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Review

Clinical Perspectives in Epitranscriptomics

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Epitranscriptomics, the study of reversible and dynamic chemical marks on the RNA, is rapidly emerging as a pivotal field in post-transcriptional gene expression regulation. Increasing knowledge about epitranscriptomic landscapes implicated in disease pathogenesis proves an invaluable opportunity for the identification of epitranscriptomic biomarkers and the development of new potential therapeutic drugs. Hence, recent advances in the characterization of these marks and associated enzymes in both health and disease blaze a trail toward the use of epitranscriptomics approaches for clinical applications. Here, we review the latest studies to provide a wide and comprehensive perspective of clinical epitranscriptomics and emphasize its transformative potential in shaping future health care paradigms.

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Introduction

Human phenotypes are defined by both genotype and gene expression regulation. Gene regulatory mechanisms such as those involving DNA methylation and other epigenetic marks have been extensively studied, resulting in a wide field of available knowledge with clinical applications [1,2]. In contrast, the epitranscriptomics field, comprising all chemical marks regulating gene expression at transcriptional, post-transcriptional, and translational levels, emerges as a newly yet-to-be-explored potential approach for the clinics of the future [3–5].

Epitranscriptomics consists in the reversible deposition of different chemical marks over the transcriptome, formulating the 'epitranscriptome'. Epitranscriptomic marks can be found on both coding and noncoding RNAs and often exert different functions depending on the RNA type and location in which they are deposited on the transcript. Deposition, removal, and binding proteins of epitranscriptomic marks are known as writers, erasers, and readers, respectively. Readers control and direct the RNA landscape and regulate essential functions such as RNA processing, export, stability, degradation, and translation initiation [6–10]. Since disruption of the homeostatic landscape of epitranscriptomic marks underpins numerous pathologies, the understanding of each disease's epitranscriptomic idiosyncrasy becomes of great clinical interest [11–13].

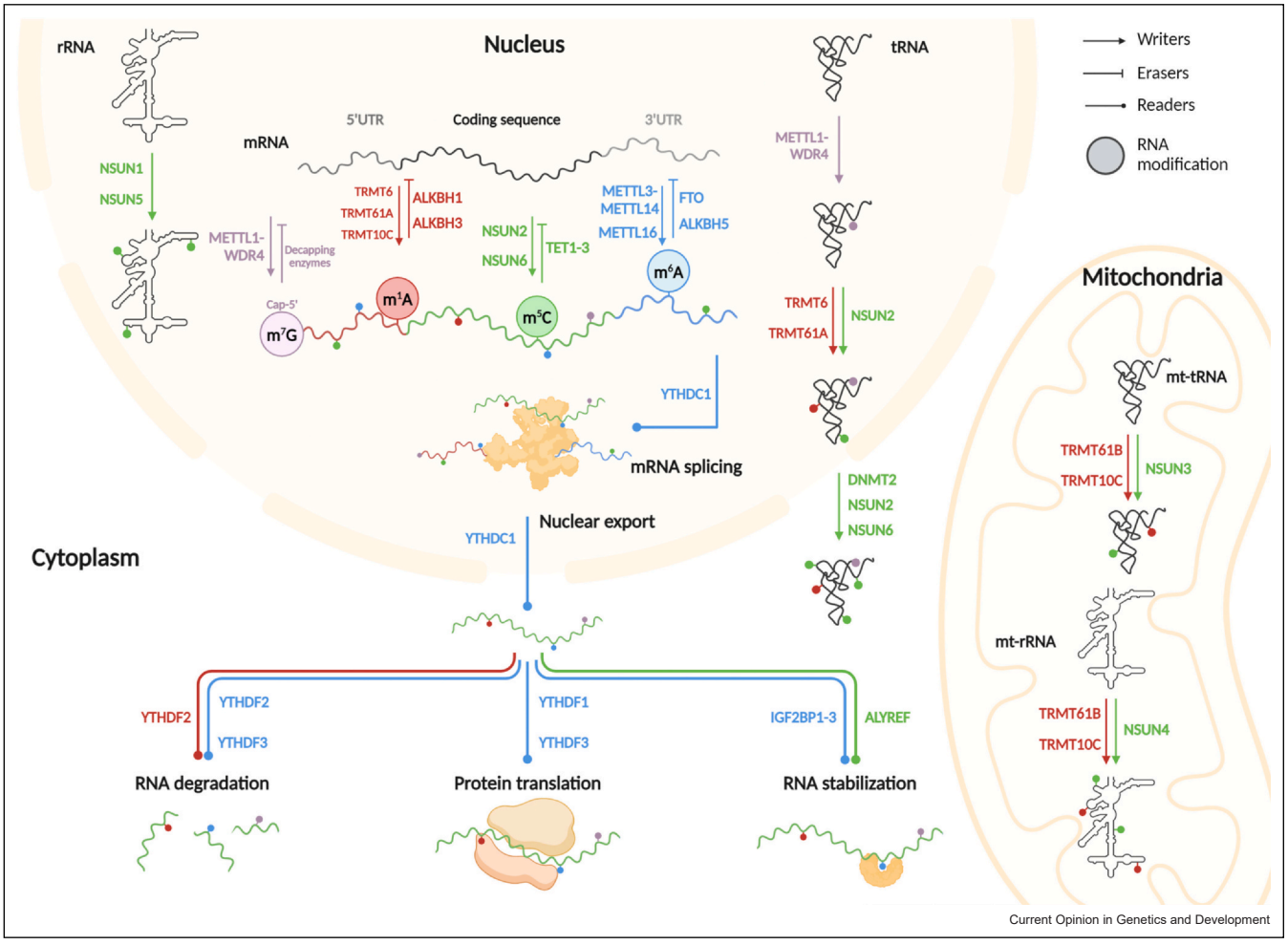
Here, we provide an overview of the main epitranscriptomic marks and their effector proteins, as well as the latest findings on their link with cancer, cardiovascular diseases, and neurological disorders and discuss their potential role as clinical biomarkers and promising targets for future therapeutic interventions.

Epitranscriptomic marks and regulatory proteins

Epitranscriptomics encompasses a plethora of chemical modifications at a single-nucleotide level. Around 170 epitranscriptomic marks have been characterized thus far, and some are crucial for regulating both metabolic and pathological processes [14].

Among the RNA modifications, N6-methyladenosine (m^6A) [15], N1-methyladenosine (m^1A) [16], 2'-O-methyladenosine (m^6Am) [17], 5-methylcytosine (m^5C) [18], N7-methylguanosine (m^7G) [19], pseudouridine (Ψ) [20] and 2'-O-methylation (2'-O-Me, Nm) [21] are notably associated with carcinogenesis and other pathologies. Each one of these exhibits a distinct set of

Figure 1



Overview of the epitranscriptome in the main RNA biotypes. Each epitranscriptomic mark is depicted with a distinct color: purple (m^7G), red (m^1A), green (m^5C) and blue (m^6A). Writers, erasers, and readers are displayed using identical colors as the corresponding mark. Created with Biorender.com.

regulatory proteins involved in their assembly, disassembly, and management, which have been detailed previously and are summarized in Figure 1 (reviewed in Refs. [22,23]).

Although Ψ is the most abundant mark in the transcriptome [22], we highlight herein those of higher clinical interest with special focus on m^6A and their main effector proteins. This mark is the best known and most abundant in mammalian mRNA. The methyltransferase-like 3 and 14 (METTL3-METTL14) heterodimer is the principal m^6A writer, catalyzing the m^6A deposition on mRNAs through the formation of a complex involving the partners VIRMA, HAKAI, WTAP, RBM15, and ZC3H13 [24,25]. Fat mass and obesity-associated protein (FTO) acts as an m^6A and m^6Am demethylase in mRNA and small nuclear RNA, as well as an m^1A demethylase in tRNA [26,27], and the m^6A readers YT521-B homology domain family 1–3 (YTHDF1–3) and YT521-B homology domain-containing 1–2 (YTHDC1–2) modulate RNA fate via m^6A-dependent regulation [28].

With regard to other epitranscriptomic marks, methyltransferase-like 1 (METTL1) acts as an m^7G writer along with WD repeat domain 4 (WDR4), mediating m^7G deposition on microRNA (miRNA), mRNA, and tRNA [29–31]. METTL1 primarily functions by regulating the global expression of proteins through the selective translation of m^7G tRNA-decoded codons. Alternatively, alpha-ketoglutarate-dependent dioxygenase AlkB homolog 3 (ALKBH3) mediates mRNA, tRNA, rRNA, and mitochondrial RNA m^1A demethylation, hence acting as an m^1A eraser [16]. Notably, NSUN family members serve as m^5C writers across multiple

RNA biotypes. NSUN2 and NSUN6 participate in tRNA biogenesis and stability [18], while NSUN3 installs m^5C modifications in mitochondrial tRNA, contributing to mitochondrial translation [32]. NSUN1 and NSUN5 are implicated in ribosomal biogenesis [33,34], while NSUN4 plays a role in mitochondrial ribosomal biogenesis, facilitating the assembly of mature subunits [35]. Additionally, NSUN2 and NSUN7 both act as m^5C writers on noncoding RNA (ncRNAs) [36,37]. Altogether, NSUN family proteins are involved in controlling RNA stability, processing, and translation [18,34].

Epitranscriptomics in pathologies

Cancer

Cancer is a heterogeneous disease comprising a wide variety of subtypes with diverse physiological alterations. Each epitranscriptomic mark presents different targets depending on cancer subtype, resulting in miscellaneous effects on its progression, invasion or metastasis.

Methyltransferase-like 3 (METTL3) and 14 (METTL14)

The METTL3-METTL14 heterodimer contributes to diverse cancer outcomes by regulating m^6A levels over oncogenic transcripts (Figure 2). Particularly, METTL3 is associated with cell identity in cancer and participates in transdifferentiation [15].

In breast cancer (BC), METTL3 displays a contradictory role in oncogenic progression depending on the cancer subtype and downstream target [38,39]. Additionally, METTL3, cooperatively with IGF2BP3, culminates in a robust programmed death-ligand 1 (PD-L1) mRNA stability, enhancing PD-L1-mediated T cell responses [40]. In nonalcoholic fatty liver disease–related hepatocellular carcinoma (NAFLD-HCC), IFN-γ+ and GZMB + CD8+ T cells decrease, which result from METTL3 overexpression and the activation of cholesterol biosynthesis. This sheds light on the synergistic approach of a METTL3-targeting therapy and immune checkpoint inhibitors in NAFLD-HCC [41]. In prostate cancer (PCa), METTL3 influences long noncoding RNA (lncRNA) MALAT1 m^6A levels and activates PI3K/Akt/mTOR signaling, producing tumor growth and malignant progression [42].

Although METTL14 functions alongside METTL3, their oncogenic roles are slightly divergent. While METTL3-dependent m^6A enhances JAK1 translation and drives colorectal cancer (CRC) progression [43], most studies have discovered the tumor suppressor role for METTL14 in CRC through a myriad of molecular mechanisms [44,45].

Fat mass and obesity-associated protein (FTO)

In most tumors, the influence of FTO in cancer progression is modulated in an m^6A-dependent manner. Its dysregulation can cause the appearance of tumors either through an increase or decrease in m^6A levels in tumor-related functional mRNAs [46,47] (Figure 2).

In gastric cancer (GC), FTO overexpression in GC cell lines increases the PI3K/Akt/mTOR pathway. FTO-mediated m^6A levels influence an uncharacterized subset of mRNAs, which collaborate in cancer development [48]. In bladder cancer (BLCA), FTO upregulation assumes a pivotal role boosting proliferation, progression, and migration through pathways such as STAT3, FTO/miR-576/CDK6, or MALAT1/miR-384/MAL2 axis [8,49,50]. In CRC, FTO regulates PD-L1 expression via m^6A modification, contributing to immune escape [46]. In an opposite manner, FTO downregulation has been reported to promote cell growth in CRC owing to MTA1 mRNA m^6A methylation. The m^6A reader IGF2BP2 facilitates CRC progression and metastasis by recognizing MTA1 [47]. In clear cell renal cell carcinoma (ccRCC), FTO also exhibits a dual role in tumor progression and suppression. Elevated FTO levels impair autophagic flux by decreasing SIK2 mRNA stability [10] while also restraining ccRCC cell growth via FTO-PGC-1α axis signaling [51]. Taken together, unraveling the molecular profile of FTO in patients is imperative for accordingly delineating and optimizing therapeutic approaches and clinical outcomes.

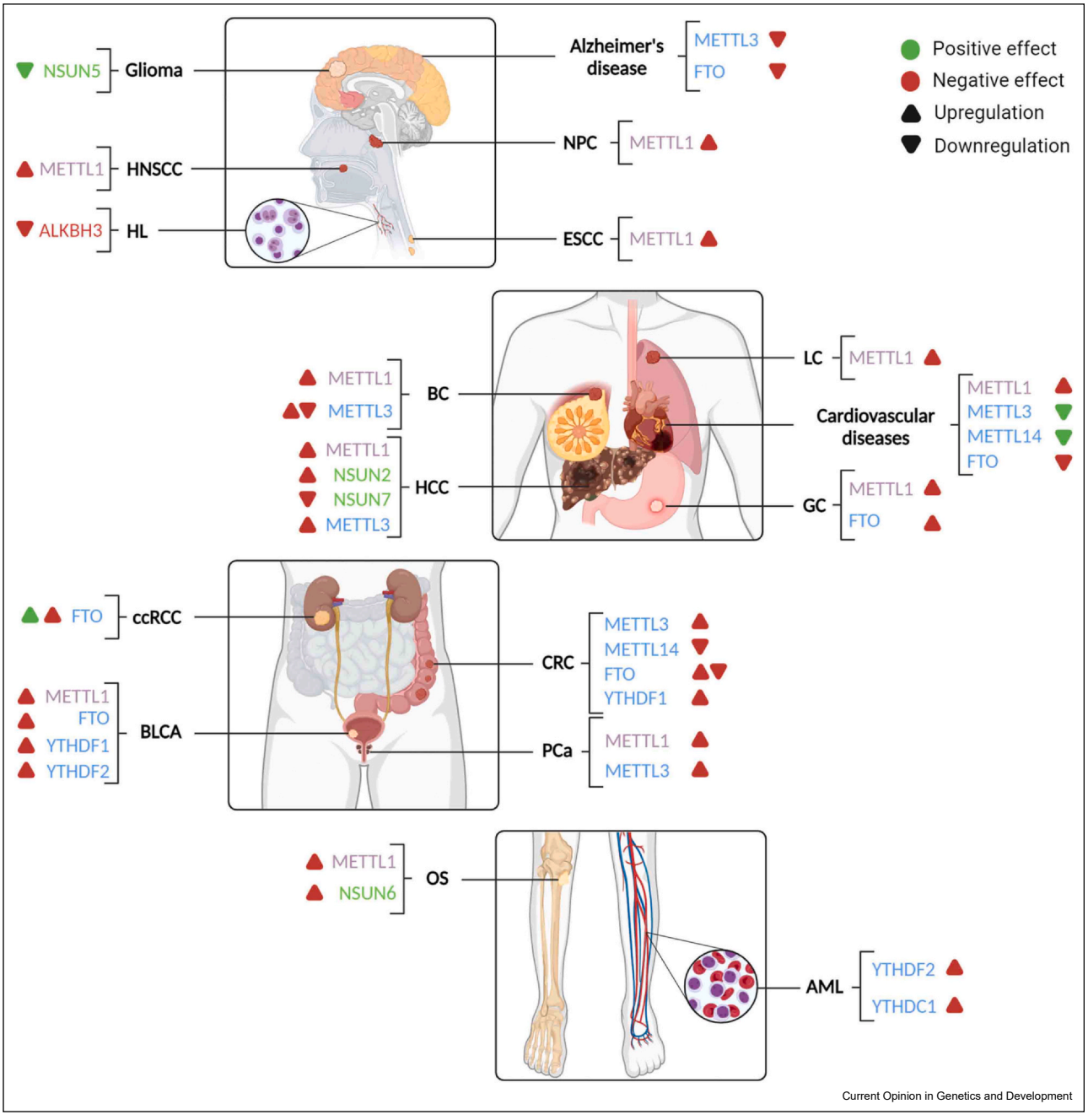
YT521-B homology domain family 1 (YTHDF1) and 2 (YTHDF2)and YT521-B homology domain-containing 1 (YTHDC1)

The mechanisms underlying these canonical m^6A regulators in cancer remain poorly understood. YTHDF1, YTHDF2, and YTHDC1 exhibit an aberrant overexpression in numerous oncogenic malignancies, affecting downstream target mRNAs and miRNAs (Figure 2).

In CRC, YTHDF1 induces tumorigenesis by facilitating ARHGEF2 translation and RhoA signaling, which have been proposed as potential inhibition targets [52]. In BLCA, YTHDF1, in an METTL3-dependent manner, increases PI3K/Akt/mTOR pathway and cancer aggressiveness via m^6A modification in RPN2 mRNA [53].

YTHDF2 is associated with RIG-I-coding mRNA degradation in BLCA, restraining RIG-I-mediated innate immune signaling and stimulating immune evasion [7]. In acute myeloid leukemia (AML), YTHDF2 intensifies leukemogenesis through the recruitment of pre-miRNA processing regulator AGO2, controlling the maturation of pre-miR-126 [54]. Additionally, YTHDC1 contributes to maintaining cell survival and the undifferentiated state in AML by protecting m^6A-mRNAs from degradation [11].

Figure 2



Role of various epitranscriptomic enzymes in diverse pathologies, including cancer, cardiovascular diseases and neurological disorders. Green denotes a favorable influence, and red indicates a detrimental impact on the patient. This figure focuses only on the most recent findings in cancer. HL: Hodgkin lymphoma; HNSCC: head and neck squamous cell carcinoma; LC: lung cancer; NPC: nasopharyngeal carcinoma. Created with Biorender.com.

Methyltransferase-like 1 (METTL1)

Most evidence suggests a strong association between METTL1 and oncogenesis through m^7G modification [29]. An imbalanced m^7G tRNA modification level leads to the specific translation of oncogenic transcripts and, consequently, tumor development [9] (Figure 2).

In head and neck squamous cell carcinoma, the METTL1-WDR4 complex participates in the post-transcriptional modification of 16 tRNAs associated with the PI3K/Akt/mTOR signaling pathway, promoting its carcinogenesis [55]. In esophageal squamous cell carcinoma (ESCC), a gene set enrichment assay discloses

that m^7G regulates both mTOR pathway and autophagy. ESCC progression and poor prognosis are caused by the inhibition of autophagy due to the abnormal activation of the mTOR pathway [19]. In PCa, METTL1 methylates tRNAs and facilitates the biogenesis of small ncRNAs derived from 5'tRNA fragments, reprogramming the mRNA translation landscape and hampering the immune response [56]. In BLCA, METTL1 overexpression modulates the processing of miR-760 in an m^7G-dependent manner, resulting in the degradation of tumor suppressor ATF3 mRNA, thereby promoting tumor progression and metastasis [57]. METTL1 also promotes tumorigenesis in various cancers, including osteosarcoma (OS), lung cancer, HCC, GC, BC, and nasopharyngeal carcinoma [29,58–62].

Other epitranscriptomic enzymes

Other epitranscriptomic marks also play a crucial but enigmatic role in cancer, especially m^1A and m^5C. Epigenetic regulation has a significant impact on several epitranscriptomic enzymes. Hypermethylation of the m^1A eraser ALKBH3 induces an increase in m^1A levels within the transcriptome of Hodgkin lymphoma, which correlates with lower survival rates [63]. The epigenetic inactivation of the m^5C writer NSUN5 results in a favorable prognosis in glioma [64], whereas the elevated NSUN6 expression in OS facilitates the proliferation, migration, and invasion of OS cells through increased EEF1A2 mRNA stability and activation of Akt/mTOR signaling pathway via m^5C modification [65]. NSUN7 epigenetic loss is associated with poor outcomes in HCC [66], and the m^5C modification of H19 lncRNA by the NSUN2 modifier enhances its stability, leading to the recruitment of the G3BP1 oncoprotein and promoting poor differentiation in HCC [67].

Cardiovascular diseases

Cardiovascular diseases are among the most prevalent causes of morbidity and mortality worldwide. The field of cardiovascular disorders has long been studied; however, the field of epitranscriptomics arises as a novel subject of inquiry (Figure 2).

Studies on the mouse heart reveal global m^6A hypomethylation in cardiomyocytes as necessary for proper regeneration [68,69]. In particular, the m^6A hypomethylation of Fgf16 mRNA due to the downregulation of METTL3 attenuates cardiac dysfunction and allows cardiomyocytes proliferation after myocardium infarction, avoiding YTHDF2-mediated mRNA decay [68]. Accordingly, the downregulation of METTL14 after acute myocardial ischemia–reperfusion prevents apoptosis and fibrosis by favoring Phlpp2 mRNA m^6A hypomethylation, which leads to little YTHDF1-mediated translation and hence the Akt-S473 pathway activation [69]. Interestingly, inhibition of METTL14 is also described to promote cardiac hypertrophy, as well as to prevent apoptosis, after exercise in neonatal rat cardiomyocytes [69]. These data suggest a protective role of m^6A writers in heart regeneration upon stress. Of note, this protective role of m^6A writers in heart regeneration is also observed in macrophages after sepsis-induced myocardial dysfunction in mice [70]. m^6A epitranscriptomics are also implicated in after-stroke vascular repair. According to a recent study [12], global m^6A hypermethylation occurs in the peri-infarct cortex of patients with acute ischemic stroke due to the downregulation of FTO, which is rescued by the endogenously expressed circular RNA circSCMH1. circSCMH1 allows nuclear translocation of FTO and thus prevents m^6A hypermethylation of Plpp3 mRNA and subsequent YTHDF2-mediated degradation, favoring repair of damaged blood vessels and after-stroke recovery [12]. FTO has also been described to contribute to cardiovascular disease–related disorders such as obesity and diabetes. In particular, FTO is crucial for β-cell function, and its overexpression triggers diabetic phenotypes, showing potential as a therapeutic approach for diabetes [71,72].

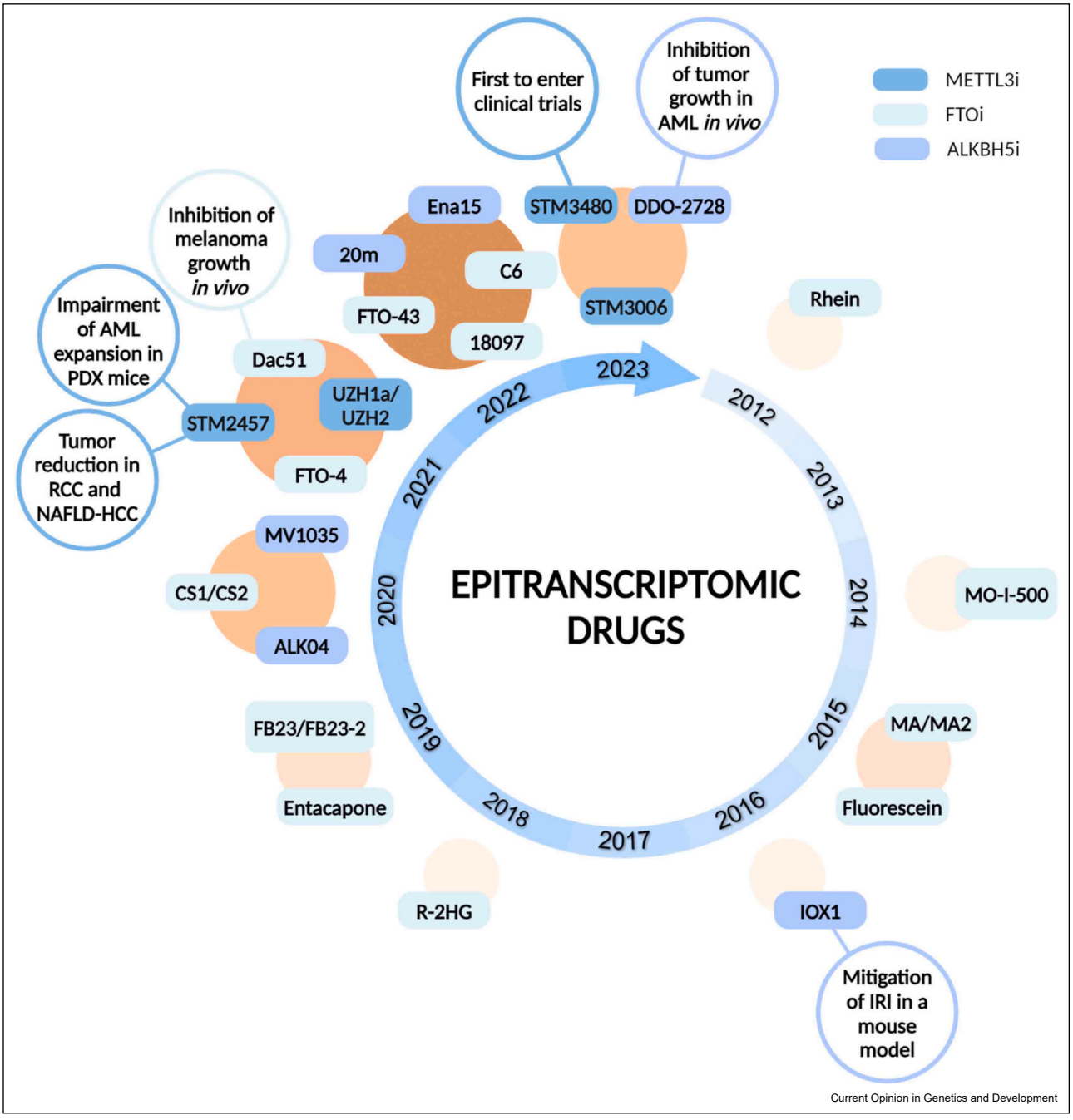
In addition to this, other epitranscriptomic marks, such as m^7G, are of great clinical interest. An example of this is displayed by a recent study showing that overexpression of TMEM11 after ischemic injury in mice triggers METTL1-mediated m^7G deposition over Atf5 mRNA [73]. This m^7G hypermethylation promotes Atf5 mRNA stability and translation, which results in decreased cardiomyocyte proliferation and heart regeneration [73]. Together, these findings demonstrate a relevant role of epitranscriptomics in the cardiovascular setting and accentuate the need for more studies examining epitranscriptomic marks other than m^6A.

Neurological disorders

Curiously, it has been demonstrated that the brain is the organ with the highest m^6A levels, and its m^6A methylome is extremely specific [74,75]. Although several studies have established connections between m^6A methylation and the onset of tumors, fewer have explored its potential association with neuropathologies.

The hippocampus and the cortex are the primary regions of the brain involved in the pathogenesis of Alzheimer's disease (AD). Some preclinical studies have already revealed distinct roles for RNA methyltransferases and demethylases in cortical development and hippocampal neurogenesis [76]. For example, METTL3 exerts a considerable influence on regulating the size of the neural progenitor pool and neuronal production, compared with FTO [76], while its silencing results in evident abnormalities in dendritic spine and synapses, along with a widespread neuronal death in the hippocampus — characteristic features of AD [13]. Additionally, the analysis of human samples from patients with AD revealed a reduction in the mRNA expression levels of METTL3 and FTO compared with the control

Figure 3



Epitranscriptomic drugs timeline. Schematic representation of the development of epitranscriptomic drugs over the years, specifically METTL3, FTO, and ALKBH5 inhibitors. Note that STM3480 (STC-15) is already in clinical trials. Created with Biorender.com.

group [77], as represented in Figure 2. Conversely, FTO downregulation contributes to memory reconsolidation [78], proving that a precise global m^6A methylation level and a fine-tuning balance between methyltransferases and demethylases are key for the proper functionality of the brain.

Epitranscriptomics as a biomarker

As described, disease progression and prognosis are characterized by altered epitranscriptomic landscapes and expression of effector proteins, which can be measured using techniques, such as nanopore sequencing or mass spectrometry [79], potentially serving as a novel biomarker option. Latest studies have employed

available biological and clinical data from patients suffering from cancer to generate prognostic models based on the expression of m^6A-, m^5C- and m^1A-related regulatory proteins through the use of computational biology [80–82]. Generally, these studies aim to link the levels of these proteins with gender, age, clinical subgroups, Kaplan-Meier survival data, and immune cell infiltration to predict overall survival and response to immunotherapy. Specifically, a model was constructed focusing on the expression of UNG, FMR1, MBD4, MBD2, NEIL1, WTAP, UHRF2, YTHDF1, and RBM15B using data from > 400 patients with skin cutaneous melanoma [80]. Another model related expression of YTHDF1, YBX1, TRMT10C, and TRMT61A to data from > 300 patients with HCC [81]. Finally, an additional one centered on the expression of IQGAP3, PTBP1, STAC3, CUX1, SLC2A1, CA2, IGBP1, DUOX1, CHAF1A, and STAC3 making use of data from > 300 patients with cervical cancer [82]. These studies prove the large applicability of epitranscriptomics data in the establishment of reliable models of biomarkers and underscore the crucial role of big data integration into machine learning approaches for such purposes.

Targeting epitranscriptomics

As reviewed, different cell- and tissue-specific epitranscriptomic landscapes are observed in health and disease. Knowledge about the physiological and pathological epitranscriptome enables the specific targeting of effector proteins through epitranscriptomic drugs in order to slow and reverse disease progression. In this context, several small molecules are under research and may soon enter the clinic (Figure 3).

Efforts in the development of epitranscriptomic drugs are currently centered on the inhibition of m^6A writers [83–85] and erasers [86–104]. STM2457 and STM2120 are small molecule inhibitors that were synthesized to inhibit the catalytic activity of the METTL3-METTL14 heterodimer [83]. Other METTL3 inhibitors (METTL3i) have been developed ever since in search of increased specificity and cellular potency, such as UZH1a/UZH2 [84], STM3006 [85], and STM3480 [85]. Of these, STM3480 (STC-15) became the first epitranscriptomic drug to enter clinical trials (NCT05584111) and holds promise as an oral bio-available treatment for subjects with advanced malignancies [85]. Parallel to METTL3i, numerous epitranscriptomic drugs have been developed for the inhibition of m^6A erasers. Briefly, FTO inhibitors (FTOi) include rhein [86], MO-I-500 [87], MA/MA2 [88], fluorescein [89], R-2HG [90], FB23/FB23–2 [91], entacapone [92], CS1/CS2 [93], Dac51 [94], FTO-4 [95], FTO-43 [96], 18097 [97], and C6 [98], while ALKBH5 inhibitors (ALKBH5i) include IOX1 [99], MV1035 [100], ALK04 [101], Ena15 [102], 20m [103], and DDO-2728 [104]. Finally, the development of drugs aiming to target other m^6A effector proteins and epitranscriptomic marks is still ongoing, with focus on the inhibition of HAKAI [105] and METTL1 [106], respectively.

Recent studies evaluating epitranscriptomic drugs *in vivo* reveal their value as possible prospective treatments. In particular, the METTL3i STM2457 impairs AML expansion in patient-derived xenograft mice and extends overall survival with no observed toxicities [83]. Furthermore, STM2457 reduces tumor growth in ccRCC [107] and NAFLD-HCC [41]. Importantly, inhibition of METTL3 entails the increase of PD-L1 levels, which suggests a potential use of METTL3i in combination with anti-PD-1 immunotherapies for cancer treatment [41,85]. FTOi and ALKBH5i have also been reported to exert therapeutic effects *in vivo*. The FTOi Dac51 inhibits tumor growth in a mouse model of melanoma [94]. The ALKBH5i IOX1 and DDO-2728 alleviates renal ischemia–reperfusion injury (IRI) in a mouse model of renal IRI [108] and inhibits tumor growth in AML-xenograft mice [104], respectively. Nevertheless, more research is required to elucidate potential clinical applications of epitranscriptomic drugs.

Conclusion

In conclusion, the emerging field of epitranscriptomics offers an unprecedented novel view of gene expression regulation at a post-transcriptional level, offering new avenues for the elucidation of the intricate mechanisms governing progression and outcomes of diseases. Consequently, the clinical potential epitranscriptomics possesses is therefore vast and promising. As such, further research will undoubtedly contribute to uncovering its great clinical potential.

Recent studies interrogating epitranscriptomic landscapes associated with different diseases have largely contributed to the modeling of epitranscriptomic biomarkers for prognosis and treatment response prediction. Furthermore, the development of drugs targeting epitranscriptomics-related effector proteins holds great therapeutic promise, paving the way for its future use in targeted therapies in various diseases, including cancer, cardiovascular diseases, and neurological disorders.

Although m^6A is the most well-characterized epitranscriptomic mark, ongoing research continues to shed light on the role of other epitranscriptomic modifications and their effector proteins in health and disease. Deeper insights into the entire human epitranscriptome and its

crosstalk with other gene-expression regulatory pathways will soon shift the paradigm and revolutionize our comprehension of disease pathogenesis and clinical strategies.

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Data Availability

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

Declaration of Competing Interest

None.

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- • of special interest
- •• of outstanding interest

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