# Epitranscriptomics in Drug Response: Emerging Regulators of Pharmacology and Personalized Medicine

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## EPITRANSCRIPTOMICS IN DRUG RESPONSE: EMERGING REGULATORS OF PHARMACOLOGY AND PERSONALIZED MEDICINE

***Abstract:*** *Epiatranscriptomics which involves the study of the chemical modification of RNA molecules without altering the nucleotide sequence has rapidly emerged as a significant aspect of gene regulation with the long-term implications on pharmacology and personalized medicine. The most prevalent RNA modifications, the most studied of which have been examined in the most detail, are N6-methyladenosine (m6A), pseudouridine, and 5-methylcytosine that control RNA stability, splicing, translation and degradation. The new developments have demonstrated that these changes are not merely regulating physiological functions, but are also playing a major role in the development of chronic diseases, the development of cancers and other neurological issues. It is worth mentioning that epitranscriptomic alterations have a strong impact on drug absorption, distribution, metabolism and excretion (ADME), which dictates the therapeutic efficacy and toxicity. Dysregulation of the RNA-modifying enzymes such as METTL3, FTO, and ALKBH5 has been linked to variable drug responses, drug resistance, and adverse reactions and can also be considered as new biomarkers and therapeutic targets. The integration of epi-transcriptomic into*

*drug development will be an invigorating area, e.g. the discovery of predictive biomarkers, the identification of small-molecule agonists or antagonists of RNA-modifying enzymes, and the potential application of RNA-editing technology to generate precision therapy. The area is however threatened by such problems as lack of detection resolution, situation-specific roles of RNA alterations, safety issues of therapeutic targeting. To eliminate these limitations, standard protocols, technology, and a blend of artificial intelligence and multi-omics will be necessitated. This article illustrates that the alterations in RNA are molecular, affect the drug response, and can be used in precision medicine. The connection of the molecular processes to the therapeutic opportunities will make epitranscriptomics the new epoch of pharmacology, and the path to the actual personalized treatment of drugs.*

***Keywords:*** Epitranscriptomics, RNA modifications, m6A, drug response, personalized medicine, biomarkers, pharmacology.

# 1. INTRODUCTION

There are wide differences in drug response amongst individuals, which have traditionally been attributed to pharmacogenomics (differences in enzyme, transporter and receptor metabolism of drugs due to genetic differences), and pharmacoepigenomics (epigenetic changes of DNA and histones due to genetic differences) [1]. Nevertheless, a third layer of regulation epitranscriptomics has become a pivotal player in drug efficacy and toxicity determination in the past few years [2,3]. Epiteranscriptomics is defined as subsequent chemical modifications of RNA molecules, including N6-methyladenosine (m6A) and 5-methylcytosine (m5C), N1-methyladenosine (m1A) and pseudouridine (Ps). These changes are dynamically displayed, reversible and closely controlled by particular enzymes referred to as writers (methyltransferases), erasers (demethylases) as well as readers (RNA-binding proteins). EpitRNA and epitranscriptomic alterations can significantly regulate the expression of genes by varying the modification of RNA splicing, stability, localization, and translation [4]. Recent findings indicate that epitranscriptomic changes have an effect on the expression of drug-metabolizing enzymes (e.g., CYP450s), drug transporters (e.g., ABC family), drug targets (receptors, kinases), as well as important signaling pathways (NF-kB, PI3K/Akt, MAPK). This renders them important factors influencing drug absorption, distribution, metabolism, excretion (ADME), and pharmacodynamics [5,6,7]. Since they are involved in cancer chemotherapy resistance, psychiatric drug response variability, metabolic diseases and immunotherapy responses, epitranscriptomics is a study that is gaining momentum in the personalized medicine field [8]. Contrary to genetic changes, RNA changes are non-permanent, which opens up a promising prospect of pharmacological treatment with small molecule inhibitors, RNA-based therapy and natural products [9]. As such, epitranscriptomics should be the foundation of the contemporary pharmacology as it offers new biomarkers to stratify patients and new therapeutic targets to overcome their resistance to drugs. Throughout this review, the mechanistic roles of RNA modifications in drug response are discussed, along with their role in key diseases, as biomarkers, and in treatment strategies, emerging therapeutic strategies are examined, and the existing challenges and future outlooks are identified.

# 2. BASICS OF EITRANSCRIPTOMICS

Epiteranscriptomics is a term that is used to describe chemical modifications of RNA molecules that control their processing, stability, transportation, and translation without changing their underlying nucleotide sequence [4]. There are over 170 known RNA modifications however, few of them are significant in terms

of drug response and disease pathogenesis [10]. The most prevalent of these internal modifications in messenger RNA (mRNA) includes N6-methyladenosine (m6A) which has been shown to control splicing, stability, and translation efficiency and is highly associated with processes of cancer progression and chemotherapy resistance [11]. In the same way, 5-methylcytosine (m5C) which is present in mRNA, tRNA, and rRNA regulates the RNA export, translation, and protein synthesis and has been linked to tumor growth and drug resistance [12]. N1-methyladenosine (m1A) is found in both tRNA and mRNA, and is known to alter the mRNA secondary structure, ribosome affinity and piloting, and recent evidence indicates that it can play a role in stress response and tolerance to drugs [13]. The most frequently present RNA modification, pseudouridine (Ps), also promotes the stability of RNAs and codon-anticodon complementation as well as has been associated with drug target protein regulation and therapeutic RNA [14]. This regulation is not fixed but dynamically controlled by three groups of proteins: writers add chemical groups (i.e. METTL3, METTL14, WTAP m6A; NSUN2 m5C); erasers remove modifications (i.e. FTO, ALKBH5 m6A); and readers RNA-binding proteins that perceive modified RNAs and mediate their behavior (i.e. YTH domain proteins, IGF2BP family, and HNRNPC). Altogether, these modifications and their regulators serve important functional purposes in cells by regulating mRNA splicing, isoform expression, by regulating RNA stability and degradation, by regulating translation efficiency and protein synthesis and finally they influence cell differentiation, stress response and immune activation [15,16,17,18].

## 3. EPITRANSCRIPTOMICS AND PHARMACOLOGY

The epi-transcriptomic alterations are also important in drug response regulation by controlling the levels of expression and functions of drug-metabolizing enzymes, transporters, drug targets and drug signaling [19]. Drug metabolism is one of the processes which are most affected. RNA methylation regulates the cytochrome P450 (CYP450) enzymes that are involved in metabolising a significant percentage of the therapeutic agents [20]. To discuss this, the variation of the stability and translation of CYP3A4 mRNA by m6A could inter-individually vary the clearance of anticancer, antiepileptic, and immunosuppressive drugs [21]. On the same vein, alterations of RNA on phase II enzymes like UDP-glucuronosyltransferases (UGTs) and glutathione-S-transferases (GSTs) can dictate the extent to which toxic compound metabolites are neutralized, which has a direct effect on drug toxicity and therapeutic outcome [22].

Epit scriptomics also has an influence on another important area, drug transport [6]. Transport of drugs, including P-glycoprotein (ABCB1) and the members of the ABC family of transporters, are strictly controlled at the RNA level. Their transcriptional fate is altered by Epiteranscriptomic modifications, especially, m6A and m5C modifications, thus, altering multidrug resistance. In cancer, e.g., higher levels of RNA methylation of the ABC transporters may boost the efflux of drug treatments: doxorubicin and cisplatin, decrease intracellular drug concentration and lead to drug treatment failure [23].

RNA modifications also form drug targets such as receptors, enzymes, and kinases [6]. These targets can be silenced or activated by epi-transcriptomic changes in order to increase or decrease therapy sensitivity or resistance [24]. An example of such a system is the estrogen receptor in breast cancer, where the pathogenic m6A regulation changes the receptor expression and leads to tamoxifen resistance [25]. In addition to direct targets, the RNA modifications modify larger cellular signaling pathways that mediate the action of drugs [24]. The most important pathways in inflammation, survival and apoptosis include NF-kB, PI3K/Akt and MAPK, which are epitranscriptomically regulated and thus it helps to tune down the response to anticancer, anti-inflammatory and immunomodulatory therapy [26].

## 4. EPITRANSCRIPTOMICS IN MAJOR DISEASE AREAS AND DRUG RESPONSE

Epitextratranscriptomic control has become a key factor in the pathogenesis of various illnesses and has a powerful impact on the effect of patients to pharmacological interventions [27]. RNA modifications

including m6A, m5C, and pseudouridine have been widely dysregulated in cancer, including tumor initiation, progression, metastasis, and therapy response [28]. METTL3 overexpression has been associated with elevated oncogenic gene translation (MYC) and the opposite of this where m6A readers (IGF2BPs) are dysregulated has been associated with tumor cell survival and chemoresistance [29]. M6A modification is an altered modification that promotes leukemogenesis in acute myeloid leukemia and determines the sensitivity to tyrosine kinase inhibitors, and RNA methylation alterations are observed to help breast and lung cancer cells resist tamoxifen, cisplatin, or immunotherapies. In this way, the targeting of RNA-modifying enzymes is currently being considered as a new anticancer therapeutic approach [30].

The epitranscriptomic alterations play an essential role in neuronal plasticity, formation of memory, and stress response in neurological disorders [31]. It has been demonstrated that abnormal m6A methylation can be found in neurodegenerative disease, including Alzheimer and Parkinson disease, in which m6A methylation changes the synaptic protein levels and inflammatory signaling [32]. Not only do these alterations hasten the progression of the disease, but also influence the sensitivity of the neuroprotective drugs and cholinesterase inhibitors [33]. Also, the efficacy of antidepressants has been demonstrated to be affected by RNA methylation, which alters the monoamine neurotransmitter pathways, indicating a direct relationship between psychiatric pharmacotherapy and epitranscriptomics [34].

Epittranscriptomics is progressively being cited as a factor in drug response in the area of cardiovascular diseases [35]. RNA alterations also control cardiac hypertrophy, vascular inflammation, and lipid metabolism that influence statin, antihypertensives, and antiplatelet therapies [36]. As an example, m6A-driven control of the mRNA stability of PCSK9 and LDL receptor promotes the way cholesterol is processed and responsiveness to statins. Likewise, RNA methylation regulates the platelet reactivity and endothelial activity, thus affecting the performance of antithrombotic agents.

RNA alterations are utilized by pathogens and host cells in the regulation of immune reactions and efficacy of medication in inflammatory and infectious diseases [37]. To evade host immune-surveillance, viral RNAs are often modified with m6A, and that is also what SARS-CoV-2, HIV, and influenza do [38]. These mutations have an impact in the effectiveness of the antiviral drugs and the ease of the viruses to multiply [39]. RNA methylation on the host side affects the immune cell cytokine output and reaction to anti-inflammatory drugs, such as corticosteroids and biologics [40]. This is particularly essential in autoimmune disorders such as inflammatory bowel disease and rheumatoid arthritis whereby the epitranscriptomic patterns are under investigation as a possible measure of treatment effectiveness [41].

Combinations of data in the domains of immunology, neurology, cardiology and cancer reveal that epitranscriptomics regulates inter-individual differences in therapy response besides drives disease biology [42]. This novel field presents novel prospects in the production of personalized drugs and prognostic biomarkers by relating the alteration of RNA to drug outcomes [43].

## 5. THERAPEUTIC TARGETING OF EPITRANSCRIPTOMIC MODIFIERS

The emergence of epitranscriptomic machinery as a potential target of therapeutic intervention has become possible since alterations in RNA are reversible and can be targeted pharmacologically [44]. The most studied of them are m6A regulators. The m6A writer METTL3 was been found to be implicated in numerous cancers and that small molecule inhibitors like STM2457 demonstrated strong antileukemic effects by offering to m6A installation of oncogenic transcripts. Likewise, in oncology, the erasers of m6As, FTO and ALKBH5 are under investigation since their overexpression facilitates tumorigenesis and chemoresistance [45]. Meclofenamic acid derivatives and rhein which are FTO inhibitors have shown to

sensitize cancer cells to chemotherapy and immune checkpoint blockade that has translational potential [46].

Cancer is not the only target of epipeatranscriptomic. In the neurological field, the control of m6A regulators is currently under investigation in improvements of neuroplasticity and neurodegeneration [47]. Small molecules with the ability to regulate m6A can recover synaptic activity in Alzheimer and enhance antidepressant responses to antidepressants [48]. RNA-modifying enzyme inhibition is also under consideration in the cardiovascular field in order to correct aberrant lipid metabolism and vascular inflammation to enhance the effect of statins and decrease resistance to the drugs [49].

Other RNA modifications like the m5C and pseudouridine in addition to m6A have therapeutic potential [50]. The dysregulated m5C writers such as NSUN2 have been linked to cancer metastasis, and chemotherapy resistance, and are therefore appealing drug targets [51]. In line with this, pseudouridine synthases are under investigation as part of ribosome biogenesis as well as translation fidelity, and the inhibitors have already given early preclinical performance [52]. New CRISPR-based RNA editing methods also broaden the repertoire of specific epitranscriptomic interventions that are able to repair pathological RNA editing without affecting the underlying genome [53].

The emerging scientific trend is the creation of combination therapy, in which the epitranscriptomic inhibitor is combined with current drugs to circumvent resistance [54]. As an illustration, METTL3 inhibitors, in combination with tyrosine kinase inhibitors, have been found to be more effective in treating leukemia, and FTO inhibition can be used to re-immune-checkpoint-resistant tumors. These strategies emphasize the epitranscriptomic modulation in therapy.

All in all, therapeutic targeting of enzymes of RNA modification is an emerging field of drug discovery [55]. As several of the inhibitors are already in the preclinical and early clinical phase, the field is ready to apply epitranscriptomic knowledge to precision medicines that have the potential to transform the treatment outcome in cancer, neurological, cardiovascular, and inflammatory diseases [56].

## 6. CLINICAL IMPLICATIONS AND PERSONALIZED MEDICINE

Due to the introduction of epitranscriptomics into clinical practice, the environment of personalized medicine has been transformed by providing new biomarkers and treatment options that no longer rely on standard genomic and proteomic platforms [57]. As the RNA modifications are dynamic and reversible, they can give a real-time picture of cell statuses, disease dynamics and drug responsiveness [58]. This renders them very desirable diagnostic and prognostic biomarkers [59]. As an illustration, the m6A regulators of cancer prognosis and treatment outcome, including METTL3, FTO, and ALKBH5, are modulated in the blood or tissue samples, whereas the specific RNA methylation signatures are becoming predictors of response to chemotherapeutic agents and immunotherapies.

The implications of epitranscriptomic profiling in pharmacogenomics and drug dosing also are high. Differences in patterns of RNA modification can be used to explain the differences in responses of patients with similar genetic backgrounds on similar drug [60]. As an example, the pharmacokinetics and drug clearance are affected by the differential m6A methylation of drug-processing enzymes and transporters, and thus affect the effectiveness and toxicity of chemotherapeutics, antidepressants, and cardiovascular medications. By incorporating the results of epitranscriptomic studies into patient stratification, these clinicians may choose the most effective treatment at the appropriate dose without causing any adverse events and with the greatest positive effect.

It is also an area that is opening the door to individual therapeutic interventions [61]. However, the emergence of small-molecule inhibitors and RNA-editing technologies that target individual epitranscriptomic enzymes have made personalized treatment nowadays so that the individual profile of

RNA modification can be used to tailor the treatment. Indicatively, a patient with a tumor having a high METTL3 activity level could be introduced to METTL3 blockers along with conventional therapy, and patients with a tumor having an FTO-based resistance could be subjected to selective FTO blockers. Likewise, in neurodegenerative disorders, the patient-specific patterns of RNA modifications can be used to inform the application of the targeted epitranscriptomic modulators to repair neurons [62].

Notably, the existing multi-omics tools may be complemented with epitranscriptomic analysis to combine both to establish a holistic approach to precision medicine [63]. Clinical translation is becoming possible as the mapping of epitranscriptomic landscapes at single-base resolution has become quicker due to the development of high-throughput sequencing methods like MeRIP-seq and nanopore direct RNA sequencing [64].

## 7. CHALLENGES, LIMITATIONS AND FUTURE DIRECTIONS

Although the potential of epitranscriptomics is huge, there are a number of obstacles and constraints to the field, which are likely to be overcome before the full clinical application can be achieved [65]. A significant problem is the inability of methods of detection due to technical limitations [66]. Existing sequencing systems, including MeRIP-seq, offer useful information on RNA modification, but do not possess resolutions at a single-base level and typically demand large amounts of RNA, which excludes their application in clinical applications. Although newer technologies such as nanopore direct RNA sequencing have an advantage of being more accurate, there exist concerns of sensitivity, throughput, and cost [67].

The role of RNA modification is also context-dependent and is another challenge [68]. The identical modification, m6A, can produce oncogenic and tumor-suppressive effects and depend on the cellular environment, tissue type and the stage of the disease [69]. This duality makes it difficult to target therapy, with either inhibition or facilitation of a modification having undesired effects [70]. Moreover, due to the overlapping and redundancy between various RNA modifications, an extra layer of complexity is added [71]. The inhibition of one of the enzymes can induce the activation of other compensatory mechanisms that can decrease the therapeutic effect and enhance the chances of off-target effects [72].

Specificity and safety are key issues as far as drug development is concerned [73]. The majority of epitranscriptomic enzyme inhibitors are still at the preclinical stage, and their effects on physiological functions in the long term are not well understood [74]. RNA modifications control core process such as the translation and splicing thus, systemic inhibition of such enzymes might result in toxicity [75]. It is an important direction to develop highly selective modulators, which are capable of differentiating between pathological and physiological RNA modifications [76].

Biomarkers and standard protocols to epitranscriptomic profiling are also needed in clinical translation [77]. Currently, the best agreed-upon procedures are not in place to determine the reliability of evaluation of RNA alterations in patient samples, making it harder to achieve reproducibility and substantially validate studies [78]. To integrate epitranscriptomics in precision medicine, the combination of multiple efforts will be required to gain reference datasets and bioinformatics pipelines alongside quality-control criteria [79].

In the foresight, the future trends in epitranscriptomics are to develop next-generation sequencing more affordable, sensitive and with a higher resolution to allow it to be used in clinical practice on a regular basis [80]. Developments in CRISPR-based edits of RNA and programmable epitranscriptomic infrastructure will likely transform therapeutic interventions in a way to enable specific manipulation of RNA modifications in a patient-specific way [81]. Moreover, by integrating epitranscriptomic data with AI-based drug discovery and multi-omics combination, the process of new drug targets and predictive biomarkers will be faster [82].

At the end, the future of epitranscriptomics is the possibility to connect simple science with clinical medicine, which will offer a new opportunity in diagnosis, treatment, and individual health care [83]. The solution to the transformative potential of this technology will be overcoming the existing technical, biological, and translational problems [84].

## 8. CONCLUSION

Epitextranomics has become a revolution in the field of biomedical studies that provides a new understanding of how RNA modification governs gene expression and can affect health and disease. As compared to genetic mutations, they are dynamic and reversible such that they make them highly attractive as biomarkers and therapeutic targets. The evidence is growing that, epitranscriptomic regulators like METTL3, FTO, and ALKBH5 have central roles in drug response, cancer progression, metabolic regulation and in neurological processes and therefore have the capability to transform personalized medicine.

The inclusion of epitranscriptomics into drug discovery and clinical practice offers a chance to improve the treatment efficacy, minimize adverse reactions, and create individual treatment plans. With more precise stratification of patients, forecasting drug responses and personalizing treatment to maximize benefit, clinicians can soon profile the patterns of RNA modification to classify patients. Besides, inventions of small-molecule inhibitors, RNA editing technology, and next-generation sequencing systems are taking the field a step nearer to clinical application.

Nevertheless, serious issues still persist, such as technical constraints of detection techniques, context-related effects of manipulations and necessities of very specific and safe therapeutic modulators. The efforts to overcome these difficulties will involve the interdisciplinary cooperation of molecular biologists, pharmacologists, clinicians and computational scientists. The next step towards integrating epitranscriptomics into precision medicine is bound to be faster and faster due to the future advances in sequencing technologies, CRISPR-based RNA editing, and AI-driven prediction models.

To sum up, epitranscriptomics is the new dimension of pharmacology as well as a paradigm shift in personalized medicine. Reconstruction of the epitranscriptomic code will be one step closer to achieving the vision of the personalization of therapy, i.e. drug treatment being optimized based on the unique set of RNA modifications in a patient. As it keeps developing, epitranscriptomics will become the key to the future of drug therapy, filling the gap between the molecular processes and clinical outcomes.

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