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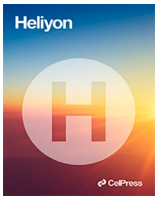

Review article

Emerging roles of N^6-methyladenosine in arsenic-induced toxicity

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ABSTRACT

Arsenic can cause extensive toxic damage after entering the body of humans and animals by altering a variety of events. As the most common form of methylation modification of RNA in eukaryotic cells, N^6-methyladenosine (m^6A) is widely involved in regulating RNA processing, translation and degradation, thus playing important role in various pathophysiological processes. Emerging studies have demonstrated that m^6A modification is synergistically mediated by methyltransferases, demethylases and methyl-binding proteins. Recently, emerging studies have shown that m^6A modification and its regulatory proteins play important roles in arsenic toxicity through mediating various key signaling pathways. We comprehensively analyzed the mechanisms by which m^6A modification and its regulatory proteins contribute to arsenic toxicity. Our reviews offer a scientific foundation for the development of preventive and control strategies to mitigate arsenic-induced toxicity, with an emphasis on an epigenetic approach.

1. Introduction

Arsenic, a prevalent environmental metalloid contaminant, is ubiquitous in water, soil, and the atmosphere. It enters the body of humans and animals mainly through the digestive and respiratory systems [1,2]. Previous studies have shown that even low concentrations of arsenic can exert harmful health effects and increase the risk of various diseases [3,4]. More importantly, prolonged exposure to arsenic has been associated with the development of lesions in the skin, lungs, liver, and kidneys [5–8]. Over the past few years, numerous studies have delved into the mechanisms underlying arsenic toxicity, encompassing both genetic and epigenetic effects [9,10]. Recent research has validated that both abnormal DNA methylation and alterations in the levels of Long Non-Coding RNAs (LncRNAs) and microRNAs (miRNAs) play significant roles in the toxic mechanisms of arsenic [11–13]. More noteworthy is that RNA methylation, especially, N^6-methyladenosine (m^6A) modification, also involved in arsenic toxicity and has received more and more attentions [14–16].

In this paper, the keywords "arsenic" combined with "m^6A" or "N^6-methyladenosine" were used to retrieve relevant articles in PubMed, Excerpta Medica Database, China National Knowledge Infrastructure, Wanfang, and Chinese BioMedical Literature Database.

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Table 1
Basic characteristics of the core literature related to the pivotal roles and mechanisms of m^{6}A modifications and its regulatory proteins in arsenic-induced toxicity.

Author(Year)	Article Type	Study Topic	Refs
Wadgaonkar P et al. (2024)	Review	The mechanisms of arsenic-induced endoplasmic reticulum stress and the role of each UPR pathway in the various cancer types	[1]
Zhou L et al. (2024)	Research article	The importance of the FTO-ATF3 signaling axis in neuronal oxidative stress from an m^{6}A perspective	[10]
Yang F et al. (2023)	Research article	The role of m6A in arsenite-induced skin lesions through the activation of the JAK2/STAT3/Krt signaling axis	[25]
Chen H et al. (2019)	Research article	Changes of RNA N(6)-methyladenosine in the hormesis effect induced by arsenite on human keratinocyte cells	[28]
Gu S et al. (2018)	Research article	N(6)-methyladenosine mediates the cellular proliferation and apoptosis via microRNAs in arsenite-transformed cells	[29]
Qiu T et al. (2023)	Research article	AS3MT facilitates NLRP3 inflammasome activation by m(6)A modification during arsenic-induced hepatic insulin resistance	[31]
Zhang J et al. (2023)	Research article	m(6)A methylation-mediated PGC-1alpha contributes to ferroptosis via regulating GSTK1 in arsenic-induced hepatic insulin resistance	[32]
Bai L et al. (2018)	Research article	m6A memethylase FTO regulates dopaminergic neurotransmission deficits caused by arsenite	[36]
Zhao T et al. (2023)	Research article	N(6)-methyladenosine plays a dual role in arsenic carcinogenesis by temporal-specific control of core target AKT1	[37]
Cui YH et al. (2021)	Research article	Autophagy of the m(6)A mRNA demethylase FTO is impaired by low-level arsenic exposure to promote tumorigenesis	[38]
Gao M et al. (2022)	Research article	m6A demethylation of cytidine deaminase APOBEC3B mRNA orchestrates arsenic-induced mutagenesis	[39]
Zhang H et al. (2023)	Research article	Role of abnormal SUMO modification of FTO protein in arsenic induced oxidative damage of DNA	[40]
Wang P et al. (2024)	Research article	H3K18 lactylation promotes the progression of arsenite-related idiopathic pulmonary fibrosis via YTHDF1/m6A/NREP	[46]
Zhao T et al. (2020)	Research article	N(6)-methyladenosine mediates arsenite-induced human keratinocyte transformation by suppressing p53 activation	[48]

Repeatability studies and some less related articles were excluded from the literatures contained the above keywords, and then read in detail and sorted, organized, analyzed and summarized. The basic characteristics of the core literature which related to the pivotal roles and mechanisms of m^{6}A modifications and its regulatory proteins in arsenic-induced toxicity are shown in Table 1. We summarized the roles and mechanisms of m^{6}A modification and its regulatory proteins in arsenic toxicity according to latest studies in present review. And our summary will provide a scientific basis for finding prevention and control strategies of arsenic-induced toxicity from the epigenetic perspective.

2. Roles of m^{6}A methyltransferases in arsenic toxicity

It is widely accepted that m^{6}Amodification is synergistically regulated by methyltransferases, demethylases, and methyl-binding proteins, which has been extensively summarized in previous reviews [17–20]. As previously reported, methyltransferases are responsible for regulating the levels of m^{6}A modification on various RNAs. The well known methyltransferases include methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), methyltransferase-like 16 (METTL16), and Wilms' tumor 1-associated protein (WTAP) [21–24]. And these methyltransferases were all involved in arsenic-induced pathological processes such as oxidative stress, insulin resistance and cellular malignant transformation through catalyzing the generation of m^{6}A modification on RNAs [25–32]. In detail, METTL3, the most studied methyltransferase of m^{6}A modification, has been well established to regulate the development of arsenic-induced skin lesions and cancer progression [25,28–30]. Specifically, METTL3 may be involved in the toxicity in arsenic-exposed individuals by targeting and modulating the cytokine signaling 3 (SOCS3)-mediated Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway. In detail, arsenic exposure upregulated m^{6}A methylation of SOCS3 via METTL3, which inhibited the activation of the JAK2/STAT3 signaling pathway via SOCS3 and lead to the accumulation of Krt1 and Krt10, ultimately lead to arsenic-induced skin toxicity [25]. In addition, treatment of human keratinocytes with low-dose arsenic can up-regulate total RNA m^{6}A levels and expressions of m^{6}A methyltransferases (METTL3, METTL14 and WTAP). This up-regulation fosters cell viability by bolstering resistance to oxidative stress. Conversely, high doses of arsenic result in decreased m^{6}A levels, intensifying oxidative stress, and suppressing cell activity [28]. Similarly, the levels of m^{6}A modification and methyltransferases METTL3, METTL14 and WTAP were all increased in bronchial epithelial cells which were chronically treated with low-dose sodium arsenic. These methyltransferases may regulate multiple miRNA levels in an m^{6}A modification-dependent manner, ultimately participating in arsenic-mediated malignant transformation [29]. In contrast to the results from lung adenocarcinoma A549 cells, in which m^{6}A levels on total RNAs were reduced after short exposure of arsenic, the expressions of METTL3 were lower in lung tumor tissues than in normal lung tissues [30].

As another important methyltransferase for m^{6}A modification, METTL14 also has a crucial role in arsenic-induced insulin resistance in hepatocytes [31,32]. In detail, inorganic arsenic promoted the METTL14-mediated m^{6}A modification. When intervening with

the METTL14 levels would reverse arsenic-induced insulin resistance. This may be due to METTL14 enhances the stability of the NOD-like receptor thermoprotein structural domain-associated protein 3 inflammatory vesicle mRNA in an m^6A modification-dependent manner [31]. In addition, METTL14 facilitates m^6A modification on peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α) mRNA, of which protein expression were inhibited in a YTHDF2-dependent manner, thus decreasing antioxidant enzyme glutathione S-transferase K1 expression and ultimately leading to the accumulation of reactive oxygen species and insulin resistance in hepatocytes [32]. These studies suggested that METTL14 may be involved in arsenic-induced insulin resistance in an m^6A modification-dependent manner.

In conclusion, the results of the existing studies have indicated that m^6A methyltransferases play crucial roles in arsenic-induced toxicity, which may be achieved by regulating the level of m^6A modification on multiple mRNA. These studies revealed a potential association between m^6A methyltransferases and arsenic-induced skin, lungs and liver toxicity. However, it still needed to accumulate more detailed experimental data and analysis results in order to further explore and confirm the detail roles and mechanisms of m^6A methyltransferases in arsenic toxicity. In future studies, the interaction mechanism between m^6A methyltransferase and arsenic toxicity can be investigated in depth to better prevent and control the health problems caused by arsenic exposure.

3. Roles of m^6A demethylases in arsenic toxicity

Unlike methyltransferases, demethylases can remove m^6A modifications on various RNAs [33]. Currently, there are two recognized types of demethylases, namely the fat mass and obesity associated protein (FTO) and Fe(II)/α-KG-dependent dioxygenases AlkB family member 5 (ALKBH5) [34,35]. Emerging studies have indicated that both FTO and ALKBH5 were involved in the regulation of arsenic toxicity [36–43]. In detail, arsenic significantly increased m^6A modification levels on total RNAs in PC12 cells, which were regulated by FTO thus affecting dopaminergic neurotransmission in arsenic-induced neurocytotoxicity [36]. In addition, FTO also can reduce the m^6A modification on Serine/threonine-protein kinase AKT1 mRNA, and then inhibiting the degradation of AKT1 mRNA to promote the expression of AKT1 during arsenic-induced malignant transformation of skin cancer cells. On the contrary in the arsenic-treated skin cells, the FTO-mediated m^6A modification can inhibit the expression of AKT1 [37], implicating that FTO-regulated of m^6A modification may act as a double-edged sword in arsenic carcinogenesis. Moreover, Cui et al. pointed out that in keratinocytes, low-level arsenic treatment can stabilize FTO by inhibiting the autophagy receptor p62-mediated selective autophagy [38]. Similarly, upregulation of FTO in turn could inhibit autophagy, leading to a positive feedback loop in which arsenic induces malignant transformation by up-regulating FTO [38]. Further studies found that developmental down-regulated gene 4-like (NEDD4L) levels expressed by neural progenitor cells were a key target of arsenic-induced FTO upregulation, indicating that regulating developmental NEDD4L levels or epidermal-specific FTO deletion may prevent arsenic-induced skin tumorigenesis [38]. In human non-small cell lung cancer patients, FTO protein was highly expressed and positively correlated with levels of the cytidine deaminase APOBEC3B (A3B) suggesting that A3B is a downstream target of FTO in arsenic-treated lung tissue, and may reduce DNA mutations by targeting the FTO/m^6A axis [39]. An *in vitro/ex vivo* study conducted using C57BL6/J mice and BEAS-2B human pulmonary bronchial epithelial cells has revealed that arsenic exposure leads to an abnormal increase in Small Ubiquitin-like Modifier modification of FTO. The research suggests that reducing FTO expression can significantly elevate DNA oxidative damage levels in a manner dependent on m^6A [40]. Based on the aforementioned studies, it can be inferred that FTO is likely involved in the regulation of multiple tissue damage and carcinogenesis induced by arsenic, as it catalyzes the demethylation of m^6A modifications. However, further studies on the specific mechanisms of FTO in arsenic toxicity are still needed to be explored *in vivo* and *vitro* levels, thus being good benefit for developing new therapeutic strategies to mitigate or prevent arsenic-induced detrimental health effects.

ALKBH5, the other demethylase that regulates m^6A modification in addition to FTO, also involved in arsenic toxicity by regulating m^6A modification [31,41,42]. Specifically, ALKBH5 was an independent risk factor to affect the prognosis of gastric cancer, which can promote the proliferation and metastasis of gastric cancer. That is, ALKBH5 may promote gastric carcinogenesis by down-regulating the levels of m^6A modification of frizzled protein 4 (FZD4) mRNA, which results in the elevation of FZD4 mRNA expression [41]. In addition, by establishing a model of inorganic arsenic-induced early hepatic insulin resistance in mice, it was found that the expression of ALKBH5 was significantly elevated [31]. This provided a new target for the treatment of inorganic arsenic-induced insulin resistance in liver tissues. The results from Chen et al. showed that the expression of m^6A demethylase ALKBH5 was decreased significantly in the ovaries of high-dose arsenic-exposed rats [42]. This study suggested that arsenic administration during weaning to sexual maturity may affect ovarian reserve, which may be related to the alteration levels of m^6A demethylation modification in the ovaries.

In essence, these findings collectively indicate that arsenic exposure results in disrupting levels of FTO and ALKBH5. They revealed a potential association between m^6A demethylases and arsenic-induced toxicity in skin, lung, stomach and so on. Consequently, modulating the expression of FTO and ALKBH5 could represent a pivotal strategy for mitigating arsenic-induced toxicity. However, even though these above studies have revealed that arsenic exposure can cause FTO and ALKBH5 dysregulation, the specific mechanisms which arsenic affects FTO and ALKBH5 expression may vary depending on factors such as cell type, tissue characteristics, arsenic concentration and exposure duration. In a word, the specific mechanisms need to be further elucidated.

4. Roles of m^6A methyl-binding proteins in arsenic toxicity

It is widely acknowledged that methyl-binding proteins contribute to the biological roles of m^6A modification. Though the latest reviews have synthesized the functions and categories of m^6A modification binding proteins [43,44], their specific biological function in toxicity induced by various chemical substances are waiting to be further clarified. In recent years, m^6A methyl-binding proteins, especially YTH domain family protein 1 (YTHDF1) and YTH domain family protein 2 (YTHDF2), in arsenic toxicity have been

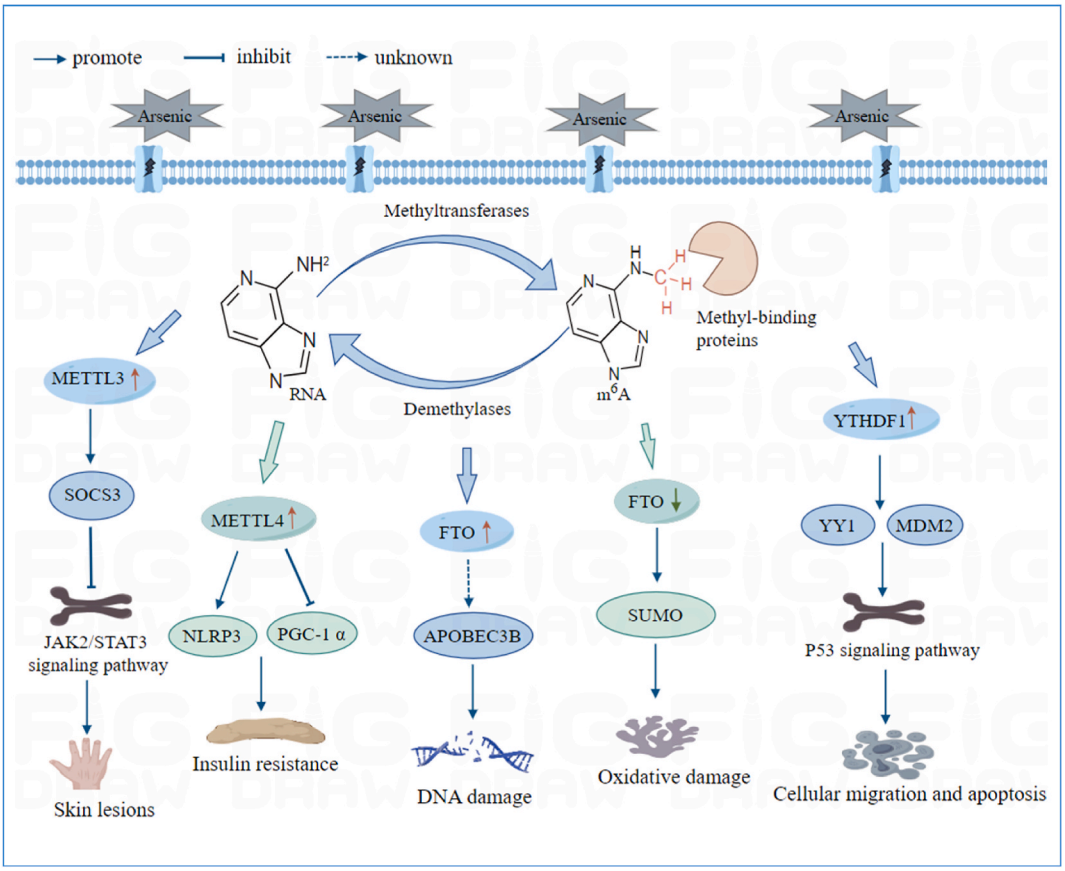

Fig. 1. Roles of N^6-methyladenosine (m^6A) and its regulatory proteins in arsenic-induced toxicity. Arsenic can alter the N^6-methyladenosine and its regulatory proteins level in various physiopathological processes, such as skin lesions, insulin resistance, DNA damage. The symbols of ↑ (red) or ↓ (green) indicate the upregulation or downregulation of m^6A and its regulatory proteins.

extensively reported [45–51]. It has been reported that m^6A methylation on total cellular RNAs increased and the expression of YTHDC2 and YTHDF3 accordingly changed during sodium arsenic-induced oxidative stress in human embryonic lung fibroblasts [45]. Similarly, the study basing on idiopathic pulmonary fibrosis also demonstrated that arsenite was able to elevate global levels of m^6A modification, YTHDF1 expression, and m^6A-modified neuronal proteins P311 mRNA level, thereby promoting fibroblast-to-myofibroblasts transformation [46]. In addition, the process of lung cancer caused by arsenic was affected by m^6A methyl-binding proteins, and the expression of m^6A methyl-binding protein YTHDF1 in early lung adenocarcinoma patients was significantly increased in comparison with healthy volunteers [47]. A separate study demonstrated that m^6A upregulated the expression of the p53 regulator tumor suppressor gene PR domain-containing protein 2 by stimulating the translation of the chromosome 11 gene YY1 and the oncogene murine double minute 2 mRNA via YTHDF1 during the arsenic-induced transformation of human keratinocytes [48]. This finding uncovers a novel function of m^6A modification in arsenic-induced transformation of human keratinocytes, specifically by inhibiting p53 activation. It follows that arsenic exposure may cause further alterations in YTHDF1 by affecting the level of m^6A modifications, or mediate the disruption of the expression of relevant molecules by YTHDF1 leading to disease. In conclusion, the relationship between YTHDF1 and arsenic toxicity may involve multiple levels, including RNA modification, gene expression regulation, cellular stress response, and disease occurrence. An in-depth study of these connections can help to reveal the molecular mechanisms of arsenic toxicity and provide a theoretical basis for the development of new strategies to combat arsenic-related diseases.

YTHDF2, the another m^6A methyl-binding protein, was confirmed to be crucial in a variety of physiopathological processes [14,49,50]. The latest study have found that arsenic can promote oxidative stress and YTHDF2 phase separation in a concentration dependent manner in human keratinocytes. Interestingly, pretreatment with N-acetylcysteine significantly alleviated arsenite-induced oxidative stress as well as inhibited YTHDF2 phase separation. The underlying mechanisms may be associated with N-acetylcysteine pretreatment reverse the elevation of m^6A methylesterases while reduction of m^6A demethylases induced by arsenic [14]. This study demonstrated that arsenic-enhanced oxidative stress may play a crucial role in m^6A modification-mediated YTHDF2 phase separation. Meanwhile, it was shown that YTHDF2 could promote arsenic-induced malignant transformation of human keratinocytes by enhancing cell proliferation and inhibiting cell apoptosis [14]. In addition, results from a previous study indicated that the proliferation and differentiation capacity of neural stem/progenitor cells was significantly decreased in YTHDF2 conditional knockout mouse

Table 2
Roles of N^6-methyladenosine and its regulatory proteins in arsenic toxicity.

Author（Year）	Species	Subjects	Concentrations	Duration	Effects	m^6A Modificationforms	Regulatory Proteins	Mechanisms	Refs
Yang F, Zhang A (2023)	Human	HaCaT cells	10 μM arsenite	treatment for 24 h	Skin lesions	Methyltransferases	METTL3 ↑	METTL3 catalyzed the formation of m^6A modification on SOCS3 mRNA	[25]
Chen H, Zhao T, Sun D, et al (2019)	Human	HaCaT cells	1μM, 2 μM arsenite	treatment for 24 h	Enhanced cell viability	Methyltransferases	METTL3 ↑ METTL14 ↑ WTAP ↑	m^6A modification is associated with the arsenic-driven hormesis on cytotoxicity	[28]
Gu S, Sun D, Dai H, et al (2018)	Human	HBE cells	2.5 μM $NaAsO_2$	treatment for 13 weeks	Cellular proliferation and apoptosis	Methyltransferases	METTL3 ↑ METTL14 ↑ WTAP ↑	m^6A-mediated miRNAs regulated pathways which are closely associated with cellular proliferation and apoptosis	[29]
Qiu T, Wu C, Yao X, et al (2023)	Mice	C57BL/6J mice	4 mg/L As_2O_3	drink water containing As_2O_3 at 4 mg/l for 6 weeks	Hepatic insulin resistance	Methyltransferases	METTL14	Arsenic promoted NLRP3 expression and inflammasome activation via METTL14-dependent m^6A methylation	[31]
Zhang J, Song J, Liu S, et al (2023)	Rat	Sprague-Dawley rats	2.5 and 5 mg/kg $NaAsO_2$	For 3 months by oral gavage	Hepatic insulin resistance	Methyltransferases	METTL14 ↑	The inhibition of PGC-1α protein expression is dependent on m^6A methylation	[32]
Bai L, Tang Q, Zou Z, et al (2018)	Mice	C57BL/6J mice	0.5 mg/L, 5 mg/L, 50 mg/L arsenite	drink water containing arsenite for 6 months	Neurocytotoxicity	Demethylases	FTO	FTO attenuated the ability of arsenic-treated dopaminergic neurotransmission defects	[36]
Zhao T, Sun D, Xiong W, et al (2023)	Human	HaCaT cells	1 μM arsenite	treatment for 22 weeks	Malignant transformation of skin cancer cells	Demethylases	FTO	FTO reduced the m^6A modification on AKT1 mRNA	[37]

embryos, which may be related to the fact that YTHDF2 modulation of neurodevelopmental by promoting m^6A-dependent degradation of neurodevelopment-related mRNA targets [50]. These results indicate that the abnormal levels of YTHDF2 also involved in the arsenic toxicity.

In summary, even though some progressions have been made in the area of m^6A methyl-binding proteins and arsenic toxicity, the specific molecular mechanisms of m^6A methyl-binding proteins in arsenic toxicity are still not fully understood and further studies are needed.

5. Conclusions and prospect

The m^6A modification and its regulatory proteins has attracted much attention as a hot topic and frontier in epigenetic research. They are involved in a variety of biological processes such as oxidative stress, iron death, and endoplasmic reticulum stress by affecting the selective splicing, stability, translation and subcellular localisation of various RNAs. Arsenic exposure may produce different degrees of toxic effects on the human body, and long-term arsenic exposure may even produce carcinogenic effects. It is noteworthy that arsenic can affect the occurrence and development of various diseases by affecting m^6A levels and its regulatory protein expressions. We summarized the roles of m^6A modification and its regulatory proteins in arsenic toxicity, as shown in Fig. 1 and Table 2. However, due to the diversity of the m^6A modifications and their regulatory proteins, the current understanding of the mechanisms of the mutual regulation between the m^6A modification and arsenic toxicity may only be the tip of the iceberg. The interaction mechanisms of m^6A modification and arsenic toxicity remain to be elucidated. It is noteworthy that in the field of environment and health,

Cui YH, Yang S, Wei J, et al (2021)	Human	HaCaT cells	100 nM arsenite	treatment for 28 weeks	Cell autophagy	Demethylases	FTO ↑	Autophagy of FTO is impaired by low-level arsenic exposure to promote tumorigenesis	[38]
Gao M, Qi Z, Feng W, et al (2022)	Human	A549 cells	2 μM arsenic	treatment for 6 h	DNA damage and mutagenesis	Demethylases	FTO ↑	m^6A demethylation of A3B mRNA orchestrates arsenic-induced mutagenesis	[39]
Zhang H, Yu Z, Wang F, et al (2023)	Mice	C57BL/6J mice	-	-	DNA oxidative damage	Demethylases	FTO ↓	Arsenic caused abnormally increasing SUMO modification of FTO and downregulating the FTO expression	[40]
Wang P, Xie D, Xiao T, et al (2024)	Mice	C57BL/6J mice	0, 10, or 20 ppm $NaAsO_2$	drink water containing $NaAsO_2$ for 6 months	Idiopathic pulmonary fibrosis	Methyl-binding proteins	YTHDF1 ↑	H3K18 lactylation promotes the progression of arsenite-related idiopathic pulmonary fibrosis via YTHDF1/m^6A/NREP	[46]
Zhao T, Sun D, Zhao M, et al (2020)	Human	HaCaT cells	1 μM $NaAsO_2$	treatment for 5 months	Cellular migration and apoptosis	Methyl-binding proteins	YTHDF1	m^6A upregulated the expression of the negative p53 regulator, YY1 and MDM2 through YTHDF1-stimulated translation of YY1 and MDM2 mRNA	[48]

Note: The symbols of ↑ （red） or ↓（green）indicate the upregulation or downregulation of m^6A regulatory proteins.

sporadic studies have shown that the involvement of m^6A modifications and their regulatory proteins in the toxic damage caused by environmental pollutants. In view of the important roles of m^6A modifications and their regulatory proteins in diseases, the inter-regulatory relationship between m^6A and its regulatory proteins in environmentally related diseases will be worthy of in-depth exploration.

CRediT authorship contribution statement

Rongxian Li: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Chaojie Wu:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Yuan Zhao:** Writing – original draft, Formal analysis, Data curation. **Shiyi Jiang:** Writing – original draft, Formal analysis, Data curation. **Junben Huang:** Writing – original draft, Formal analysis, Data curation. **Xiuyun Huo:** Writing – original draft, Formal analysis, Data curation. **Chang Deng:** Writing – original draft, Formal analysis, Data curation. **Zuoshun He:** Writing – original draft, Formal analysis, Data curation. **Shiyan Gu:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation. **Jie Yang:** Writing – original draft, Formal analysis, Data curation.

Data and code availability statement

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

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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