RNA Modifications

Subjects: Biology

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RNA modifications are diverse post-transcriptional modifications that regulate RNA metabolism and gene expression. RNA modifications, and the writers, erasers, and readers that catalyze these modifications, serve as important signaling machineries in cellular stress responses and disease pathogenesis.

RNA modifications disease

1. Introduction

RNA modifications are covalent chemical modifications of RNA molecules. To date, over 100 chemical modifications of RNA species have been identified [1][2]. The regulation and function of RNA modifications have recently emerged as pivotal mechanisms that regulate a wide range of biological and pathological processes, giving rise to the field known as epitranscriptomics.

RNA modifications are regulated through the coordination of ‘writers’, ‘erasers’ and ‘readers’, which deposit, remove, and recognize RNA modifications, respectively (Figure 1A). These enzymes represent key elements in patterning the epitranscriptomic landscape.

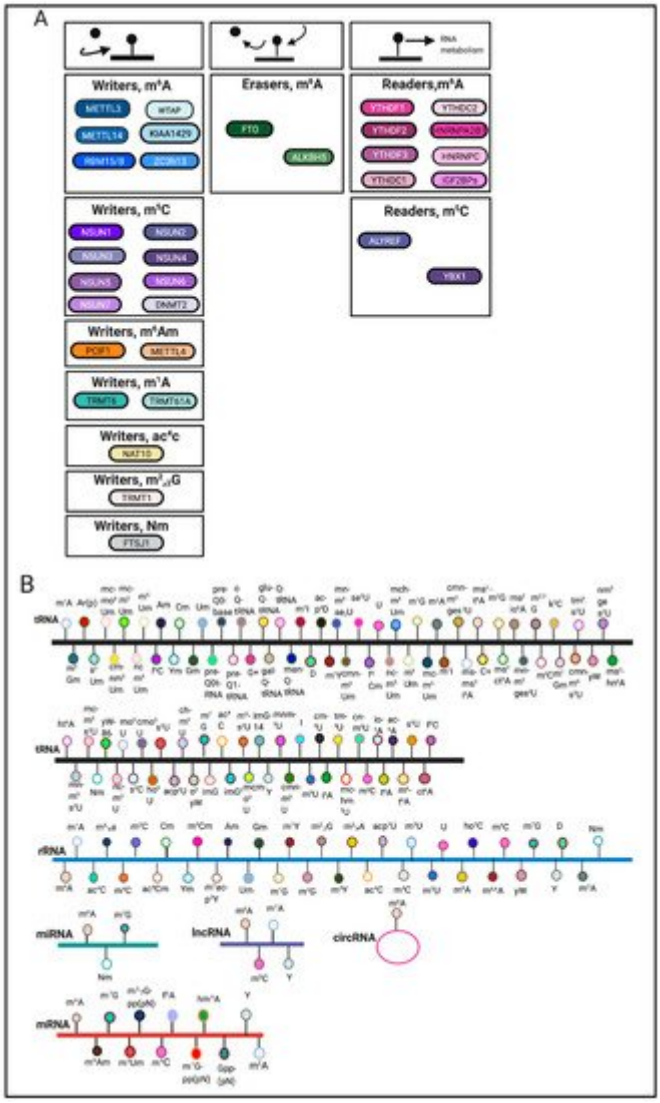

Figure 1. Overview of RNA modifications. (**A**). Writers, erasers and readers involved in catalyzing various RNA modifications. (**B**). Noted are RNA modifications that have been identified on tRNA, rRNA, mRNA, miRNA, lncRNA, circRNA [1][2][3][4][5][6][7][8]. The schematic was created using BioRender.

RNA modifications can occur on various RNA species including mRNA, tRNA, rRNA and other non-coding RNAs [9] (Figure 1B). Among these RNA species, transfer RNAs (tRNAs) contain the most RNA modifications [10]. One of the most abundant modifications on tRNA and rRNA is 5-methylcytosine (m^5C) [11]. In comparison, mRNA modifications were more difficult to identify and characterize due to their low-abundance. The advent of sophisticated sequencing technologies and methods has generated a renewed interest in mRNA modifications.

2. RNA Modifications in Diseases

2.1. Cancer

The role of RNA modifications in cancer is cell-type and context-dependent and has been reviewed extensively in various types of cancer [12][13][14][15][16][17][18][19][20][21][22] and are highlighted in Figure 2. Rare RNA modifications

have been described in cancer type-specific contexts, such as glioblastoma, and are detailed in [23]. An active area of research seeks to elucidate the role of RNA modifications in non-coding RNAs and other RNA species in the context of cancer, which are reviewed elsewhere [24].

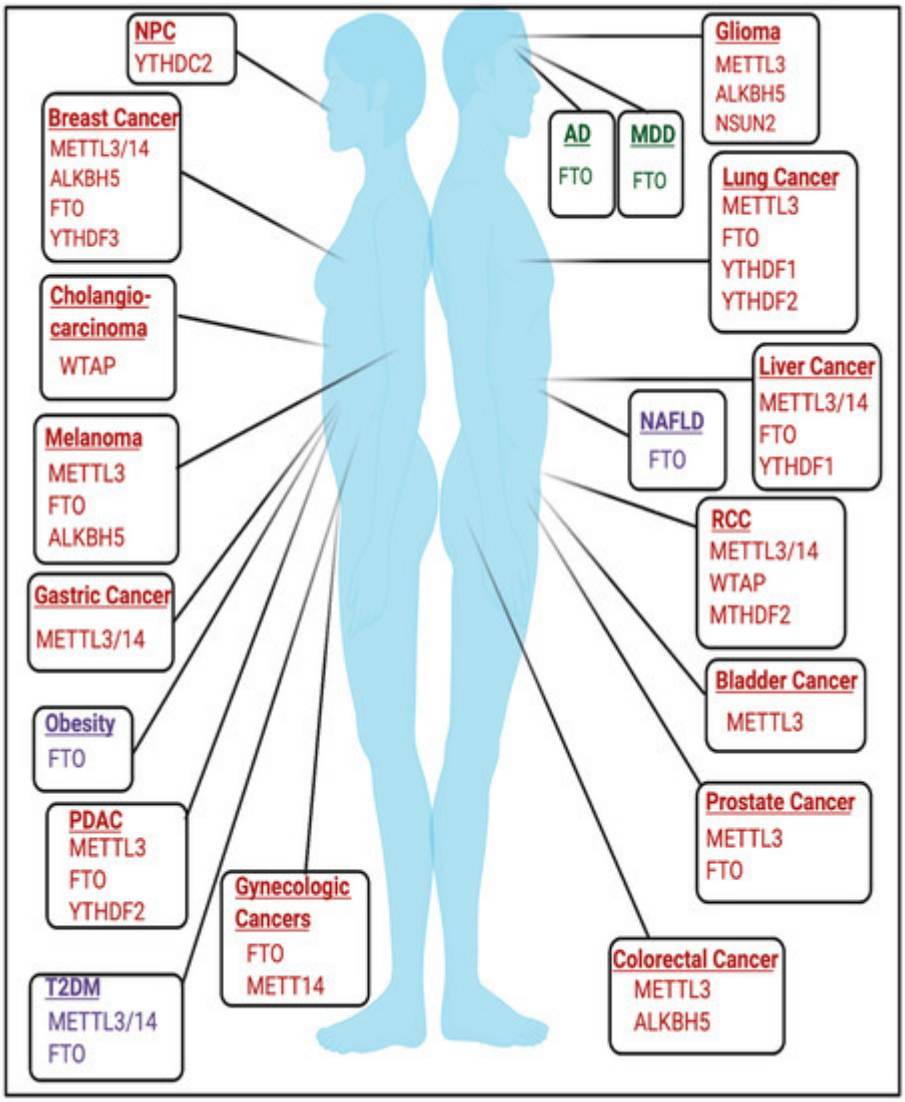

Figure 2. RNA Modifications in diseases. Highlighted are the regulators of RNA modifications that have established roles in regulating disease pathogenesis across genders as well as sex-specific diseases such as breast cancer, gynecologic cancers, and prostate cancer. Windows in red are modifiers implicated in cancer. Windows in purple are metabolic diseases. Windows in green are neurologic diseases. Not pictured are developmental disorders. The schematic was created using BioRender.

2.2. Developmental and Neurologic Disorders

The role of RNA modifications in the context of developmental and neurological disorders remains an active area of study. m^6A has been previously found to play important roles in embryonic development and neurobiological functions [25][26]. The roles of m^6A and other RNA modifications in mediating neurologic function are further discussed elsewhere [25][27][28][29][30].

The necessity of m^6A in development is emphasized by early embryonic lethality in *mettl3* KO mice [31]. Conditional *mettl3* knockout in murine brains also resulted in severe developmental defects within the cerebrum and cortex and induced apoptosis in cerebella granule cells (CGCs) [32]. FTO may also be important in mediating development as expression of catalytically inactive mutant *FTO*(R316Q) resulted in severe growth defects [33]. Mutations in tRNA methyltransferases have been implicated in developmental disorders and are detailed in [34]. *NSUN2* mutations have been linked to microcephaly, intellectual disability, and Dubowitz Syndrome, which is characterized by growth and mental retardation [35][36][37]. Additionally, homozygous frameshift mutations in *TRMT1*, a writer for $m^2{}_2G$, have been linked to intellectual disability [38]. Mutations and polymorphisms in *FTSJ1*, a writer for 2′O-methylribose, have also been linked to X-linked mental retardation [39][40][41][42][43]. Furthermore, targets of fragile X mental retardation protein (FMRP), a protein that is commonly mutated in Fragile X Syndrome, were enriched for m^6A, and FMRP targets were targeted for degradation by YTHDF2 [44].

2.2.1. Alzheimer's Disease

m^6A increases and distinct m^6A patterning were found in the cortex and hippocampus of APP/PS1 transgenic mice, which are used to model Alzheimer's Disease (AD) [45]. Additionally, AD-associated SNPs that decreased *FTO* expression were identified in Caucasian and Caribbean Hispanic populations [46]. AD patients also showed changes in small RNA modifications, which are detailed in [30].

2.2.2. Major Depressive Disorder

m^6A and m^6Am may be also implicated in major depressive disorder (MDD) as m^6A and m^6Am patterning were dysregulated in patients with MDD [47]. Conversely, the *FTO* variant rs9939609 was associated with a lower risk of developing MDD [48][49]. FTO may be also be involved in the development of anxiety, as $fto^{-/-}$ mice show increased anxiety-like behavior and hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis [50].

2.3. Metabolic Disorders and Diseases

FTO is a major driver in contributing to the pathogenesis of several metabolic diseases and therefore serves as a therapeutic target in this context.

2.3.1. Obesity

One of the strongest predictors of obesity is believed to be SNP rs9939609 in *FTO* [51][52][53][54][55][56]. *FTO* SNPs rs17817449 and rs3751812 also increased obesity risk in north Indian and Pakistani populations, respectively [57][58]. *fto* overexpression in mice also resulted in a dose-dependent increase in body mass and increased food intake [59][60]. However, these studies are m^6A-independent. Conversely, previous studies have identified that FTO-mediated m^6A demethylation regulates mRNA splicing in adipocytes and genes involved in sterol metabolism, which therefore may provide a mechanism by which FTO promotes obesity at the molecular level [61]. The role of FTO in metabolism is further reviewed elsewhere [62]. Identifying the m^6A-dependent and m^6A-independent functions of FTO in mediating obesity remains an active area of research.

2.3.2. Diabetes

In addition to obesity, m^6A sequencing of type-two diabetes mellitus (T2DM) patients revealed overall changes in m^6A patterning and hypomethylation of mRNA transcripts involved in insulin biogenesis, secretion, and pancreatic

-cell biology [63][64]. *FTO* mRNA expression was also higher in some T2DM patients [65]. Additionally, *METTL3/METTL14* expression was decreased in -cells of patients with T2DM, and METTL14 specifically may be essential for insulin secretion and

-cell survival [63][64][66]. However, the role of m^6A in mediating T2DM may be tissue and context-dependent as *METTL3* and m^6A levels were increased in liver tissue from T2DM patients [67].

2.3.3. Non-Alcoholic Fatty Liver Disease

Increased expression of *fto* was induced by a high-fat diet, resulting in increased lipogenesis and induction of non-alcoholic fatty liver disease (NAFLD), a disease that is commonly associated with obesity [68][69][70]. Identifying the m^6A-dependent and m^6A-independent functions of FTO in this context requires future study.

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