

ScienceDirect



Crosstalk between histone/DNA modifications and RNA *N*⁶-methyladenosine modification

Yushuai Wang^{1,*}, Huilin Huang^{2,*}, Jianjun Chen^{3,4} and Hengyou Weng^{1,5,6}



N⁶-methyladenosine (m⁶A) is the most prevalent internal RNA modification in eukaryotic messenger RNAs (mRNAs), regulating gene expression at the transcription and posttranscription levels. Complex interplay between m⁶A and other well-studied epigenetic modifications, including histone modifications and DNA modification, has been extensively reported in recent years. The crosstalk between RNA m⁶A modification and histone/DNA modifications plays a critical role in establishing the chromatin state for the precise and specific fine-tuning of gene expression and undoubtedly has profound impacts on both physiological and pathological processes. In this review, we discuss the crosstalk between RNA m⁶A modification and histone/DNA modifications, emphasizing their sophisticated communications and the mechanisms underlying to gain a comprehensive view of the biological relevance of m⁶A-based epigenetic network.

Addresses

 ¹ Guangzhou National Laboratory, Guangzhou 510005, China
 ² Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, China

³ Department of Systems Biology, Beckman Research Institute of City of Hope, Monrovia, CA 91016, USA

⁴ Gehr Family Center for Leukemia Research & City of Hope Comprehensive Cancer Center, City of Hope, Duarte, CA 91010, USA
 ⁵ Bioland Laboratory (Guangzhou Regenerative Medicine and Health Guangdong Laboratory), Guangzhou 510005, China

⁶ The First Affiliated Hospital, State Key Laboratory of Respiratory Diseases, Guangzhou Medical University, Guangzhou 510005, China

Corresponding authors: Chen, Jianjun (jianchen@coh.org), Weng, Hengyou (weng_hengyou@gzlab.ac.cn), *These authors contributed equally.

Current Opinion in Genetics & Development 2024, 86:102205

This review comes from a themed issue on ${\rm Molecular}$ and ${\rm Genetic}$ ${\rm Basis}$ of ${\rm Disease}$

Edited by François FUKS and Michael Kharas

Available online xxxx

https://doi.org/10.1016/j.gde.2024.102205

0959–437X/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

After the central dogma of molecular biology was first proposed by Francis Crick in 1956 [1], modifications on DNA and proteins have been discovered to regulate this process [2,3]. During the last decade, RNA modifications, especially N^6 -methyladenosine (m⁶A), were found to also contribute to gene expression control [4–9]. Therefore, the regulation of genetic information becomes more stereoscopic and complicated instead of simply flowing from DNA to mRNA and then to protein. Uncovering the crosstalk between chromatin (include DNA and histones) and RNA would help to understand the regulatory network controlling gene expression more comprehensively.

RNA m⁶A modification, similar to most of the modifications on DNA and protein, is reversible and dynamic, with 'writer' and 'eraser' proteins being identified for catalyzing and removing the methylation marks, respectively. The m⁶A modification in RNA is deposited into a conserve DRACH (D = G/A/U; R = G/A; H = A/C/U) motif by the methyltransferase complex (MTC) consisting of METTL3 (methyltransferase like 3)-METTL14 (methyltransferase like 14)-WTAP (Wilms' tumor 1-associating protein) and other cofactors and has a distinctive feature of being enriched near the stop codon [10-12]. FTO (fat mass and obesityassociated protein) and ALKBH5 (AlkB homolog 5) are two demethylases that could remove m⁶A modifications [13–15]. These m⁶A modifications couples with different layers of gene regulation through being recognized by 'reader' proteins including members of the YT521-B homology (YTH) family (YTHDF1/2/3) [16-18], YTH domain-containing proteins (YTHDC1/ 2) [19,20], and insulin-like growth factor 2 mRNAbinding proteins (IGF2BP1/2/3) [21], which exert a great influence on the metabolism and function of target RNAs.

Accumulating evidence suggests that the deposition of m⁶A marks along RNAs is determined by histone modifications cotranscriptionally and in turn RNA m⁶A governs the deposition of local DNA methylation or histone marks (Figure 1). The crosstalk among these epigenetic events represents a new layer of gene expression regulation.





Epigenetic and epitranscriptomic modifications add additional complexity to the gene expression control of the Central Dogma. Orange lines show the effect of epigenetic and epitranscriptomic modifications on the Central Dogma, in which transcription, RNA processing, RNA export, RNA stability, or translation are regulated by such modifications. Green lines denote crosstalk among epigenetic and epitranscriptomic modifications. 5-hydroxymethylcytosine; Me, methylation; Ac, acetylation.

Histone modification guides RNA N^6 -methyladenosine modification

Histones are basic proteins that condense DNA into chromatin. Numerous post-translational modifications have been identified in histones and found to influence the structure of chromatin, resulting in transcriptional activation or repression [22,23]. In a previous study, we found the distribution pattern of mRNA m⁶A is not random but determined cotranscriptionally by the active histone mark, H3K36me3 [24]. We showed that 69.2% of m⁶A peaks overlapped with the H3K36me3 modification and that reducing cellular H3K36me3 by knocking down its methyltransferase SETD2 or overexpression of its demethylase KDM4A resulted in a significant decrease of RNA m⁶A levels without affecting expression or interaction of the critical MTC components, suggesting that H3K36me3 can guide m⁶A deposition. Mechanistic studies revealed that H3K36me3 could be recognized by the m⁶A 'writer' METTL14, which recruits the MTC to deposit m⁶A marks on newly transcribed mRNAs cotranscriptionally (Figure 2a). The H3K36me3-Mettl14m⁶A axis is crucial for the *in vitro* differentiation of mouse embryonic stem cells (mESCs) and provides the first evidence for the crosstalk between histone and RNA modifications [24].

Impact of RNA *N*⁶-methyladenosine on histone modifications/chromatin state

On the other hand, RNA m⁶A also regulates the modification of histones and chromatin state (Figure 2b). Li et al. reported that transcripts produced from chromatin without the repressive histone mark H3K9me2 were more enriched for m⁶A compared with those with H3K9me2, and deletion of METTL3/METTL14 resulted in an increased H3K9me2 level without altering the expression of its methyltransferases or demethylases [25]. They further found that the m⁶A reader YTHDC1 recruits the H3K9me2 demethylase KDM3B to chromatin, especially where m⁶A was deposited, leading to H3K9me2 demethylation and gene expression [25].

Chromatin-associated RNAs (caRNAs) interact with chromatin through cis, trans, or cis-trans manners and have been identified as key players in transcriptional regulation [26,27]. Liu et al. showed that m⁶A could be deposited by METTL3 cotranscriptionally onto caRNAs, including enhancer RNAs (eRNAs), promoterassociated RNAs (paRNAs), and repeat RNAs, which were recognized by YTHDC1 to facilitate their degradation [28]. Depletion of *Mettl3* or *Ythdc1* in mESCs reduces m⁶A abundance and increases the expression level of caRNAs, through recruiting active transcription factors (e.g. CBP/EP300 and YY1) and repelling repressive factors, such as PRC2 (polycomb repressive complex 2), leads to open chromatin state at caRNA loci and elevated transcription rates of the downstream genes [28] (Figure 2c). Another study reported that YTHDC1 is recruited to chromatin by m⁶A-marked repeat RNAs, such as IAP (intracisternal A particle) and LINE1 (longinterspersed element-1) retrotransposons, and physically



Crosstalk between m⁶A RNA modification and chromatin state. (a) Histone H3K36me3 modification guides RNA m⁶A modification through recruiting METTL14 and the MTC complex cotranscriptionally; (b) YTHDC1 recruits the H3K9me2 demethylase KDM3B to chromatin to demethylate H3K9me2; (c) Reducing m⁶A on caRNAs increases caRNAs abundance and leads to open chromatin state and active transcription; (d) m⁶A-marked TE RNAs are recognized by YTHDC1, which recruits SETDB1 and/or TRIM28 to establish H3K9me3 marks on 2C-related retrotransposons; (e) RBFOX2 facilitates methylation of paRNAs by recruiting RBM15, the latter can interact with YTHDC1 and therefore promoting chromatin silencing through recruiting PRC2 complex at genomic sites occupied by RBFOX2; (f) FXR1 recognizes m⁶A and recruits TET1 to demethylate adjacent DNA, leading to increased chromatin accessibility; (g) YTHDC2 binds m6A-modified HERV-H RNAs and recruits TET1 to remove 5mC and prevent epigenetic silencing from LTR7/HERV-H genomic loci. Pol II, RNA polymerase II; TF, transcription factor.

the H3K9me3 methyltransferase interacts with SETDB1 (SET domain bifurcated histone lysine methyltransferase 1) to mediate H3K9me3 deposition and repress 2C-like transition [29]. Therefore, Ythdc1 KO dampened SETDB1-dependent H3K9me3 deposition and resulted in the subsequent reactivation of transposable element (TEs) and programmed cells into a 2Clike totipotency state, which could be recapitulated by Mettl3 KO [29] (Figure 2d). Similar findings were also reported by other groups [30,31] (Figure 2d). Chen et al. reported that YTHDC1, through binding the mºAmarked LINE1 RNAs on chromatin, promotes the formation of the LINE1-NCL partnership and the chromatin recruitment of KAP1 (also known as Tripartite motif-containing 28 [TRIM28]) to establish H3K9me3 marks on 2C-related retrotransposons and repress the 2C program [30]. Xu et al. showed that METTL3-mediated m⁶A modification on IAP RNAs could be recognized by YTHDC1, which recruits METTL3 to facilitate the recruitment of SETDB1 and the associated factor TRIM28 to IAP elements for the deposition of the H3K9me3 repressive mark on chromatin [31]. It should be noted that in these studies, shRNA-mediated knockdown or CRISPR-based knockout were used to induce stable gene silencing. Chelmicki et al. instead used degron-mediated system to induce acute depletion of METTL3 and METTL14 and also observed an increase of IAP mRNA [32]. However, no obvious change in H3K9me3 was observed, suggesting distinct effects of early or stable m⁶A perturbation on histone modification, which should be carefully taken into account in future study. Another study reported that m⁶A-modified eRNAs recruit YTHDC1 to partition into liquid-like condensates, which in turn facilitate the assembly of Bromodomain containing 4 (BRD4) coactivator condensates and their recruitment to enhances, leading to gene activation [33].

In addition to METTL3 and YTHDC1, other m⁶A regulators also participate in the regulation of chromatin state. In mESCs, Fto KO increases m⁶A on LINE1 RNAs and results in the close of local chromatin, characterized by decreased H3K4me3 and H3K27ac as well as increased H3K9me3 levels at these loci [34]. The

Figure 2

FTO-LINE1 RNA axis also contributes to mouse oocyte and embryonic development [34]. Recently, RBFOX2 (RNA binding fox-1 homolog 2) was identified as an m⁶A-binding protein that plays a role in regulating m⁶Amodified caRNAs [35]. RBFOX2 facilitates methylation of paRNAs by recruiting the MTC component RBM15, the latter can interact with YTHDC1 and therefore promoting chromatin silencing and transcription suppression through recruiting PRC2 complex at genomic sites occupied by RBFOX2 [35] (Figure 2e).

Influence of RNA *N*⁶-methyladenosine on DNA methylation

DNA 5-methylcytosine (5mC) of CpG dinucleotides is the most common DNA methylation event in mammals, which is commonly associated with gene silencing [36,37]. Very recently, the formation of m⁶A has been suggested to couple with DNA demethylation (Figure 2f, g), highlighting the potential crosstalk between them in physiologic and pathologic processes. Deng et al. found that METTL3-mediated m⁶A can be recognized by FXR1 (FMR1 autosomal homolog 1), which recruits the 5mC demethylase TET1 cotranscriptionally and directs it to demethylate adjacent DNA cytosines, leading to altered chromatin accessibility and gene transcription in esophageal squamous cell carcinoma cells [38]. Sun et al. develop CARGO-BioID to capture TE-associated proteins and found that YTHDC2 occupies genomic loci of the retrotransposon LTR7/HERV-H in hESCs through interaction with m⁶A-modified HERV-H RNAs [39]. Furthermore, they found that YTHDC2 interacts with TET1 to remove 5mC and prevent epigenetic silencing from LTR7/HERV-H genomic loci, which leads to the inhibition of neural differentiation of hESCs [39].

Inter-regulation of N^6 -methyladenosine and other modifications

In addition to the above-mentioned direct crosstalk. extensive studies indicate that m⁶A and histone modifications regulate each other indirectly by affecting expression of writers or erasers of the other modification. For example, deficiency of Mettl14 stabilizes transcripts of CBP/p300, leading to a significant increase in H3K27ac and the loss of embryonic neural stem cell selfrenewal [40]. m⁶A was also found on transcripts of *Ezh2* and its reduction upon Mettl3 knockdown decreased both Ezh2 protein expression and H3K27me3 levels, resulting in defects in neurogenesis and neuronal development [41]. Translation of histone H3K4 methyltransferases, such as SETD1A, SETD1B, and KMT2D, could be enhanced by m⁶A modifications. This facilitates the transcriptional activation of genes associated with stage-specific erythroid progenitor transcription programs [42]. In addition, YTHDF2 deficiency stabilizes mRNA of the histone methyltransferase KDM6B, promoting H3K27me3 demethylation and subsequent activation of transcription of multiple proinflammatory cytokines [43]. IGF2BP2 stabilizes mRNA of PRMT6, resulting in the increase of H3R2me2a modification and the subsequent suppression of MFSD2A expression, which restricts docosahexaenoic acid levels and maintains leukemia stem cells [44]. On the other hand, KDM5C mediates the demethylation of H3K4me3 in the promoter region of METTL14, thereby repressing the transcription of METTL14 in colorectal cancer [45]. Promoter of IGF2BP2 is occupied by active transcription marks, including H3K27ac, H3K4me3, and H3K79me2, resulting in the elevation of IGF2BP2 expression and the subsequent stabilization of its m⁶A target transcripts in acute myeloid leukemia (AML) [46].

Conclusion and perspectives

The aforementioned studies, including direct or indirect regulation between RNA m⁶A and DNA/histone modifications, have demonstrated extensive interplay between these epigenetic regulation events. The impact of histone modification on m⁶A deposition may provide a mechanism for the faithful transmission of epigenetic information across generations and, together with the influence of m⁶A on histone modifications or DNA methylation, enable the coordination of various levels of gene regulation. Due to the spatial proximity between newly transcribed RNAs and chromatin, one would expect more crosstalk between RNA m⁶A modification and other cotranscriptional processes to be found that fine-tune chromatin state and gene expression globally and control cell fate decision. It is possible that other histone methylations, acetylations, or DNA methylations also have crosstalk with m⁶A or other types of RNA modifications to eventually shape the transcriptome. Looking forward, there are still many interesting questions needed to be explored.

First, how m⁶A modification in long noncoding RNA (lncRNA) and caRNAs participates in the crosstalk with chromatin and the corresponding biological processes warrants further study. It was reported that YTHDC1 recognizes m⁶A marks on the *XIST* lncRNA [47]; however, how the binding of YTHDC1 to *XIST* leads to gene silencing remains unclear. Liu et al. showed that TE-derived RNAs predominantly target the chromatin regions of their respective subfamilies [28]. Intriguingly, TEs contribute significantly to the generation of regulatory noncoding RNAs (ncRNAs), including micro-RNAs and lncRNAs, in which m⁶A methylation has been found to regulate their maturation and function. It is likely that TE-derived ncRNAs could affect TE or non-TE transcripts by sequence complementarity. In

addition, ncRNAs could also regulate the formation of heterochromatin boundaries to maintain stable gene expression patterns. Whether and how TE-derived ncRNAs contribute to the chromatin state and boundaries formation in an m⁶A-dependent manner are interesting and have yet to be investigated.

Second, are there other RNA modifications functioning in stem cell development and diseases via regulating chromatin? More than 170 RNA modifications have been discovered till now, with increasing number of proteins being added to the list of regulatory proteins of such modifications [48]. m⁶A modification has provided a great example of studying the function and mechanisms of other RNA modifications, including but not limited to N^1 -methyl adenosine (m¹A), 5-methylcytosine (m⁵C), and pseudouridine (Ψ) [49,50]. With the identification of more nuclear-restricted modifiers of such modifications. the mask of these modifications in vital cellular processes will be revealed in the near future. More importantly, our understanding of the interplay between these modifications and chromatin may have clinical significance. For instance, an m⁵C-mediated mechanism was responsible for 5-azacytidine (5-AZA) resistance in leukemia cells, in which NSUN1, a writer of m⁵C RNA modification, interacts with the chromatin regulator BRD4 and the actively elongating RNA polymerase II to create active chromatin region; this association, as well as the RNA m⁵C level, was increased in 5-AZA-resistant leukemia cell lines and in myelodysplastic syndromes/ AML patient samples [51], shedding light on the role of RNA modification and the resulting chromatin state on drug response. These crosstalk interactions can not only provide biomarkers for cancer therapy but also insightful mechanisms for the development of new therapeutic strategies. For instance, combining m⁶A enzyme inhibitors with inhibitors of specific histone modifications or DNA methylation could be explored. Directly targeting the crosstalk, rather than the modifications themselves, may also prove to be effective.

Finally, as the interactions between epitranscriptomics and epigenetics are becoming increasingly pervasive, a deeper and more precise understanding of the molecular basis of m⁶A turns out to be essential to grasp the biological significance of its involvement in development and various diseases. One of the challenges is the development of more advanced m⁶A sequencing techniques [8]. Antibody-based sequencing methods lack sitespecific information of m⁶A, and the absolute abundance cannot be precisely determined. In addition, modifications on ncRNAs, such as rRNA and tRNA, cannot be adequately evaluated. Ultraviolet cross-linked immunoprecipitation techniques can distinguish m⁶A at single-nucleotide resolution; however, their detection rate is comparatively low. The advancement of new techniques that require limited amount of RNA material while provide base-resolved m⁶A profiles with improved quantitative information would significantly propel research in this field.

CRediT authorship contribution statement

Yushuai Wang: Writing – original draft preparation. Huilin Huang: Writing and drawing – original draft preparation. Jianjun Chen: Conceptualization, Writing – review & editing. Hengyou Weng: Conceptualization, Writing – original draft preparation, review & editing.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

This work was supported in part by the National Key R&D Program of China 2020YFA0112403 (H.W.), 82270168 (H.W.) and 82173058 (H.H.) from National Natural Science Foundation of China, 2021A1515010425 (H.H.) from Guangdong Basic and Applied Basic Research Foundation, GZNL2023A02009 (H.W.) and GZNL2023A02010 (H.W.) from Major Project of Guangzhou National Laboratory, the Pearl River Talent Recruitment Program 2021ZT09Y233 (H.W.). J.C. is supported by the National Institutes of Health (NIH) Grants R01 CA271497 (J.C.), R01 CA243386 (J.C.), R01 CA280389 (J.C.), R01 CA236399 (J.C.), and DK124166 (J.C.), as well as the Simms/Mann Family Foundation (J.C.).

We apologize to the authors whose works could not be cited due to space constraints.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- •• of outstanding interest
- Cobb M: 60 years ago, Francis Crick changed the logic of biology. PLoS Biol 2017, 15:e2003243.
- Schneider-Poetsch T, Yoshida M: Along the central dogmacontrolling gene expression with small molecules. Annu Rev Biochem 2018, 87:391-420.
- 3. Gibney ER, Nolan CM: Epigenetics and gene expression. *Heredity* 2010, **105**:4-13.
- Fu Y, et al.: Gene expression regulation mediated through reversible m(6)A RNA methylation. Nat Rev Genet 2014, 15:293-306.
- Murakami S, Jaffrey SR: Hidden codes in mRNA: control of gene expression by m(6)A. Mol Cell 2022, 82:2236-2251.
- Yue Y, Liu J, He C: RNA N6-methyladenosine methylation in post-transcriptional gene expression regulation. Genes Dev 2015, 29:1343-1355.

- 7. Huang H, Weng H, Chen J: The biogenesis and precise control of RNA m(6)A methylation. *Trends Genet* 2020, 36:44-52.
- Deng X, et al.: The roles and implications of RNA m(6)A modification in cancer. Nat Rev Clin Oncol 2023, 20:507-526.
- Weng H, Huang H, Chen J: RNA N (6)-methyladenosine modification in normal and malignant hematopoiesis. Adv Exp Med Biol 2019, 1143:75-93.
- Linder B, et al.: Single-nucleotide-resolution mapping of m6A and m6Am throughout the transcriptome. Nat Methods 2015, 12:767-772.
- Ping XL, et al.: Mammalian WTAP is a regulatory subunit of the RNA N6-methyladenosine methyltransferase. Cell Res 2014, 24:177-189.
- Liu J, et al.: A METTL3-METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. Nat Chem Biol 2014, 10:93-95.
- Jia G, et al.: N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol 2011, 7:885-887.
- Zheng G, et al.: ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. Mol Cell 2013, 49:18-29.
- Weng H, Huang H, Chen J: N(6)-methyladenosine RNA modification in normal and malignant hematopoiesis. Adv Exp Med Biol 2023, 1442:105-123.
- Wang X, et al.: N(6)-methyladenosine modulates messenger RNA translation efficiency. Cell 2015, 161:1388-1399.
- Xu C, et al.: Structural basis for the discriminative recognition of N6-methyladenosine RNA by the human YT521-B homology domain family of proteins. J Biol Chem 2015, 290:24902-24913.
- Shi H, et al.: YTHDF3 facilitates translation and decay of N(6)methyladenosine-modified RNA. Cell Res 2017, 27:315-328.
- Xiao W, et al.: Nuclear m(6)A reader YTHDC1 regulates mRNA splicing. Mol Cell 2016, 61:507-519.
- 20. Xu C, et al.: Structural basis for selective binding of m6A RNA by the YTHDC1 YTH domain. Nat Chem Biol 2014, 10:927-929.
- Huang H, et al.: Recognition of RNA N(6)-methyladenosine by IGF2BP proteins enhances mRNA stability and translation. Nat Cell Biol 2018, 20:285-295.
- Bannister AJ, Kouzarides T: Regulation of chromatin by histone modifications. Cell Res 2011, 21:381-395.
- 23. Henikoff S, Shilatifard A: Histone modification: cause or cog? Trends Genet 2011, 27:389-396.
- Huang H, et al.: Histone H3 trimethylation at lysine 36 guides m
 (6)A RNA modification co-transcriptionally. Nature 2019, 567:414-419

bit and RNA modifications, showing that m⁶A RNA modification is guided by histone H3K36me3. The m⁶A writer METTL14 could recognize H3K36me3 and deposit m⁶A cotranscriptionally on nascent RNAs through recruiting the MTC. This crosstalk is crucial for the differentiation of mESCs.

- Li Y, et al.: N(6)-Methyladenosine cotranscriptionally directs the demethylation of histone H3K9me2. Nat Genet 2020, 52:870-877.
- Li X, Fu XD: Chromatin-associated RNAs as facilitators of functional genomic interactions. Nat Rev Genet 2019, 20:503-519.
- 27. Tang J, et al.: The chromatin-associated RNAs in gene regulation and cancer. Mol Cancer 2023, 22:27.
- 28. Liu J, et al.: N (6)-methyladenosine of chromosome-associated
 regulatory RNA regulates chromatin state and transcription. Science 2020, 367:580-586.

This study reveals that m⁶A on caRNAs can globally fine-tune chromatin state and therefore plays a role in the control of transcription.

29. Liu J, et al.: The RNA m(6)A reader YTHDC1 silences
 retrotransposons and guards ES cell identity. Nature 2021, 591:322-326

This study reveals that YTHDC1 recognizes a subset of m⁶A-marked TEderived transcripts and suppresses retrotransposon expression by recruiting SETDB1 to deposit H3K9me3, which ultimately leads to repression of 2C-like transition in mouse early embryonic development.

- Chen C, et al.: Nuclear m(6)A reader YTHDC1 regulates the scaffold function of LINE1 RNA in mouse ESCs and early embryos. Protein Cell 2021, 12:455-474.
- 31. Xu W, et al.: METTL3 regulates heterochromatin in mouse embryonic stem cells. Nature 2021, 591:317-321.
- Chelmicki T, et al.: m(6)A RNA methylation regulates the fate of endogenous retroviruses. Nature 2021, 591:312-316.
- **33.** Lee JH, *et al.*: Enhancer RNA m6A methylation facilitates transcriptional condensate formation and gene activation. *Mol Cell* 2021, 81:3368-3385 e9.
- Wei J, et al.: FTO mediates LINE1 m(6)A demethylation and
 chromatin regulation in mESCs and mouse development. Science 2022, 376:968-973.

This study reveals that m⁶A-methylated LINE1 RNA is a major substrate of FTO in mESCs. FTO-mediated m⁶A demethylation of LINE1 maintains their abundance and contributes to promoting local chromatin openness and activating LINE1-containing genes.

 Dou X, et al.: RBFOX2 recognizes N(6)-methyladenosine to
 suppress transcription and block myeloid leukaemia differentiation. Nat Cell Biol 2023, 25:1359-1368.

This study discovered that RBFOX2 acts as a chromatin factor to recognize m⁶A on paRNAs and recruit RBM15 to facilitate their methylation. The recruited RBM15 physically interacts with YTHDC1 and recruits PRC2 for downstream chromatin silencing and transcription suppression of the RBFOX2-bound loci. This regulation axis plays a critical role in myeloid leukemia.

- Moore LD, Le T, Fan G: DNA methylation and its basic function. Neuropsychopharmacology 2013, 38:23-38.
- Breiling A, Lyko F: Epigenetic regulatory functions of DNA modifications: 5-methylcytosine and beyond. Epigenetics Chromatin 2015, 8:24.
- Deng S, et al.: RNA m(6)A regulates transcription via DNA
 demethylation and chromatin accessibility. Nat Genet 2022, 54:1427-1437.

In this study, the authors demonstrated a robust interaction between FXR1 and the DNA 5-methylcytosine dioxygenase TET1. FXR1 recruits TET1 to m⁶A-methylated RNAs, initiating demethylation of nearby DNAs, leading to reprogrammed chromatin accessibility and altered gene transcription.

- Sun T, et al.: Crosstalk between RNA m(6)A and DNA methylation regulates transposable element chromatin activation and cell fate in human pluripotent stem cells. Nat Genet 2023, 55:1324-1335.
- Wang Y, et al.: N(6)-methyladenosine RNA modification regulates embryonic neural stem cell self-renewal through histone modifications. Nat Neurosci 2018, 21:195-206.
- **41.** Chen J, et al.: **m(6)A regulates neurogenesis and neuronal development by modulating histone methyltransferase Ezh2**. *Genom Proteom Bioinforma* 2019, **17**:154-168.
- Kuppers DA, et al.: N(6)-methyladenosine mRNA marking promotes selective translation of regulons required for human erythropoiesis. Nat Commun 2019, 10:4596.
- Wu C, et al.: Interplay of m(6)A and H3K27 trimethylation restrains inflammation during bacterial infection. Sci Adv 2020, 6:eaba0647.
- 44. Cheng Y, et al.: Decoding m(6)A RNA methylome identifies PRMT6-regulated lipid transport promoting AML stem cell maintenance. Cell Stem Cell 2023, 30:69-85 e7.
- Chen X, et al.: METTL14-mediated N6-methyladenosine modification of SOX4 mRNA inhibits tumor metastasis in colorectal cancer. Mol Cancer 2020, 19:106.

- Weng H, et al.: The m(6)A reader IGF2BP2 regulates glutamine metabolism and represents a therapeutic target in acute myeloid leukemia. Cancer Cell 2022, 40:1566-1582 e10.
- 47. Patil DP, et al.: m(6)A RNA methylation promotes XIST-mediated transcriptional repression. *Nature* 2016, 537:369-373.
- **48.** Pinello N, Sun S, Wong JJ: **Aberrant expression of enzymes regulating m(6)A mRNA methylation: implication in cancer**. *Cancer Biol Med* 2018, **15**:323-334.
- 49. Huang H, Weng H, Chen J: m(6)A modification in coding and non-coding RNAs: roles and therapeutic implications in cancer. *Cancer Cell* 2020, **37**:270-288.
- 50. Dong S, et al.: N(6)-methyladenosine steers RNA metabolism and regulation in cancer. Cancer Commun 2021, 41:538-559.
- Cheng JX, et al.: RNA cytosine methylation and methyltransferases mediate chromatin organization and 5azacytidine response and resistance in leukaemia. Nat Commun (1) 2018, 9:1163.