulation mechanisms in diseases and drug responses (75,76). As illustrated in Figure 2, the m^{6}A reader HNRNPA2B1 is up-regulated in multiple myeloma and negatively correlated with a favorable prognosis. It promotes multiple myeloma progression (such as promoting cell proliferation and inhibiting cell apoptosis) by stabilizing the mRNA of ILF3 and AKT3 (77). Another example of a reader is YTHDF2, which causes the decay of PD-1, CXCR4 and SOX10, and then sensitizes melanoma cells to interferon γ and anti-PD-1 (76). As a subtype of YTHDF, YTHDF1 mediates m^{6}A-increased translation of Snail that is a key transcription factor of the epithelial–mesenchymal transition, which has been considered as a negative prognostic factor for the overall survival rate of liver cancer patients (78).

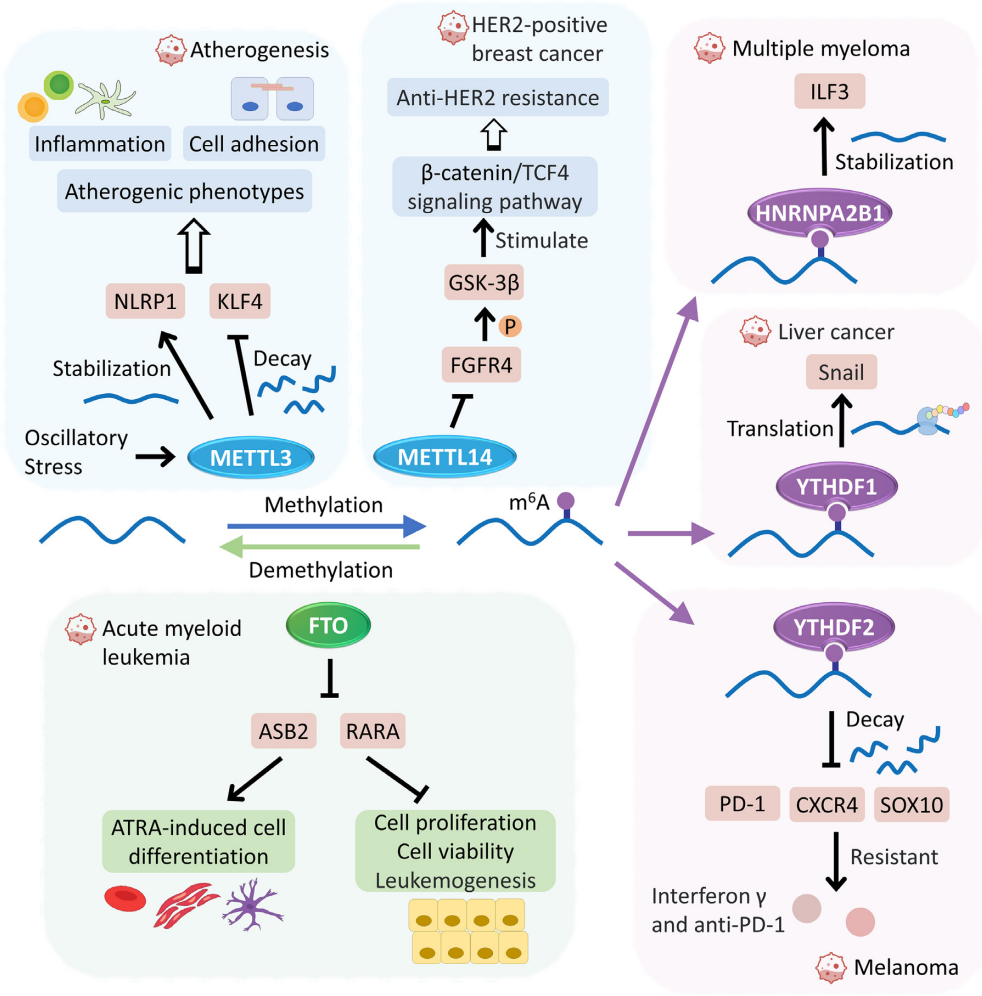

Figure 2. Representative examples describing the roles and corresponding molecular mechanisms of each m^{6}A regulator in disease development and drug response. The m^{6}A writer METTL3 can induce hypermethylation of NLRP1 and KLF4, and then up-regulate NLRP1 while downregulating KLF4 to elicit an atherogenic responses such as inflammation and cell adhesion. METTL14 decreases FGFR4 expression which could phosphorylate GSK-3β and stimulate β-catenin/TCF4 signaling to drive anti-HER2 resistance. FTO, as an eraser, promotes leukemogenesis and inhibits all-*trans*-retinoic acid-induced leukemia cell differentiation via reducing the m^{6}A level in mRNA transcripts of *ASB2* and *RAR*. The m^{6}A readers, HNRNPA2B1, YTHDF1 and YTHDF2 individually promote multiple myeloma progression via stabilizing ILF3 mRNA, upregulating key transcription factors of the epithelial–mesenchymal transition in cancer via increasing translation of Snail, and sensitize melanoma cells to interferon γ and anti-PD-1 by causing the decay of PD-1, CXCR4 and SOX10.

The description and statistics of regulators in M6AREG. For each m^{6}A regulator shown in M6AREG, the detailed descriptions on its general information were provided online, which included regulator name, synonyms, gene name, sequence, protein family, biological function, regulator type, a full list of potential target genes of the regulator and other molecular information associated with the external links to NCBI Gene (59), UniProt (60), etc. The potential targets for a certain m^{6}A regulator were discovered based on the transcriptomic studies collected from GEO (79), such as RIP seq, CLIP-seq, eCLIP-seq, PARCLIP-seq, iCLIP-seq and RNA-seq. For each regulator and its targets, detailed information such as gene name, experimental method, fold change, cell line and the external links to GEO (79), NCBI Gene (59), UniProt (60), etc. was also described. A diagram of the mechanism of each m^{6}A regulator was also provided in the regulator page of the M6AREG database, which included representative information of its role in m^{6}A modification, interactions with other regulators, target genes, etc. A full list of experimentally validated disease development and drug responses that were mediated by this regulator was provided, and detailed information, such as the m^{6}A regulation pattern, *in vivo*/*in vitro* model and pathway, was also provided.

All in all, 14 m^{6}A writers were reported to be involved in the development of 57 diseases by targeting 317 RNAs in 469 cell lines, and two m^{6}A erasers were found to participate in the development of 49 diseases by targeting 164 RNAs in 335 cell line models. The studies on mechanisms showed that m^{6}A writers and erasers regulated different cellular processes (such as the cell cycle and immunity) by regulating 89 and 64 signaling pathways (such as apoptosis, mTOR signaling and nucleotide excision repair), respectively. These regulators greatly affected the efficacies of a

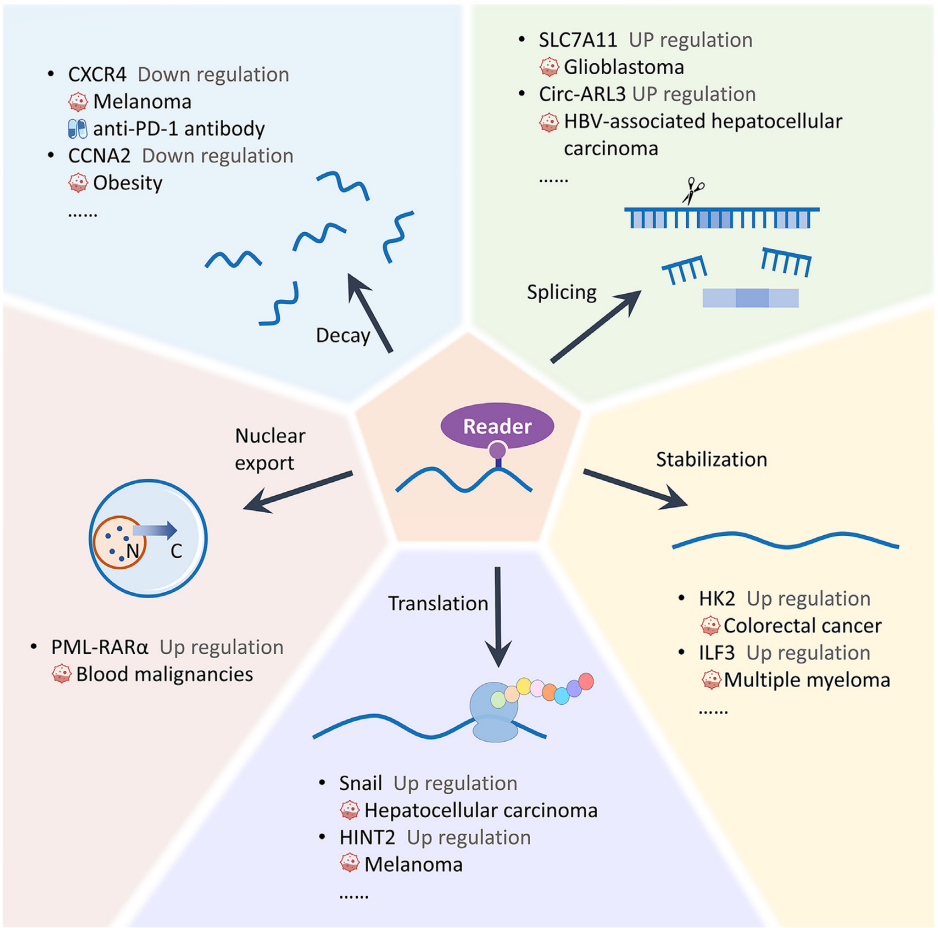

Figure 3. Different roles and mechanisms of m^{6}A readers in various cell processes. Once the RNAs have been modified, different m^{6}A writers will bind to the modification sites and perform diverse functions (RNA nuclear export, stabilization, translation, splicing and decay), which results in the up-/down-regulation of target genes. All RNAs that are involved in the regulation of disease occurrence/development and drug response of m^{6}A writers were collected and explicitly described in M6AREG.

variety of drugs (such as cisplatin and sorafenib). Moreover, 15 m^{6}A readers were identified to participate in the development of 41 diseases by targeting 217 RNAs in 391 cell lines, which were actively involved in 73 signaling pathways and significantly affected the responses of a variety of drugs.

For an m^{6}A-based database, it is key to provide a quantitative description on the up-/down-regulation of the m^{6}A target genes. The RNA-seq data were therefore incorporated into this newly developed database. First, a systematic review was conducted in GEO (79) to retrieve the regulator-related RNA-seq data by searching keywords such as 'm^{6}A Regulator Name', 'm^{6}A Regulator Name + RNA sequencing', 'm^{6}A Regulator Name + RNA seq', and so on. The comparative data that studied the gene expression variations by knocking out, knocking down or overexpressing certain regulators were collected, which led to a total of 236 GEO datasets. Second, these newly collected datasets were carefully reviewed, and those datasets without a clearly stated data pre-processing method or of <2 samples for the control/case group were excluded from our analysis (80,81). As a result, a total of 144 datasets were identified for subsequent differential expression analyses. Third, the 'raw read count' and 'TPM' datasets were analyzed using the DESeq2 and limma packages, respectively (82–84), and the 'RPKM' and 'FPKM' datasets were transformed to 'TPM' and then analyzed using the limma package (85). The genes identified as significantly differentially expressed (fold change >1.5 and *P*-value <0.05) were considered as regulated by the studied regulator (86,87). Finally, the differential expression patterns of 33 889 target genes that were regulated by at least one regulator were collected, and the quantitative description of such a regulated expression patten was provided in the regulator page and target page of the M6AREG database (as illustrated in Figure 4). Detailed information such as experimental conditions, cell line and species was also described.

The m^{6}A-centered regulation of disease development

Dynamic m^{6}A modification is reported to be involved in multiple biological processes by affecting gene expression of multiple levels including tissue development, self-renewal and differentiation of stem cells, circadian rhythm, heat shock, metabolism, metastasis and sex determination (15). With the advances in technology, increasing evidence

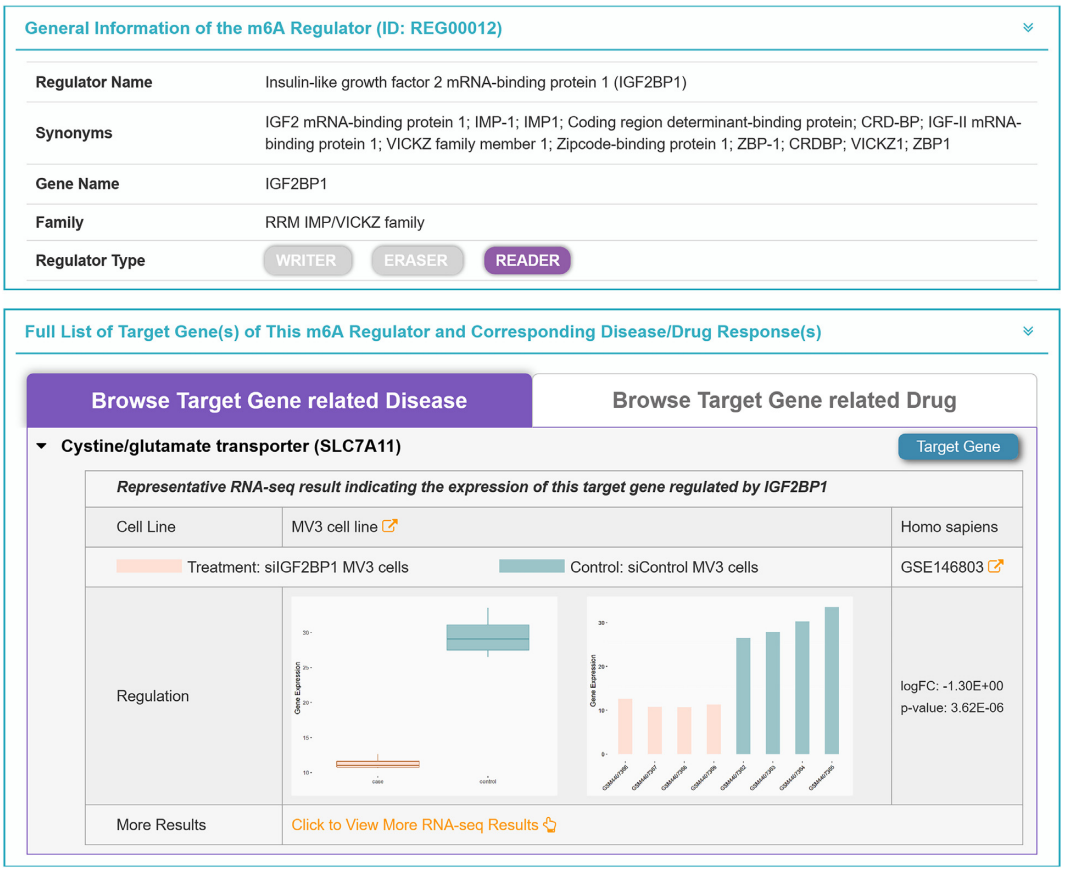

Figure 4. Quantitative description of the regulation pattern of target genes by m^{6}A regulators. For a target gene and corresponding m^{6}A regulator, the differential gene expression of the target gene in cells with treatment (knockout, knockdown and overexpression) and control cells was provided in the form of a bar chart and boxplot together with fold change and *P*-values, which were based on the RNA-seq data collected from the GEO. Detailed information such as cell line, species and experimental condition was also explicitly described. Pink, target gene expression of the cells with treatment; blue, target gene expression of the control cells.

showed that m^{6}A modification plays crucial roles in the occurrence/progression of various disease (7–12). Recent literature indicated that m^{6}A modification could be a new molecular tool to understand the occurrence and progression of diseases, which is regulated by many m^{6}A regulators (24,88,89), and an increasing number of m^{6}A regulators and their corresponding target gene were identified to have clinical implications in either diagnosis/prognosis or therapy for various diseases (24,90,91).

To obtain such m^{6}A-centered regulation data, the disease-specific regulation data of both molecules and pathways were systematically reviewed and explicitly described in M6AREG. A total of 165 diseases were identified to be regulated by m^{6}A modification according to the latest International Classification of Diseases (56). In particular, a total of 747 RNA molecules (e.g. mRNA, lncRNA, miRNA and cirRNA) and 78 pathways (physiological/pathological) that were regulated by 30 regulators (e.g. METTL3, FTO and YTHDF2) were collected. First, general information on each disease related to an m^{6}A regulator and target genes (such as autophagy-related protein, cyclin-dependent kinase, microRNA and lncRNA) were provided. Second, as illustrated in Figure 5, the involved cellular processes of each target gene were described, which included cell growth, cell cycle, cell migration, cell proliferation and macrophage infiltration. Third, the regulation mechanisms of target genes in m^{6}A-centered disease responses were also collected, which included the m^{6}A regulators involved, up-/down-regulation of target genes and regulated pathways (e.g. PI3K–Akt signaling, TNF signaling and JAK–STAT signaling). Such data on m^{6}A-centered regulation were essential for understanding of the mechanism underlying target genes in m^{6}A-centered disease response. Fourth, besides the involved cellular processes and regulation mechanism data, *in vitro* and *in vivo* disease models were also illustrated in M6AREG. As described in Figure 5, a total of 200 cell lines of various diseases together with 23 model organisms were collected and provided in this newly developed database. Fifth, the comprehensive information for each target gene can be accessed by clicking the 'Target Info' button, which includes target name, synonyms, gene name, chromosomal location, functions and links to existing databases (59–61). Meanwhile, the comprehensive data of m^{6}A regulators can be accessed by clicking the 'Regulator Info' buttons, and both the pathways altered by the m^{6}A regulators and the corresponding *in vitro* models were directly linked to the KEGG (92) and Cellosaurus (93) databases.

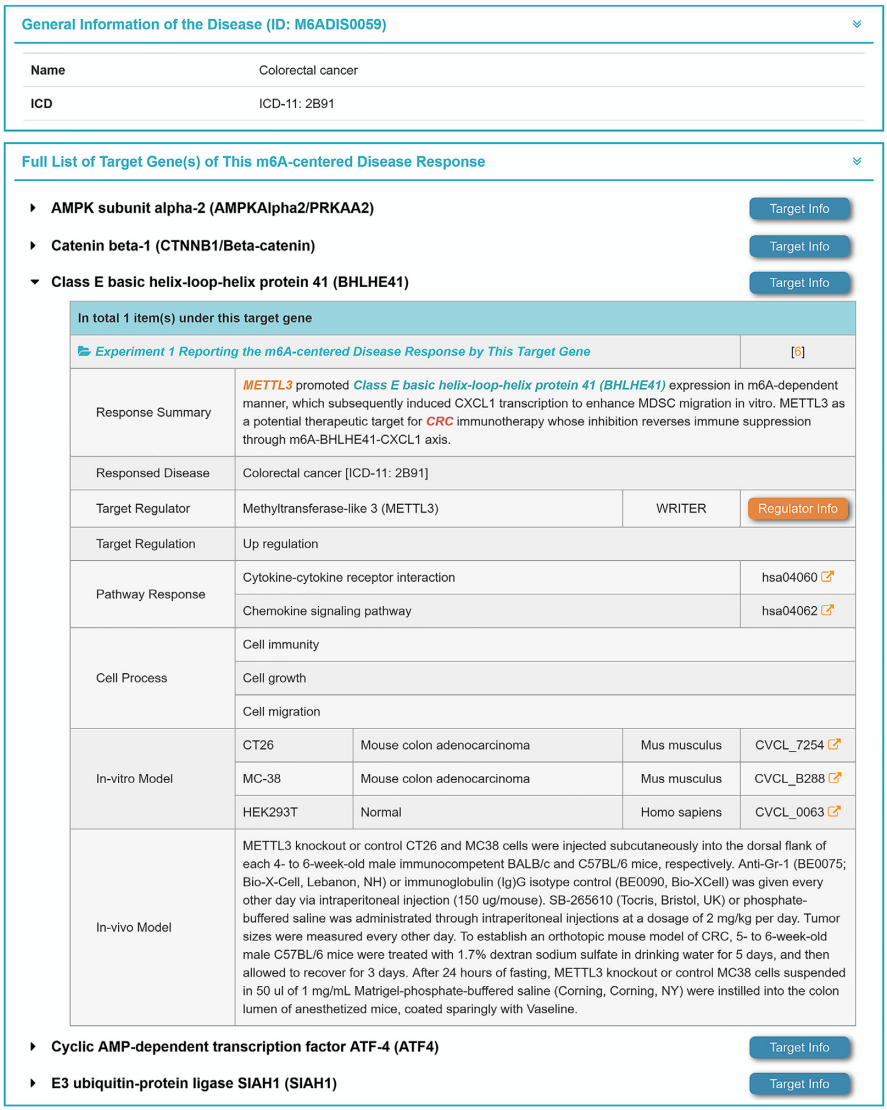

Figure 5. Regulation of target genes and pathways by m^{6}A regulators in disease occurrence and progression. The detailed mechanism underlying m^{6}A-centered disease responses is shown, which included a summary of disease responses, the m^{6}A regulators involved, up-/down-regulation of target genes, regulated pathways, cellular processes and *in vitro*/*in vivo* disease models used. Extended descriptions can be accessed by clicking the corresponding differently colored buttons.

The m^{6}A-centered regulation of drug responses

In the course of drug therapy, the clinical treatment effect on a patient can be seriously affected by the lack of alternative drugs and mutations in drug response-related genes (94). An increasing number of studies showed that the m^{6}A modification plays a vital role in drug response of various diseases, which could be regulated by various m^{6}A regulators and multiple target genes modulated by the same regulator (15,73,95). The m^{6}A regulators altered drug responses by modulating drug–target interaction and drug-mediated cell death signaling. On the one hand, m^{6}A modification interfered with drug efficacy that was mediated by a multidrug efflux transporter, drug-metabolizing enzyme and drug target (96–98). On the other hand, alterations of the m^{6}A modification can inhibit drug-mediated cell death by inducing DNA damage and modulating its repair capacity (73). A number of studies indicated that m^{6}A regulators or their corresponding target genes have potential as drug–effect biomarkers in disease (99,100), and diverse xenobiotics could bind to m^{6}A regulators and modify their activities, resulting in regulation of disease progression or drug response (53,54).

As shown in Figure 6, a total of 70 drugs were identified to be regulated by 21 regulators, which were verified by *in vitro*/*in vivo* experiments. General information on each drug [such as drug name, synonym, clinic status, structure, formula, International Chemical Identifie (InChI) and InChIKey] is provided, and a list of m^{6}A target genes associated with this drug response are described in M6AREG. For each m^{6}A target gene, the summary of the target-regulated drug response, response disease, involved regulator, target regulation, pathway response, cellular process and *in vitro*/*in vivo* models are also described

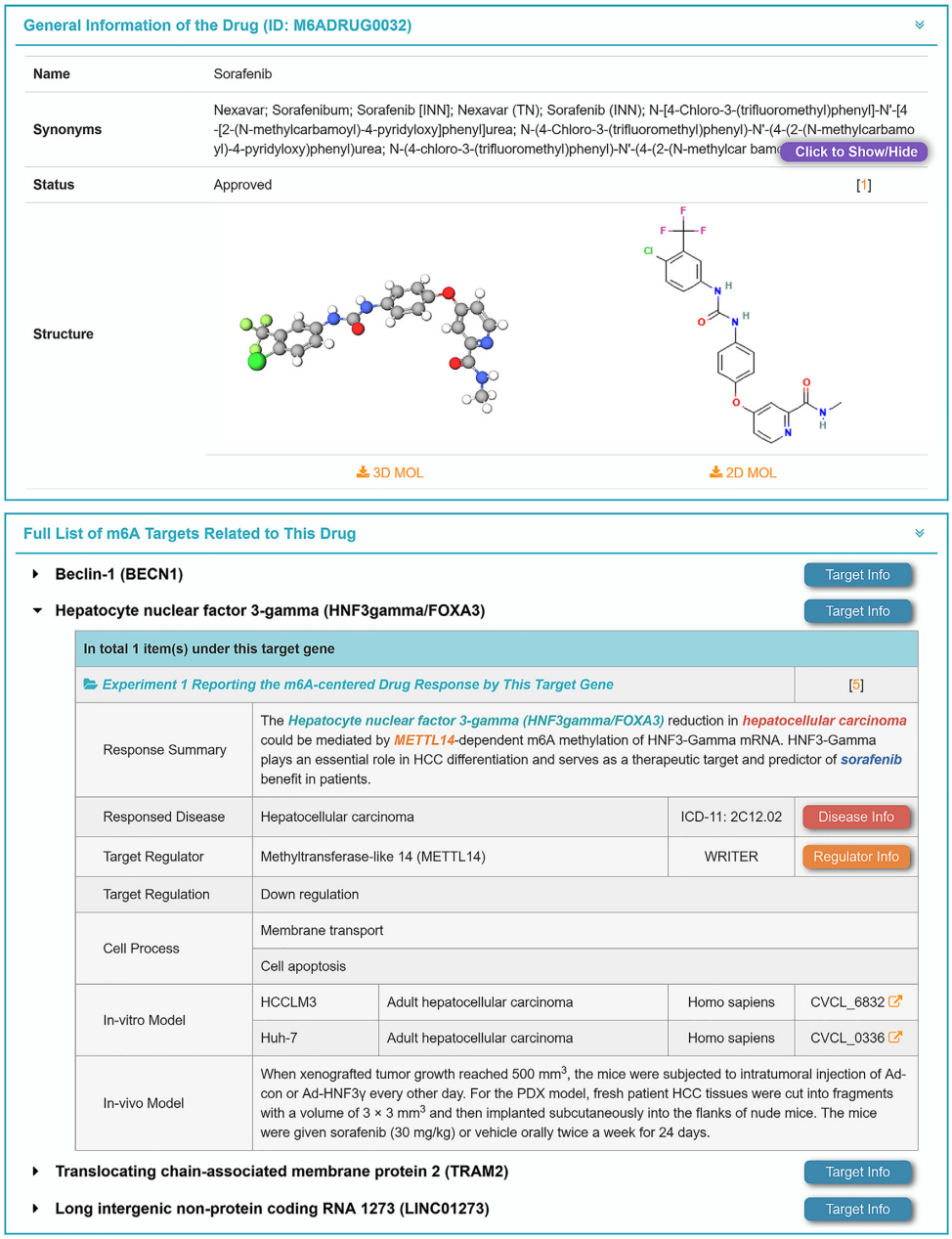

Figure 6. A typical page describing the m^{6}A-centered regulations of drug responses. General information on the drug and its m^{6}A targets are shown. For each target, the experimentally validated mechanisms are explicitly described. The regulation data are linked to their cell line or animal models, and extended information (such as each involved disease, target gene and regulated pathway) can also be retrieved by clicking the corresponding differently colored buttons.

(illustrated in Figure 6). Moreover, the additional description of each target, m^{6}A regulator and disease relevant to this drug can be accessed through clicking 'Target Info', 'Regulator Info' and 'Disease Info', respectively. All in all, a total of 146 experimentally verified targets, 36 pathways (physiological/pathological), 46 cellular processes, 269 cell lines and 75 *in vivo* animal models were found to be involved in identifying drug response alterations which were mediated by m^{6}A modification, which are all provided in M6AREG. Based on those data provided on M6AREG's drug page, the user can readily retrieve a list of m^{6}A targets that were involved in the therapeutic effects of the corresponding drug described.

Moreover, it is well known that some of the leading causes of drug efficiency include the mutation/altered expression of target proteins, deregulated drug transporters and altered drug metabolism, and the m^{6}A regulators are reported to play a vital role in affecting the drug response by acting on the related molecules (73,101–105). Thus, the potential drug responses mediated by a specific m^{6}A regulator are collected into M6AREG. First, three types of critical proteins (drug targets, transporters and metabolic enzymes) were identi-

fied from experimentally verified targets of m^{6}A regulators. Second, the drugs targeting these three types of critical proteins were collected. As a result, a total of 4258 drugs including 593 approved drugs were found to interact with these types of targets that were regulated by m^{6}A modification. All drugs can be accessed at the bottom of the regulator page, which provides the drug name, drug clinical status and mechanism leading to the drug response. Detailed information can be retrieved by clicking the button 'Drug Info'.

M6AREG data standardization, access and retrieval

To facilitate users accessing and analyzing the M6AREG data, the collected raw data were carefully cleaned up and then systematically standardized. The standardizations included (i) all M6AREG diseases were standardized based on the latest version of the International Classification of Disease (56); (ii) all genes, RNAs, proteins, pathways and *in vitro* models in M6AREG were standardized and cross-linked to popular databases (such as NCBI Gene, HGNC, miRbase, Ensembl, UniProt, KEGG and Cellosaurus); and (iii) M6AREG drugs were cross-linked to a variety of well-established databases (such as TTD, PubChem and DrugBank). All data in the M6AREG database can be viewed, accessed and downloaded online without a login requirement by all users.

CONCLUSION

Epigenetic modifications (e.g. histone modifications, DNA methylation and RNA modifications) regulate gene expression without changing the DNA sequence and play pivotal roles in diseases and drug responses (106–108). RNA methylations are considered as a significant epigenetic modification, and those widely studied include N^6-methyladenosine (m^{6}A), 2′-*O*-methyladenosine (m^{6}Am), N^1-methyladenosine (m^{1}A), 5-methylcytosine (m^{5}C) and pseudouridine (ψ), whose dynamic changes can affect the fate of target RNAs and play critical roles in various bioprocesses. Similar to m^{6}A modification, most of these methylation types are modulated by three types of regulators (writer, eraser amd reader), and play an important role in affecting the stability, translation, alternative splicing, nuclear export and secondary structure of RNAs. Moreover, different methylation types show diversity in preferred target RNAs and modification sites (109–111). Since the methylations account for >50% of 170 different types of naturally occurring modifications in RNAs (110), it is necessary to develop a system-wide method/tool to facilitate their efficient detection, as well as to explore the molecular mechanism of RNA methylation in target RNAs and their corresponding roles in disease development and drug response.

All in all, the M6AREG is unique in (i) providing the data of m^{6}A-centered regulation on disease development and drug responses, (ii) explicitly describing the molecular mechanisms underlying each regulation and (iii) fully referencing the collected data by cross-linking to existing databases. Since the accumulated data in the M6AREG are valuable for researchers in diverse disciplines such as pathology and pathophysiology, clinical laboratory diagnostics, and medicinal biochemistry and drug design, this new database is expected to have great implications for the future conduct of m^{6}A-based regulation studies. M6AREG is now freely accessible and fully downloadable by all users without any login requirement at: https://idrblab.org/m6areg/

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