

Emerging roles of the RNA modifications N6-methyladenosine and adenosine-to-inosine in cardiovascular diseases

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Cardiovascular diseases lead the mortality and morbidity disease metrics worldwide. A multitude of chemical base modifications in ribonucleic acids (RNAs) have been linked with key events of cardiovascular diseases and metabolic disorders. Named either RNA epigenetics or epitranscriptomics, the post-transcriptional RNA modifications, their regulatory pathways, components, and downstream effects substantially contribute to the ways our genetic code is interpreted. Here we review the accumulated discoveries to date regarding the roles of the two most common epitranscriptomic modifications, N⁶-methyl-adenosine (m⁶A) and adenosine-to-inosine (A-to-I) editing, in cardiovascular disease.

INTRODUCTION

Cardiovascular diseases

Cardiovascular diseases (CVDs) cause more than one-third of all deaths worldwide. Almost half of the 18.6 million people that die annually to CVDs are due to ischemic heart disease (IHD), making it the leading single cause of death.^{1–2} Altogether, a total of 523 million people suffer from these diseases—including 197 million patients with IHD—and their disease burden is manifested as an annual loss of 393 million disability-adjusted life years.² In the United States, this translates into an annual expense of \$352 billion in direct health care costs and lost productivity.³ In the European Union, this cost is approximated as \$255 billion.⁴ Moreover, further contributing factors to the snowballing effect of CVDs are major other global phenomena, such as the increasing world population, westernization of life habits, and the increased proportion of aged individuals, as recently reviewed for atherosclerosis, the common underlying disease of most CVDs.⁵ In more than every 10th person over 65 years of age, CVDs, IHD in particular, eventually manifest as heart failure (HF),⁶ a severe syndrome associated with 5-year mortality rates of 43.3%–48.5%.^{7–8} Alarming, the prevalence of HF in the elderly population is expected to be over 30% by the year 2030.⁹

The high morbidity and mortality attributable to CVDs have initiated massive efforts to reduce their burden. Many revolutionary inventions, such as new molecular entity drugs and biological therapies,^{10–12} non-invasive imaging methods,^{13–14} sophisticated endovascular interventions,^{15–16} and implantable devices,¹⁷ have helped to

improve disease prognosis in terms of relative reduction in morbidity and, in some instances, mortality.

However, the fact that CVDs remain the single most fatal and morbid group of pathologies forces us to reach further. Generally, this quest is divided into stages of primary, secondary, and tertiary prevention.¹⁸ The contemporary advances in cardiovascular medicine have predominantly concentrated on either secondary or tertiary prevention; i.e., to diagnose and treat CVDs after their earliest possible manifestation or to stall symptomatic diseases from development of further complications, respectively. Effective primary prevention of disease, on the other hand, requires identification and intervention at the level of upstream factors causally responsible for initiating the development of disease.

Atherosclerosis manifests as fatty, inflamed, and calcified deposits in the walls of arteries. It is the underlying pathologic process in most CVDs, jointly termed atherosclerotic CVDs or atherosclerotic cardiovascular diseases (ACVDs).¹⁹ Distinct pathological entities arise based on the affected principal anatomic sites (Table 1).

Factors such as smoking, hypertension, high cholesterol, obesity, systemic inflammation, and genetics all contribute to the development of CVDs. Nevertheless, the causative factor triggering ACVD development has not yet been identified.^{5,19} Hypotheses on the etiology of atherosclerosis include, for example, infectious agents,²⁰ as well as gut-microbiota-produced circulating metabolites,²¹ such as trimethylamine-N-oxide²² and phenylacetylglutamine.²³

Ribonucleic acids (RNAs) constitute a critical upstream hub for cellular response control at the intersection of our genetic code and its translation. RNA is subject to multiple levels of processing, including both canonical and alternative splicing,²⁴ tailing,²⁵ and biochemical modifications.^{26–27} All of these processes are not only

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Table 1. Main types of ACVDs with respective common abbreviations, anatomic sites, and typical clinical entities with typical symptoms

ACVD	Abbreviation(s)	Anatomic site	Typical presentation(s)
Stroke, cerebrovascular accident	None, CVA	Intracranial arteries (also thromboemboli from extracranial arteries, heart, or shunting from the venous system)	Sudden unilateral paralysis or paresthesia in any part of the body; abrupt trouble to speak or understand speech; sudden disturbance of either posture or sight (homonymous hemianopsia), sudden first-of-its-kind severe headache
Carotid artery disease	CAD	Carotid arteries	As in stroke with an addition of a relatively pathognomonic sudden unilateral loss of sight (<i>amaurosis fugax</i>)
Ischemic heart disease, coronary artery disease	IHD, CAD	Coronary arteries	<i>Stable</i> : exertion-inducible chest pain (<i>angina pectoris</i>), dyspnea, fatigue, dizziness, lower extremity edema <i>Unstable</i> : abrupt pressing chest pain not relieved at rest, reflective pain in upper body, severe fatigue, dizziness, light-headedness, nausea, cold sweats, variable (malignant) arrhythmias, syncope, sudden unexpected death
Aortic aneurysms	TAA, TAAA, AAA	Aorta	<i>Chronic/subclinical</i> : asymptomatic, dyspnea on exertion or in specific positions (thoracic), striking abdominal pulsating mass <i>Acute</i> : dissection or rupture of the sickened aortic wall, harrowing pain across back, dizziness, nausea, syncope, massive both hyperacute and acute mortality
Mesenteric ischemia	None	Visceral arteries	<i>Chronic</i> : unwanted weight loss, diarrhea, idiopathic consistent temporary postprandial stomach pain <i>Acute</i> : severe abdominal pain, nausea, vomiting, fever, organ necrosis, sepsis, high acute mortality
Peripheral artery disease, arteriosclerosis obliterans	PAD, ASO	Arteries of the lower extremity	<i>Chronic</i> : disability, vascular claudication (reduced walking distance due to ischemic muscle pain) <i>Critical</i> : rest pain, ischemic ulcers, gangrenes, cold extremities, amputations <i>Acute obstruction</i> : intense pain, loss of distal muscle functions and numbness, white and cold extremity

critical for governing RNA function, cellular homeostasis, and physiological responses but, when dysregulated, they also lead and contribute to the development of disease.

Epitranscriptomics and the common internal RNA adenosine modifications: m⁶A and A-to-I

In the 1940s, Conrad Waddington introduced dynamic chemical modifications to nucleic acids, initially recognized in deoxyribonucleic acid (DNA) as epigenetic alterations.²⁸ However, nitrogen-5'-methylated cytosine was first discovered in 1925 in a living organism as an integral part of tuberculinic acid, a toxic noncanonical nucleic acid produced by *Mycobacterium tuberculosis*.²⁹ Compared with DNA modifications, the first reports regarding epitranscriptomics, or RNA epigenetics—the field of research on post-transcriptional biochemical modifications of RNA bases—were obtained decades later in the 1960s and 1970s. First, methionine-dependent methylation of pre-ribosome RNA was identified to be mandatory for its functional maturation in the HeLa cancer cell line.³⁰ Multiple different types of methylations in messenger RNAs (mRNAs) were first observed in the Novikoff hepatoma cell line.³¹ Thereafter, due to methodological limitations, epitranscriptomic research stagnated considerably. Only the methodological breakthroughs of the last decade, first the antibody-based enrichment of methylated RNA prior to sequencing (meRIP-seq),^{32–33} followed by both enzyme-based identifications^{34–35} and recently base-calling algorithms coupled with third-generation direct sequencing methodologies,³⁶ have

made the accurate characterization of some of these epitranscriptomic modifications increasingly feasible. Over 170 post-transcriptional modifications have been identified in nearly all RNA species.^{37,38} However, while numerous RNA decorations have been identified, only a few have been assigned a functional role so far.

Of these, the nitrogen-6-methyl-adenosine (m⁶A) and adenosine-to-inosine (A-to-I) RNA modification and editing, respectively, are the most common and most intensively studied.^{31,39} m⁶A has been shown to favor a consensus sequence DR(A/m⁶A)CH.^{32,40,41} (D = A, G, or U, R = A or G, and H = A, C or U). On average, three such sites are found in each mammalian mRNA molecule. A-to-I editing primarily occurs in the primate-specific ~300-nucleotide-long *Alu* sequences when such repeats align and pair after transcription to form double-stranded RNA (dsRNA) structures.³⁹ *Alu* sequences constitute 10% of the human genome and are enriched to gene-rich regions of the genome. The abundance and effects of these modifications are governed by designated enzyme families acting either as writers, erasers, or readers, and are summarized in Figure 1.

Writers of m⁶A to mRNA, methyltransferases, include both methyltransferase 16, N⁶-methyladenosine (METTL16), and the major writer complex that involves methyltransferase 3, N⁶-adenosine-methyltransferase complex catalytic subunit (METTL3), alongside its catalytically inactive methyltransferase 14, N⁶-adenosine-methyltransferase (METTL14) subunit, WT1-associated protein (WTAP),

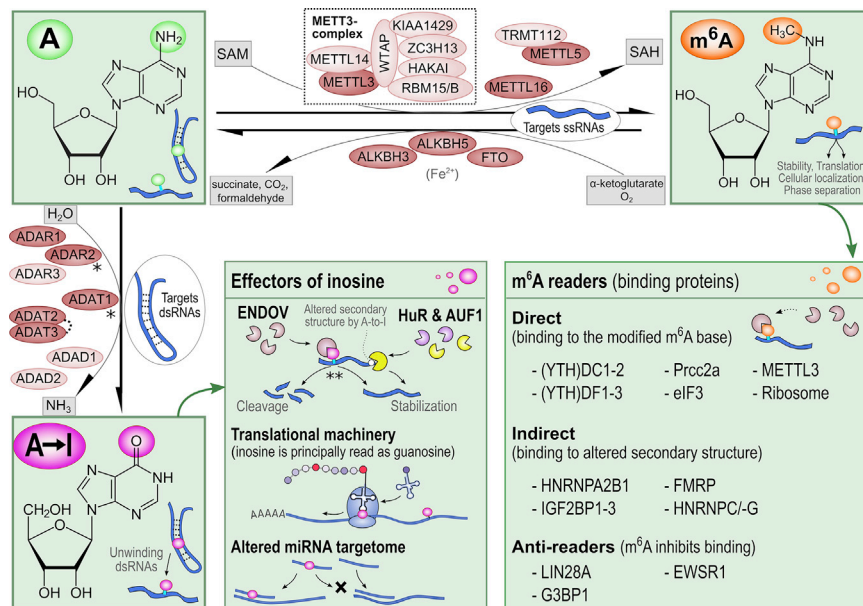


Figure 1. Depiction of the contributors responsible for A-to-I editing and m⁶A modification, respective downstream effectors, and the key effects on RNA biology

*Inositol hexakisphosphate (cofactor). **While ENDOV has been recently suggested to protect inosine-bound transcripts from degradation *in vivo*, it acts to target them for cleavage *in vitro* (see section “atherosclerosis”). While red-colored molecules harbor catalytic activity, the light-colored molecules act as non-catalytic subunits. The abbreviations are listed within the text.

as well as their interacting partners such as vir-like m⁶A methyltransferase-associated (VIRMA) protein, zinc-finger CCCH-type containing 13 (ZC3H13) protein, E3 ubiquitin-protein ligase hakai (HAKAI), and RNA-binding motif protein 15 (RBM15).³⁸ Moreover, a heterodimeric complex of methyltransferase 5, N⁶-adenosine (METTL5) and tRNA methyltransferase activator subunit 11-2 (TRMT112) write m⁶A specifically on 18S ribosomal RNAs (rRNAs).⁴² During the methylation process, S-adenosyl methionine (SAM) acts as a methyl donor and converts to S-adenosylhomocysteine (SAH). To date, three m⁶A erasers, demethylases, have been identified: widespread RNA-acting FTO alpha-ketoglutarate dependent dioxygenase (FTO) and testes-enriched alkB homolog 5, RNA demethylase (ALKBH5),³⁸ as well as tRNA-targeting alkB homolog 3, alpha-ketoglutarate dependent dioxygenase (ALKBH3).⁴³ FTO has also been described as a major eraser of N⁶,2'-O-dimethyladenosine (m⁶A_m) nucleotide and thus regulator of small nuclear RNA processing.⁴⁴ On the other hand, ALKBH3 also demethylates N¹-methyladenosines in both mRNAs and transfer RNAs (tRNAs).^{45–47} ALKBH5 is currently understood as an m⁶A-dedicated eraser principally localizing to nuclear speckles.³⁸ All these erasers depend on both α-ketoglutarate and molecular oxygen as co-substrates and Fe²⁺ as a cofactor. The readers of m⁶A, crucial for mediating its downstream effects, fall into three major categories based on their principal ways of binding to m⁶A-RNA: direct binders to the m⁶A, indirect binders to the m⁶A-dependently altered RNA secondary structures, and binders that are specifically repelled from their binding sites in RNA following m⁶A deposition (Figure 1). The two m⁶A reader families that contain an m⁶A-binding YT521-B homology (YTH) domain; the YTH N⁶-methyladenosine RNA-binding proteins 1, 2, and 3 (YTHDF1, YTHDF2, and YTHDF3, respectively); and YTH domain containing 1 and 2 (YTHDC1 and YTHDC2, respectively) constitute a major set of investigated direct readers.³⁸ These also include proline-rich

coiled-coil 2 A (PRCC2A) protein, eukaryotic initiation factor 3 (eIF3), METTL3, and ribosomes themselves.³⁸ Several indirect readers have been identified: heterogeneous nuclear ribonucleoproteins A2/B1, C, and G (HNRNPA2/B1, HNRNPC, and HNRNPG, respectively); insulin-like growth factor 2 mRNA-binding proteins 1, 2, and 3 (IGF2BP1–3); and fragile X mental retardation protein (FMRP).³⁸ Last, the lin-28 homolog A (LIN28A), EWS RNA-binding protein 1 (EWSR1), and G3BP stress granule assembly factor 1 (G3BP1) have been described to be repelled from their RNA-binding site following m⁶A methylation.³⁸

In vertebrates, A-to-I editing is carried out by three families of deaminases acting on dsRNA: ADAR (adenosine deaminase RNA specific) family in all tissues, ADAD (adenosine deaminase domain-containing) family principally in testes or brain and ADAT (tRNA adenosine deaminase) family solely targeting tRNAs.²⁷ While no cofactors for these writers have been identified, inositol hexakisphosphate has been shown to complex within the enzymatic core of adenosine deaminase RNA-specific B1 (ADAR2) and thus to be imperative for its (as well as proper editing function of ADAT1 [adenosine deaminase tRNA specific 1]).⁴⁸

While the ADAD family contains two members, *ADAD1* (adenosine deaminase domain containing 1) and *ADAD2* (adenosine deaminase domain containing 2), the ADAR family consists of three members: *ADAR1* (adenosine deaminase RNA specific), *ADAR2*, and *ADAR3* (adenosine deaminase RNA specific B2 [inactive]). Only *ADAR1* and *ADAR2* proteins have catalytic activity.²⁷ *ADAR1* gene is transcribed from two start sites to produce two N-terminally distinct isoforms, a longer and interferon (INF)-inducible *ADAR1* p150 and a shorter constitutively expressed *ADAR1* p110 isoform. *ADAR2* mRNA can undergo extensive alternative splicing in a tissue-specific manner.⁴⁹ All ADARs can directly bind dsRNA. For effective deamination, *ADAR1* and *ADAR2* undergo homodimerization. However, *ADAR3* cannot homodimerize, which has been postulated as a reason for its lack of A-to-I editing activity.²⁷ *ADAR2* is predominantly localized to the nucleus, but the *ADAR1* isoforms exhibit specifically regulated nucleocytoplasmic shuttling.²⁷

No enzymes converting inosine back to adenosine have been described. However, human antigen R (HuR), or ELAV-like RNA-binding protein 1 (ELAVL1), inosine-dependently binds RNA,⁵⁰ and endonuclease V (ENDOV)⁵¹ has been reported to cleave specifically at highly inosine-modified *Alu* sequences functioning thus as readers or effectors.

Current literature assigns diverse functions to m⁶A ranging from regulation of RNA secondary structures,³⁹ stability,⁵² translation efficiency,⁵³ compartmentalization, and degradation³⁹ to regulation of proliferation,^{54,55} motility,^{56–58} paracrine signaling,⁵⁹ phenotype,⁶⁰ and cell fate decisions.⁶¹ In addition, m⁶A RNA has been implicated as a critical contributor to numerous pathologies, including cancer, immunological and metabolic diseases, as well as CVDs.^{62,63} Indeed, m⁶A has emerged as a tissue- and context-specific hub that mediates cellular stress responses, as recently reviewed.⁶⁴ Also, A-to-I modifications participate in a multitude of RNA-related processes, including RNA stability, secondary structure and accessibility modifications, exon and intron editing, and both microRNA (miRNA) maturation and subsequent target specifications.^{27,65–68} The formed inosines are capable of altering the RNA secondary structure by disrupting the Watson-Crick base pairing to unwind the dsRNAs and form more immune-tolerable single-stranded RNAs (ssRNAs).²⁷ Indeed, ADAR1 deficiency has been linked with accumulation of intracellular dsRNAs, activation of interferon production, and various auto-inflammatory diseases.²⁷ A-to-I editing has also proved essential for the maintenance of hematopoiesis and has been linked with regulation of innate immune responses,⁶⁹ development of cancer,⁷⁰ and maintenance of neurologic functions.²⁷

N⁶-METHYLADENOSINE AND A-TO-I MODIFICATIONS IN CARDIOVASCULAR DISEASES

We begin this section by discussing RNA m⁶A and A-to-I modifications in heart development and regeneration. Next, we move on to hypertension in its various forms and its most common cardiac complications, cardiac hypertrophy, and HF. We then discuss m⁶A and A-to-I modifications in atherosclerosis, myocardial ischemia, hypoxia, fibrosis, and angiogenesis. The concluding sections consider the accumulated observations regarding aortic valve calcification and aortic aneurysms.

Figure 2 offers an overall summary of studies that have assessed either m⁶A or A-to-I RNA modifications in cardiovascular development, physiology, or disease.^{50,54–58,60,65–68,71–166,171,175} Figures 3 and 4 offer more detailed mechanistic summaries of the molecular interactions and pathways involving m⁶A and A-to-I modifications within pathophysiology of the most common vasculopathies and according to IHD pathophysiology toward HF, respectively. The current understanding of molecular pathways involved in obesity and diabetic cardiomyopathy is presented in Figure 5, in atherosclerosis in Figure 6, and pathways involved in monocyte/macrophage activation, inflammation, and foam cell formation in Figure 7.

The key observations on the roles of m⁶A modification and A-to-I editing in the cardiovascular system are listed in Tables S1 and S2, respectively. Table S3 further details the interventional results regarding m⁶A regulators in CVD models. Finally, Table S4 provides a molecular-level view into the known interactions and pathways involving the epitranscriptomic m⁶A and A-to-I modifications in cardiovascular disease.

Cardiogenesis and cardiac regeneration

Heart development begins early during organogenesis, and a four-chamber heart is already established at weeks 5–8 of gestation.¹⁶⁷ While in adult mammals the heart grows in size through hypertrophic adaptation and increased cell volume, in cardiogenesis the cardiomyocyte precursors proliferate and increase in number before differentiating into mature cardiac tissue.

A-to-I editing

The global knockouts of either *Adar1*^{-/-} or its cytosolic isoform *Adar p150*^{-/-} are nonviable due to multiple organ failures and massive global apoptosis dominating especially in the heart.^{69,168–170} Cardiomyocyte-directed ADAR1 knockouts also die because of massive cardiomyocyte apoptosis.¹⁶¹ On the other hand, ADAR p110 has been shown to be redundant for the viability of human embryonic stem cells.¹⁷¹ Deletion of either the dsRNA sensor, a melanoma differentiation-associated protein 5 (MDA5), or its downstream effector, a mitochondrial antiviral-signaling protein (MAVS), can extend the survival of *Adar1*^{-/-} mice to an immediate postpartum period. Moreover, no cardiac abnormalities were reported in the double-knockout *Adar1*^{-/-} *Mavs*^{-/-} mice. Hence, ADAR1-induced and A-to-I editing-mediated unwinding of dsRNAs seem to act as a cardiomyocyte survival pathway by keeping the dsRNA-triggered INF–MDA5–MAVS–endoplasmic reticulum (ER) stress-axis activation downstream at bay.^{172–175} El Azzouzi et al. demonstrated that knocking down ADAR1 in a cardiomyocyte-specific manner after birth induced a robust unfolded protein response (UPR)-dependent cardiomyocyte apoptosis and ventricular remodeling, which culminated in rapidly deteriorating cardiac contractile function and death.¹³⁰ In light of the above findings and considering activation of ER stress response and UPR is central in not only IHD,^{176,177} HF,^{178,179} but also in CVDs in general,¹⁸⁰ the contribution of ADAR1 p150 in controlling the MDA5–MAVS–INF-axis, ER stress, and activation of UPR in the myocardium warrants further investigation.

Unlike ADAR1, ADAR2 appears redundant for cardiogenesis. *Adar2*^{-/-} mice selectively retaining A-to-I modifications only in glutamate ionotropic receptor AMPA type subunit 2 (*GluA2*) mRNA, mandatory for murine embryogenesis and immediate postpartum development,^{181,182} had no alterations in heart morphology, relative weight, blood pressure, or atrial natriuretic peptide expression.^{132,162} Although the functional role of ADAR3 remains to be characterized in cardiogenesis, its expression in the heart greatly diminishes after birth.¹⁷¹

Interestingly, ADAR1 expression is upregulated in the regenerating hearts of tailed amphibians, and the protein is translocated from

N⁶-METHYLADENOSINE AND A-TO-I RNA EDITING

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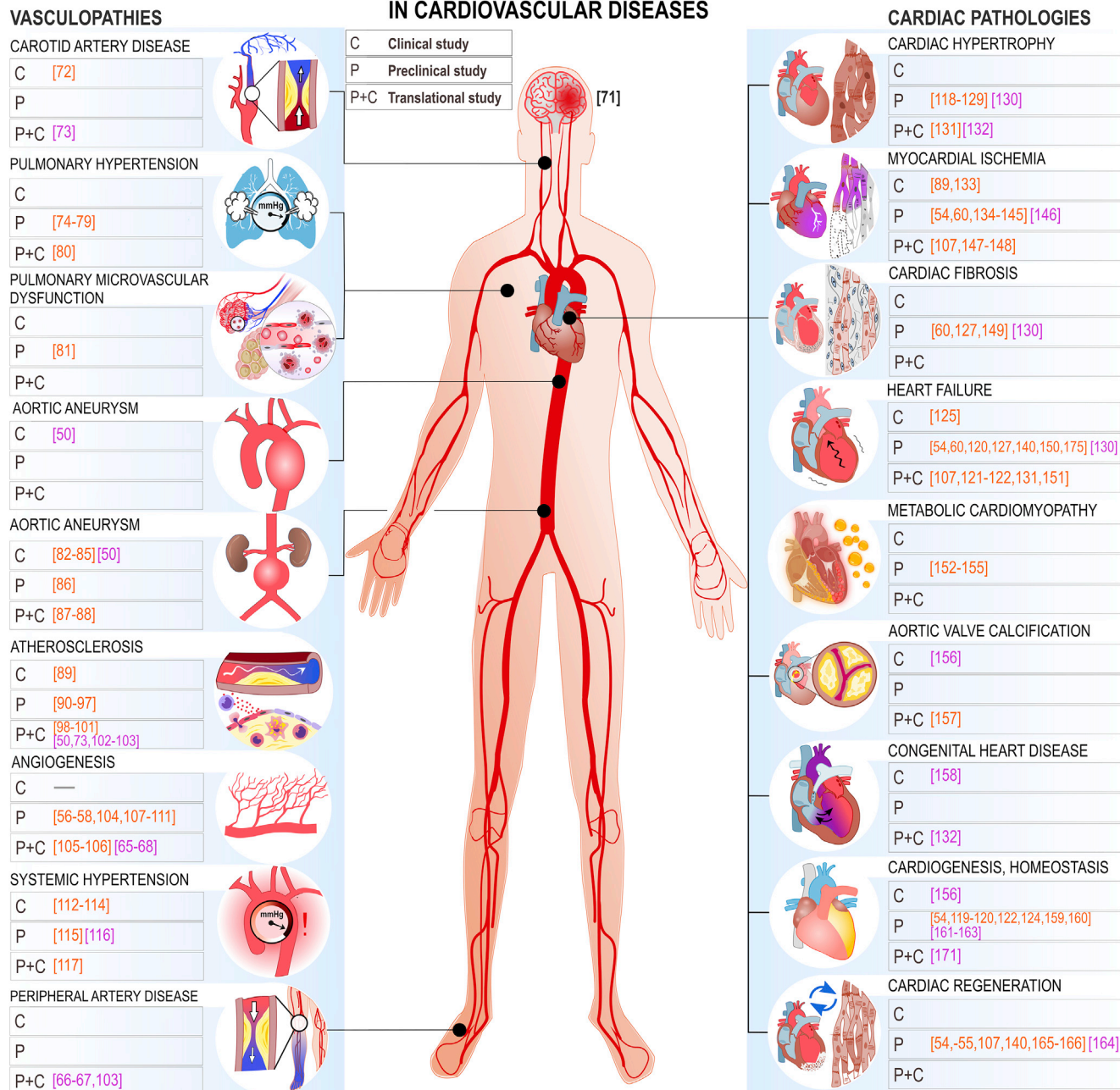


Figure 2. A schematic overview of the studies assessing m⁶A modification and A-to-I editing in CVDs to date

Colored numbers denote specific original publication reference. The black-colored reference⁷¹ forwards interested readers to a recent review specifically discussing the role of epitranscriptomic modifications in brain physiology and diseases, which is out of topic of the present review.

the nucleus to the cytoplasm.¹⁶⁴ Moreover, in ADAR1 knockouts, the ability for cardiac regeneration is lost.¹⁶⁴ In human nerve cells *in vitro*, analogous exportin-5-dependent nucleus-to-cytoplasm translocation of ADAR p110 (a mammalian counterpart for newts' ADAR1¹⁶⁴) is controlled through its phosphorylation by MKK6-p38-MSK1/2 ki-

nases (MAP kinase kinase 6-p38 kinase-mitogen- and stress-activated protein kinases 1 and 2).¹⁸³ In the cytoplasm, ADAR p110 then acts as a stress-response mediator preserving antiapoptotic mRNAs from Staufen1-mediated degradation by editing their dsRNA segments.¹⁸³ As such, the role of MKK6-p38-MSK1/2-ADAR

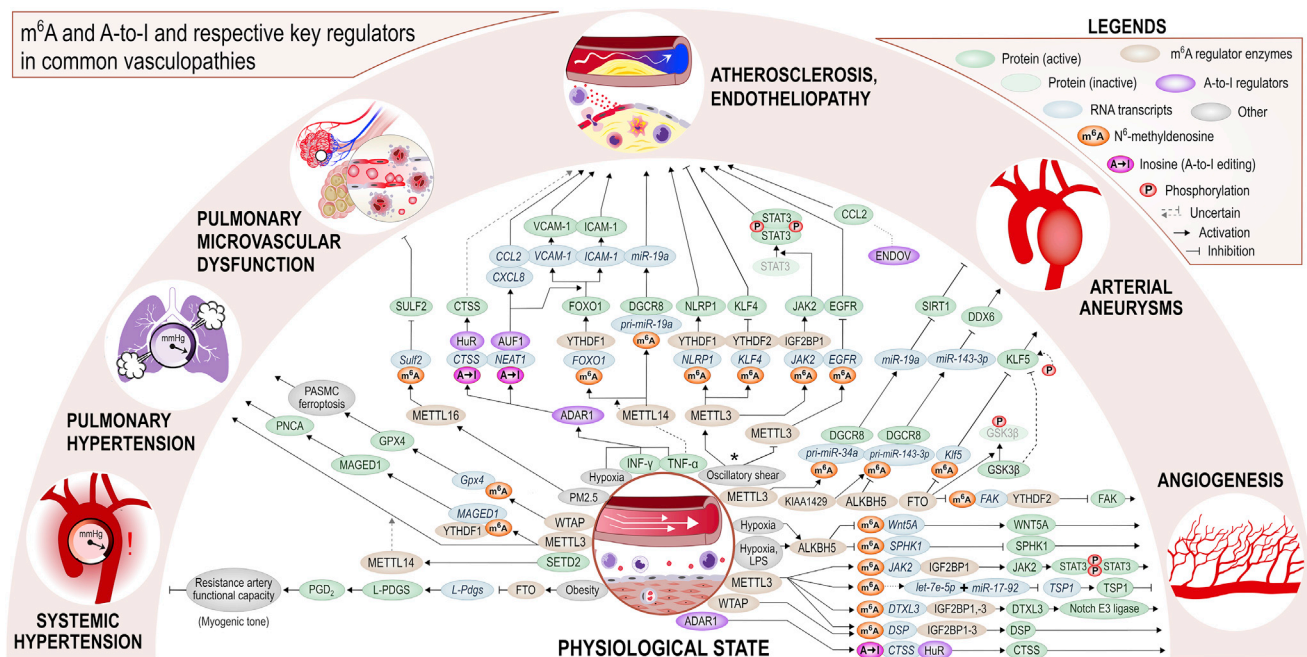


Figure 3. The unveiled molecular interactions involving m⁶A and A-to-I or respective key regulators in common vasculopathies and non-malignant angiogenesis

The number of blunted arrows for a given pathway can be used as a guide for assessing the overall effect of the pathway. *METTL3 has been described both as proatherogenic and antiatherogenic factor in endothelium subjected to oscillatory shear stress, see later discussion in section "atherosclerosis." **The direct role of m⁶A upregulating the respective downstream miRNAs remains putative. The role of m⁶A and A-to-I editing in atherosclerosis pathophysiology is presented in greater detail in Figures 6 and 7. References are listed within Table S4 according to molecular pathways illustrated here. PM2.5, fine particulate matter, diameter <2.5 μm; SULF2, sulfatase 2.

p110–Staufen1 merits further investigation as a putative mechanistic regeneration target pathway. In humans, ADAR p110 expression is enriched in the atria,¹³² and its expression is increased most in congenital septal defects.¹³²

ADAR2 also appears to be a tentative target to instigate cardiac regeneration as its overexpression stimulates proliferation and suppresses apoptosis in rat cardiomyocytes.¹⁴⁶ Regarding a putative underlying molecular mechanism, ADAR2-mediated pri-miR-34a editing, which inhibited the formation of mature miR-34a via a yet veiled mechanism, induced an upregulation of its downstream proliferation-related targets Sirtuin1, Cyclin D1, and B-cell leukemia/lymphoma 2 (Bcl2) protein.¹⁴⁶ The negative regulation of *Adar2* promoter was suggested to be due to binding of transcription factor CCAAT/enhancer-binding protein β (C/EBPβ).¹⁴⁶ As discussed later, these effects were later recapitulated in a model of myocardial infarction (MI) *in vivo*.

m⁶A modification

Akin to A-to-I editing, m⁶A has been shown to be imperative for embryogenesis.⁶¹ Without the m⁶A writer METTL3, embryonal¹⁸⁴ and hematopoietic stem cells (HSCs)¹⁸⁵ lose their self-renewal ability and accumulate cytosolic dsRNA (albeit contrasting roles have also been reported¹⁸⁶). No such similarity between these modifications is seen during cardiogenesis or imminent postnatal growth. Cardiomyocyte-specific METTL3-knockout mice demonstrate no signs of

altered cardiac histopathology, hypertrophy, or dysfunction up to 3 months after birth.¹²⁰ At 8 months of age, however, they develop dilated, relatively thin-walled hearts (eccentric hypertrophy), cardiac dysfunction, and major lethality, a classic pathophenotype of dilated cardiomyopathy (DCM).¹²⁰ *Mettl14*^{+/-} mice have also demonstrated with normal cardiac structure and function at 10 weeks of age.¹⁴³ Nonetheless, some focused m⁶A activity appears indispensable for postnatal cardiac development as heart-specific conditional knockout YTHDC1 m⁶A reader protein has been described to result in premature death of mice at 2–3 months of age due to disrupted m⁶A-dependent splicing of *Titin* pre-mRNA, accompanied by destructed sarcomere organization, DCM, and ultimately HF.¹⁵⁰ On the other hand, cardiogenesis and postnatal development seem to proceed normally in knockout mice lacking YTHDF1,^{150,187} YTHDF2,¹⁸⁸ YTHDF3,¹⁵⁰ ALKBH5,^{54,189} or either global¹¹⁹ or cardiomyocyte-targeted FTO knockout.¹²² *In vitro*, however, YTHDF1 promotes embryonic stem cell (ESC)-derived cardiomyocyte differentiation, and YTHDF3 preserves their pluripotency via a mechanism that seems unrelated to the established key transcriptional regulation pathway including transcription factors nanog homeobox (NANOG), SRY-box transcription factor 2 (SOX2), and POU class 5 homeobox 1 (POU5F1).¹⁶⁰ The expression of METTL3 and METTL14, as well as the abundance of m⁶A in RNAs, are evenly distributed in embryonic hearts, and their expression is increased by the histone deacetylase inhibitors valproic acid and Trichostatin A.¹⁵⁹

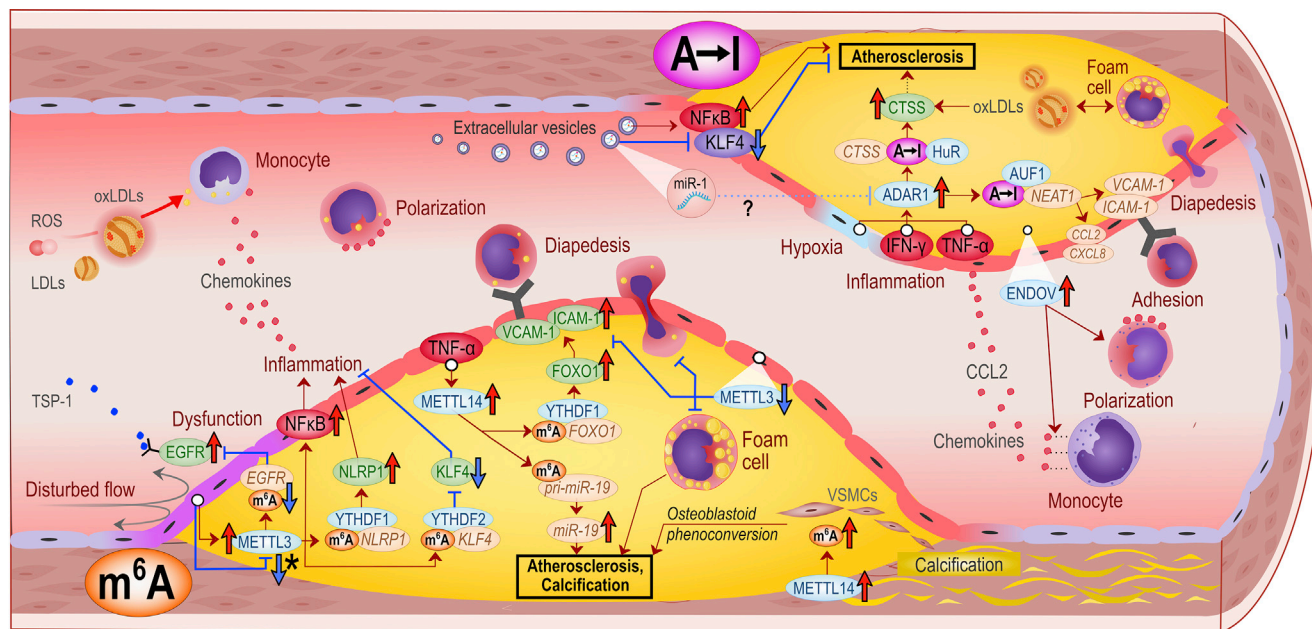


Figure 6. A summary of the key discoveries regarding adenosine-targeted epitranscriptomic alterations in atherosclerosis and arteriosclerosis to date

Red upward arrows indicate upregulated expression, red horizontal arrows indicate activation, blue downward arrows denote downregulated expression, and blue blunt-end arrows indicate inhibition. . Brown, green, and blue ellipses denote RNAs, proteins, and m⁶A regulators, respectively. Question mark represents a putative connection based on evidence from other than atherosclerotic tissues. *METTL3 has been associated with contrasting functions and expression responses in a model of early atherosclerosis with endothelial oscillatory shear stress. See section “atherosclerosis” for further discussion. The abbreviations are listed within the text.

(*Cdc42*) mRNA in its three prime untranslated region (3′UTR).^{124,209} An FTO-regulated m⁶A- and IGF2BP2-dependent increase in miR-133a repression of *Cdc42* mRNA was shown to inhibit mouse neonatal cardiomyocyte proliferation.¹²⁴ Interestingly, the myocardial expression of miR-133a increases notably at 1 week after birth, at time of closure of the mouse regenerative window.¹²⁴

Taken together, while overexpression of m⁶A erasers has been shown to increase cardiomyocyte proliferation, preserve myocardial function, and promote cardiac regeneration, the role of the METTL3 m⁶A writer in these processes appear more complex. While METTL3 knockout decreases RNA m⁶A content and promotes regenerative cardiac healing in mice, similar to eraser overexpression,¹⁴⁰ the role in rats appears to be the opposite.^{55,147} It is clear that these findings stress the need for species-specific considerations, but further efforts to identifying downstream responsive molecular pathways for potential therapeutic intervention to promote cardiac regeneration are also warranted.

Congenital heart disease

Developmental heart malformations are found in approximately 0.8% of births.²¹⁰ From whole-blood-derived RNA extracts collected from children with congenital heart disease and cyanosis, Borik et al. linked increased A-to-I levels of mediator complex subunit 13 (*MED13*) mRNA with reduced ADAR2 expression.¹⁵⁸ *MED13* is associated with hypertrophy and angiogenesis, and is regulated upstream by

miR-208, which is abundantly expressed in the heart.²¹¹ miR-208 has been further described as a promising target for therapeutic inhibition in failing heart²¹² and crucial for cardiac expression of GATA-binding protein 4 (GATA4),²¹³ a well-established transcription factor regulating cardiomyocyte phenotype, cardiogenesis, and regeneration.²¹⁴ In fruit flies, loss-of-function mutation of ADAR abates their ability to survive for hours in severe hypoxia due to impaired editing of various central nervous system (CNS)-expressed ion channel mRNAs.²¹⁵ Moreover, ADAR2 is repressed during mammalian CNS hypoxia.²¹⁶ Combined, increased A-to-I editing of blood *MED13* mRNA might represent a coping mechanism for cyanosis in children with congenital heart disease. Further, the repression in ADAR2 expression could offer access to more editing sites for the ADAR1, thus providing a possible explanation for the increased editing in *MED13* but concomitantly reduced ADAR2. *MED13* mRNA has later been shown to undergo variable transcript site-specific A-to-I editing within the transcript’s *Alu* repeat in a lymphoblastoid hypoxia cell model.²¹⁷ Consistent with the above findings, a markedly reduced expression of ADAR2 (~90%) and up to 8-fold increases in both ADAR1 p150 and p110 isoforms were reported in the blood cells of children suffering from either cyanotic or acyanotic congenital heart disease.¹³² Remarkably, based on mRNA expression analyses from samples derived from the Genotype-Tissue Expression (GTEx) project, the same study also measured both *ADAR1 p150* and *p110* isoforms to be upregulated 2- to 14-fold and *ADAR2* to be markedly downregulated (~75%–95%) specifically within human

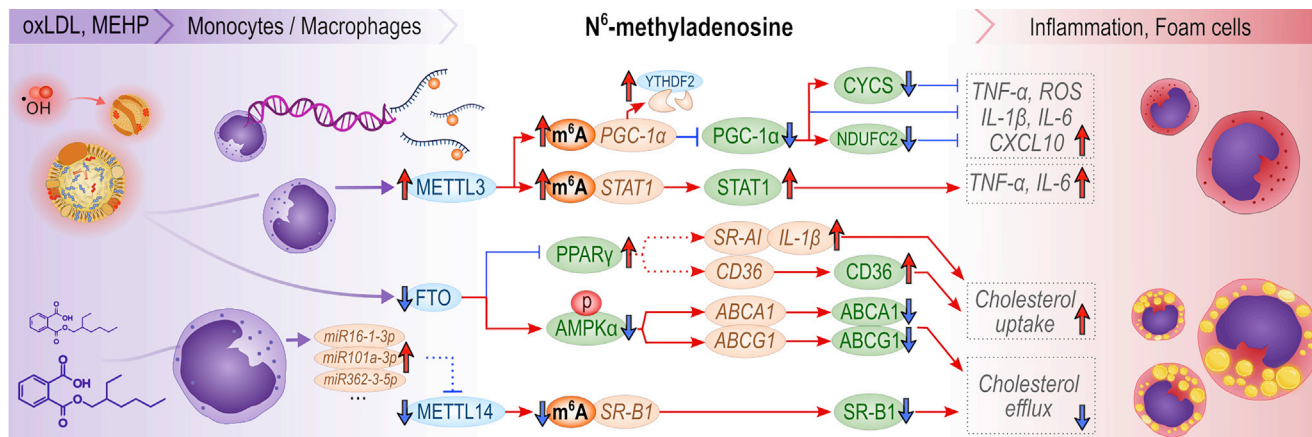


Figure 7. Currently known molecular mechanisms involving m⁶A and its key regulators during macrophage inflammation and foam cell formation

Red upward arrows indicate upregulated expression, red horizontal arrows indicate activation, blue downward arrows denote downregulated expression, and blue blunt-end arrows indicate inhibition. Dashed line represents putative relationship. Brown, green, and blue ellipses denote RNAs, proteins, and m⁶A regulators, respectively. Red ellipse denotes phosphorylation. ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; AMPK α , AMP-activated protein kinase α ; CXCL10, C-X-C motif chemokine ligand 10; PPAR- γ , peroxisome proliferator-activated receptor γ ; SR-A1, scavenger receptor class A member 1; STAT1, signal transducer and activator of transcription 1.

hearts in variable congenital heart diseases. The most pronounced up-regulations have been found in different septal defects.¹³²

Cardiovascular homeostasis

Regulation of cardiovascular homeostasis is crucial due to its absolute necessity for complex mammalian life. In humans, regulatory tracts from high- and low-pressure chemo- and baroreceptors converge upstream in the medulla to signal through sympathetic nerves and the cardiac plexus to both the heart²¹⁸ and its vessels.²¹⁹ The endocrine and paracrine regulation dominantly comprise myocardium-secreted natriuretic peptides,²²⁰ renin-angiotensin-aldosterone axis,²²¹ pituitary antidiuretic hormone, and oxytocin,²²² as well as catecholamines from adrenal medullae.²²³ While the sinus node governs autonomous cardiac contractions,²²⁴ the cardiac sarcomeres provide further functional contributions by modulating their contractility based on their level of stretching.²²⁵ Moreover, arterial flows are autoregulated in several organs, including brain²²⁶ and kidneys,²²⁷ to ensure stable flow of oxygen and nutrients despite otherwise varying systemic blood pressure.

m⁶A modification

The expression levels of m⁶A writers and erasers in heart have been reported to differ across species and according to age.^{107,122,124,134} However, a study specifically aiming to characterize the murine baseline cardiac distribution of the various m⁶A writers observed a prominent downregulation of METTL3 and METTL14—and abolished METTL16—expressions within adult myocardium compared with the embryonic state.¹⁵⁹ Interestingly, single-cell sequencing has unveiled the m⁶A writing complex's subunit WTAP to be widely expressed within adult human heart with highest enrichment within myocardial endothelium.¹³³ Moreover, the m⁶A eraser FTO seems to hold the highest expression levels of the core m⁶A governing en-

zymes within both human and murine myocardium.^{107,122,124} The abundance of m⁶A-methylated RNAs in the human myocardium (14.6%, 1,239 modified transcripts) is less than that in adult mice (24.1%, 3,208 modified transcripts).^{121,122} Moreover, myocardial m⁶A residues are potently—up to 10-fold—enriched on mRNAs compared with total RNA.^{107,120} For the sake of perspective, in adult pig livers,²²⁸ mice brain,²²⁹ and isolated basal skin progenitor cells,²³⁰ corresponding fractions of m⁶A-methylated mRNAs have measured 33% (~1.3 residues/modified gene, 4,339 modified transcripts), 53%–83% (~1.8–2.4 residues/gene, 704–1,392 modified transcripts), and 11,420 modified transcripts (~13.8 residues/modified transcript), respectively. These findings suggest that the activity of myocardial m⁶A erasers dominate over that of the m⁶A writers in the human adult heart. Such postulation is further supported when considering the preceding stoichiometric estimations suggesting each mRNA to harbor ~1–3 sites for m⁶A DR(A/m⁶A)CH consensus sequence and residues as well.^{41,42,231} Interestingly, the myocardial m⁶A residues are enriched within the translation end-sites within coding sequence (CDS) and in the beginning of the 3'UTR,¹²² a key region for translational control.²³² Although there are considerable differences in the nature of these methylated transcripts between humans and mice, they generally associate with such pathways as cardiogenesis, vasculogenesis, and energy deprivation-related oxidation.¹²²

As myocardial m⁶A modifications correlate poorly with the overall transcript abundance in the physiological state,¹²² the role of m⁶A readers is emphasized. Indeed, following METTL3 overexpression, there is an overall increase in cardiomyocyte transcriptome m⁶A content, which induces contrasting effects in terms of transcript stability at level of single transcripts. Namely, both decreased (ρ guanine nucleotide exchange factor 3 [*Arhgef3*]) and increased (myosin light chain 2 [*Myl2*]) mRNA transcript half-lives have been measured.¹²¹

Similarly, there are variable effects on transcript stability at the single-transcript level in response to METTL3 silencing.⁵⁵ Hence, a better understanding is warranted regarding the still considerably veiled functions of the m⁶A readers, such as the YTHDF family and the highly expressed IGF2BP2 within baseline myocardium.²³³

A-to-I editing

As discussed above, ADAR1 is imperative for adult cardiac homeostasis, as conditional ADAR1 knockout induces 60% mortality within 3 weeks after knockout induction due to severe cardiac dysfunction with both ER stress and UPR activation as partial underlying mechanisms to the phenotype.¹³⁰ Both ADAR p110 and ADAR2 are enriched in the atria.¹³² In a comprehensive comparison panel of tissue expressions, ADAR p110 was measured high in the nervous system and ADAR p150 dominated in vascular tissues, including aorta, and coronary as well as tibial arteries.¹³² ADAR2 is enriched in arterial tissues¹³² and its expression is reduced in various congenital cardiac malformations.¹³² In *Adar2*^{-/-} mice myocardia, rescued from embryonic lethality via introduction of a pre-edited *GluA2* mRNA,^{181,182} multiple heart-related miRNAs were downregulated, but ADAR1 expression was not induced.¹³² The most repressed miRNAs were miR-29b, miR-451b, and miR-451a, leading to increased transcription of genes including collagen type I alpha 2 chain (*Col1a2*) and insulin-like growth factor 1 (*Igf-1*).¹³² Moreover, based on the decreased A-to-I editing rate of myocardial filamin B, the authors hypothesized filamin B editing to play a still-hidden function in cardiovascular system,¹³² similarly as filamin A (FLNA) has been unveiled in hypertension.¹¹⁶ ADAR2 has been measured with identical expression levels in *ex vivo* extracted cardiac fibroblasts and cardiomyocytes.¹⁴⁶

Hypertension

Hypertension, or sustainedly elevated blood pressure, either triggers or associates with multiple cardiovascular disease processes, such as atherosclerosis,²³⁴ cardiac hypertrophy,²³⁵ coronary microvascular dysfunction,²³⁶ IHD, MI, stroke, and HF,^{237–240} as well as kidney disease and failure.²⁴¹ It is considered the leading cardiovascular disease to cause premature deaths.²⁴² While hypertension represents a prototypic multifactorial disease with multiple risk factors and varying etiologies, essential hypertension, where no specific etiology is identified, comprises 90% of cases and has been defined as a vascular pandemic due to its estimated staggering worldwide prevalence of 1.39 billion individuals.²⁴³

m⁶A modification

Emerging evidence from human functional genome-wide association studies suggest that m⁶A-related single-nucleotide polymorphisms (m⁶A-SNPs) are associated with elevated blood pressure.¹¹² These are linked to blood mononuclear cells' expression of hypertension-associated molecules, including zinc-finger protein 589 (ZNF589), β 1-adrenergic receptor, and Golgi SNAP receptor complex member 2 (GOSR2).¹¹³ ZNF589 is a member of Krüppel-associated box domain zinc-finger family of epigenetic regulators known to maintain pluripotency in HSCs,²⁴⁴ and adrenergic β 1-receptor is an independent factor in predicting the treatment outcome for hypertension

with β -blockers.²⁴⁵ The hypertension-associated m⁶A-SNP (Lys67Arg) in the *GOSR2* gene is the same as previously associated with the disease.²⁴⁶ However, experimental approaches are imperative to properly evaluate whether a functional role exists for these target gene m⁶A-SNPs in hypertension.

As an additional link between epitranscriptomics and hypertension, an SNP-variant of FTO has been associated with obesity and elevated systolic blood pressure.¹¹⁴ The contribution of FTO to vascular tone was hypothesized to be governed by two specific hypothalamic nuclei,²⁴⁷ which are known to substantially express FTO.²⁴⁸ However, a more pertinent and peripheral mechanism of action for FTO in hypertension has recently been identified. Conditional endothelium-targeted knockout of FTO during continuous lipid-diet-induced obesity, vascular dysfunction, and hypertension was found to be protective against hypertensive phenotypes via a novel FTO-mediated pathway controlling myogenic tone.¹¹⁷ Specifically, the loss of FTO upregulated endothelial prostaglandin D₂ (PGD₂) production via overexpression of its main synthase, lipocalin-type prostaglandin D synthase (L-PGDS), in resistance arteries, and thus alleviated specifically obesity-induced vascular dysfunction and hypertension but did not alter the baseline blood pressure.¹¹⁷ It is of translational and therapeutic interest that human artery specimens from obese individuals have been reported to overexpress FTO, and its pharmacological inhibition with either rhein or FB23-2 *ex vivo* also exerted favorable increases in both prostaglandin D₂ production and myogenic tone.¹¹⁷ In addition, considering that the upstream regulatory pathway responsible for the noted FTO upregulation in endothelium remains veiled, it is interesting to combine a notion that leptin, a major adipocyte-secreted systemic adipokine, has been shown to upregulate FTO in cardiomyocytes.¹¹⁸ In contrast to its beneficial role in ischemic HF (discussed later), upregulated FTO has been described as detrimental in hyperlipidemia-induced cardiomyopathy.¹⁵⁴ Hence, investigations assessing the role of leptin possibly also regulating endothelial and cardiomyocyte FTO expression in obesity-related hypertension and cardiomyopathy might reveal an unrecognized mechanism within their development.

Last, in pericytes of spontaneously hypertensive rats, the overall m⁶A methylome has been reported to be hypomethylated, which not only suggests either increased m⁶A eraser or decreased writer activity but also underlines the putative role of also other vascular cell types within hypertension development from an epitranscriptomic point of view.¹¹⁵ Taken together, although reports regarding m⁶A in hypertension remain limited, it is evident that targeted investigations to promote our understanding of m⁶A in hypertension control are needed.

A-to-I editing

Interestingly, hypoxic A-to-I editing of miR-27a-3p, which has been established to regulate endothelial *GOSR2* mRNA expression,²⁴⁹ has been shown to induce a major shift on its targetome.²⁵⁰ In aortas from hypertensive patients and mice, major ADAR2-mediated A-to-I editing events were identified in the vasculature in the actin crosslinking protein *Flna* mRNA.¹¹⁶ *FLNA* A-to-I editing is scarce

in human fetal hearts (3%) and increases considerably in adulthood (15%).¹⁷¹ Reduced *FLNA* mRNA editing, as found in human post-mortem aortic-arterial samples, strongly correlated with left ventricular hypertrophy, a strong indicator of significant hypertension during life.²⁵¹ Moreover, when *Flna* mRNA was rendered uneditable by deletion of its 228-bp intronic region, transgenic mice demonstrated increased perivascular fibrosis, diastolic blood pressure, and left ventricular hypertrophy that finally progressed to cardiac dysfunction.¹¹⁶ In hemizygotic *Flna*^{0/+} mice, vascular smooth muscle cell (VSMC)-restricted and tamoxifen-induced *Flna* knockout (*smFlna*^{0/-}) led to a drop in basal blood pressure due to impaired calcium influx and mechanotransduction.²⁵² However, global ADAR2 knockout mice have been reported to have unaltered blood pressure profiles.¹⁶²

Pulmonary hypertension

Hypertension of the pulmonary circulation is estimated to affect 1% of the global population.²⁵³ Increased pulmonary pressure greatly increases the workload of the right ventricle, which is prone to develop irreversible dilatation and failure, *cor pulmonale*, which is associated with up to 60% mortality when acute and unstable.²⁵⁴ Histopathologically, pulmonary hypertension is hallmarked by overt proliferation of VSMCs with consequent muscularization of the pulmonary artery walls. Current drugs fall short in both tackling its underlying pathophysiology and managing its disabling symptoms.²⁵⁵

m⁶A modification

While m⁶A has emerged as a regulator and potential therapeutic target in pulmonary hypertension,⁸¹ to the best of our knowledge—excluding an indirectly-relevant report observing ADAR1 to promote VSMCs proliferation and neointima formation²⁵⁶—no reports currently exist describing A-to-I editing in pulmonary hypertension. In a hypoxic pulmonary hypertension rat model, Su et al. identified several m⁶A-modified circular RNAs (circRNAs) affecting circRNA-miRNA-mRNA interactions.⁷⁴ Hyperproliferation of rat pulmonary artery smooth muscle cells (PASMCs) was associated with increased METTL3 expression. Increased m⁶A on phosphatase and tensin homolog (*Pten*) mRNA led to reduced PTEN expression in a YTHDF2-dependent manner involving the phosphoinositide 3-kinase-AKT serine/threonine kinase 1 (PI3K-Akt) pathway.⁷⁵ Moreover, YTHDF1 is upregulated alongside increased m⁶A contents in hypertensive pulmonary arteries, which were shown to promote hyperproliferation of human PASMCs *in vitro* as well as pulmonary hypertension development *in vivo* by increasing m⁶A-dependently translation of melanoma antigen gene (MAGE) family member D1 (*MAGED1*) mRNA, expression of subsequent protein, which finally led to upregulation of proliferating cell nuclear antigen (PCNA).⁸⁰ Knockdown of METTL3 abrogated all these effects.⁸⁰ Interestingly, a recent report suggests WTAP to promote PASMC ferroptosis,⁷⁹ a recently discovered morphologically (mitochondrial diminution), biochemically (iron-dependent reactive oxygen species [ROS] production), and genetically (independent of proapoptotic genes) distinct form of programmed cell death that, as recently reviewed, has been found to operate in many CVDs.²⁵⁷ Specifically, WTAP was pinpointed as proferroptotic in PASMCs via m⁶A-dependent enhanced

translation of glutathione peroxidase 4 (*Gpx4*) mRNA and subsequent GPX4 expression.⁷⁹ Further, administration of an ferroptosis inhibitor, ferrostatin-1, ameliorated pulmonary hypertension *in vivo*.⁷⁹ Moreover, WTAP has also been implicated in VSMCs hyperproliferation, a key process in pulmonary hypertension by promoting artery wall muscularization. Namely, Panax notoginseng saponin was shown to inhibit VSMC hyperproliferation via upregulating WTAP and m⁶A.²⁵⁸

Histopathologically, while the pulmonary artery-isolated rat PASMCs upregulate METTL3 writer in hypoxia, and the m⁶A erasers FTO and ALKBH5 are downregulated, m⁶A writer complex subunits METTL14 and WTAP remain unaltered.⁷⁵ On the other hand, no alterations at a level of mRNA in either *Mettl4*, *Wtap*, *Fto*, or *Alkbh5* were observed in hypoxic and hypertensive rat pulmonary arteries *in vivo*.⁷⁵ Upregulation of METTL13 and YTHDF1, and downregulation of FTO and ALKBH5, have been reported in both murine and human adult hypertension-tormented pulmonary arteries and parenchyma.^{78,80} No changes were observed in the expression of the majority of other m⁶A regulators, including METTL14, VIRMA, RBM15, YTHDF2-3, YTHDC1-2, or IGF2BP1-3.⁷⁸ Contrary to the above findings, lung tissue of rat pups with hypoxic pulmonary hypertension showed downregulated levels of m⁶A residues in RNAs, and decreased expression of METTL3, METTL14, FTO, and ALKBH5.⁷⁷

Together, the above differences delineate age-, tissue-, and cell-specific alterations of m⁶A regulators in pulmonary hypertension, thus highlighting the need for more cell-type-specific investigations. These investigations could include pulmonary endothelial cells (which seem to be enriched with YTHDF1 in human idiopathic pulmonary hypertension and fibrosis⁸⁰), fibroblasts, resident leukocytes, and pulmonary cells of the lung parenchyma. A recent study by Zhou et al. elegantly unveiled a cell-specific function for an epigenetic regulator SET domain containing 2, histone lysine methyltransferase (SETD2), in hypoxic pulmonary hypertension with its VSMC-targeted knockout as a pulmonary hypertension-promoting regulator and positive upstream regulator of METTL14 *in vivo*.⁷⁶

Altogether, as the m⁶A erasers are consistently downregulated within various pulmonary hypertension tissue specimens, and METTL3 knockdown effectively abrogates pathology development,⁸⁰ reducing overall m⁶A content could constitute an avenue for therapeutic benefit.

Cardiac hypertrophy and failure

Adult differentiated cardiomyocytes react to increased workload by increasing their size and the number of sarcomeres for better contractility.²⁵¹ Over time with, for example, increased ischemic myocardial damage and loss of cells, such hypertrophic compensation for the reduced functionality eventually fails. Decompensated hypertrophy is characterized by interstitial fibrosis, cardiomyocyte apoptosis, inadequate angiogenesis, increased ROS production, mitochondrial dysfunction, and activation of fetal gene expression programmes.^{251,259} This perilous sequence of events often culminates

in HF.^{260,261} The ensuing cardiac dysfunction is often divided into HF with either reduced (systolic dysfunction) or preserved (diastolic dysfunction) ejection fraction (HFrEF and HFpEF, respectively).

m⁶A modification

A rapidly accumulating and prominent body of evidence indicates that epitranscriptomics, and especially m⁶A, influence not only the initiation of hypertrophy but also progression toward dysfunction and ultimately HF.^{118–123,131}

Cardiac hypertrophy. While transcript hypomethylation has been shown to predominate in pressure-overloaded hypertrophic murine hearts, the number of transcripts with overall changes in m⁶A modifications measures greater than the amount of differentially expressed transcripts, suggesting notable functional role for m⁶A regulating machinery in hypertrophy.¹²² However, the functional role of METTL3 writer in hypertrophy does not appear to be straightforward. An initial study by Kmietczyk et al. revealed that at the transitory point from the acute phase of adaptation to the early hypertrophic remodeling two days after pressure-overload induction, the expression of METTL3 and the m⁶A content of several hundred mRNAs were downregulated.¹²¹ In concert, when METTL3 was overexpressed, the hypertrophic response to pressure overload was attenuated.¹²¹ However, pressure-overload-induced hypertrophy has also been associated with increased cardiomyocyte total RNA m⁶A content *in vitro*. Here, METTL3 overexpression *in vivo*, with a different mouse strain and expression method, was demonstrated to act as a spontaneous activator of hypertrophy with no external triggers, but not to affect the hypertrophic adaptation in response to pressure overload.¹²⁰ Interestingly, spontaneous hypertrophy also occurs in skeletal muscles following METTL3 overexpression suggesting conserved mechanisms.²⁶² As the obvious cause(s) responsible for the noted discrepancy within the myocardium remain unknown, validation of the findings with parallel identification of various operant downstream mechanisms can be expected to ultimately shed light on the matter.

The identified molecular mechanisms involving METTL3 in hypertrophy are complex. First, Gao et al. identified and named a novel piwi-interacting RNA, greatly overexpressed in response to cardiac hypertrophy, as cardiac-hypertrophy-associated piwi-interacting RNA (CHAPIR) and reported it to suppress METTL3 expression to ultimately promote development of pathological hypertrophy.¹²³ Hence, METTL3-mediated m⁶A methylation was proposed to be cardioprotective against pathologic growth. In finer detail, pressure-overload-induced hypertrophy was associated with increased complexing of CHAPIR with piwi-like RNA-mediated gene silencing 4 (PIWIL4), which subsequently suppressed METTL3 via direct binding, decreased poly(ADP-ribose) polymerase family member 10 (*Parp10*) mRNA m⁶A methylation, and consequently upregulated PARP10 protein via relieved YTHDF2-dependent degradation. Further downstream, increased PARP10 promoted mono-ADP-ribosylation of glycogen synthase kinase-3 β (GSK3 β), which ultimately resulted in nuclear accumulation of the transcription factor nuclear

factor of activated T cells 4 (NFATC4) and transcription induction of hypertrophy-related genes.¹²³ However, in another experimental study, with yet another stimulus for murine hypertrophy induction via long-lasting subcutaneous infusion of angiotensin II (AngII), Lu et al. pinpointed METTL3 as a potent prohypertrophic downstream player.¹²⁶ The authors showed that the deubiquitinating enzyme ubiquitin-specific peptidase 12 (USP12) is upregulated in hypertrophy, stabilizes E1A-binding protein p300 (p300), and enables it to upregulate METTL3.¹²⁶ Furthermore, as insights from skeletal muscles also suggest METTL3 to drive spontaneous hypertrophy via an m⁶A-induced YTHDF2-dependent degradation of activin A receptor type 2A (*Acr2a*) mRNA, consequently blocking a muscle-conserved anti-hypertrophic myostatin (an ACVR2A ligand) signaling pathway, it is tempting to speculate that such epitranscriptomic control also operates within myocardium.²⁶² Indeed, ACVR2A inhibition appears therapeutic after MI by (1) promoting early-stage compensatory hypertrophy (concentric hypertrophy) via activated Akt signaling, (2) reducing myocardial fibrosis, and (3) inhibiting dilative late-stage pathologic cardiac remodeling (eccentric hypertrophy).²⁶³

Aiming to delve further into the methodological differences to pinpoint putative mechanisms for the observed discrepant roles of METTL3 in hypertrophy, the prohypertrophic association for METTL3^{120,126} arises from studies that used robustly cardiomyocyte-targeted overexpression methods and distinct murine strains from those observing beneficial effects, including opposed pathological hypertrophy, preserved contractility, and post-MI angiogenesis.^{56,121,123,140} Additional studies addressing the cell-type-specific nature of the findings in various myocardial cell lineages in hypertrophy are warranted.

In addition, the direct downstream effectors of m⁶A, the m⁶A readers, are important as their altered regulation might considerably affect the way METTL3-mediated m⁶A modification is interpreted by the cells. Albeit recently challenged,²⁶⁴ the major scheme of YTHDF m⁶A reader family functions denote YTHDF2 as a repressor of m⁶A-methylated mRNAs, YTHDF1 a stabilizer of m⁶A-bound transcripts, and YTHDF3 to act in both directions.³⁸ Such divergent functions provide a functional basis for a conjecture that these readers might be differently regulated within different hypertrophy models, and underly the observed distinct phenotypes. As an indirect support for such speculation are notions that the YTHDF2-dependent *Parp10* mRNA degradation appears protective from pathological hypertrophy,¹²³ and YTHDF2 has also been denoted with similar protective role in mice and specified in mice primary cardiomyocytes to operate via m⁶A-dependent *Myh7* mRNA decay.¹²⁵ In contrast, YTHDF2 was recently revealed to promote rat cardiomyocyte hypertrophy with lncRNA MIAT (MI-associated transcript) acting as a direct positive upstream regulator of YTHDF2-mediated m⁶A-dependent degradation of carnitine palmitoyltransferase 1A (*Cpt-1a*) mRNA downregulating subsequently CPT-1a protein, a rate-limiting enzyme in mitochondrial fatty acid oxidation related to PPAR α signaling.¹²⁹ Such divergent functions for a single YTHDF paralog during qualitatively varied modeling species and conditions add another layer of regulation to

be considered. Furthermore, as upregulation of both *Ythdf2* and YTHDF2 in 0.2 μM AngII-treated rat cardiomyocytes seems to wane with more potent 1 μM AngII induction, the quantitative aspects also warrant standardization.¹²⁹

No targeted genetic interventions against either YTHDF1 or YTHDF3 in hypertrophy have yet been reported, not to mention the almost totally veiled role of the litany of other established m⁶A readers (Figure 1). Indeed, the antihypertrophic effects of miR-133a, targeting effectively m⁶A-methylated RNAs via its complementary m⁶A-motif in its seed sequence, has been reported to depend on IGF2BP2 complexing with the m⁶A-methylated target transcripts.¹²⁴ As IGF2BP2 is a major myocardial paralog of the IGF2BP m⁶A reader family²³³ with established upstream regulators lncRNA Airn (antisense of IGF2R non-protein coding RNA) in cardiomyocytes²⁶⁵ and high-mobility group AT-hook 2 (HMGA2) protein in skeletal myoblasts²⁶⁶ controlling migration, apoptosis, and proliferation of these cells, targeted investigations toward this m⁶A reader may also yield some clarification. Last, the role of cardiac hypertrophy-promoting mitogen-activated protein kinase/extracellular regulated MAP kinase (MAPK/ERK) pathway²⁶⁷ also warrants attention, as it was recently shown to positively regulate m⁶A methylation through phosphorylation-dependent stabilization of the METTL3 writer complex.²⁶⁸ Maslinic acid, a pentacyclic triterpenoid known to inhibit the ERK pathway activation, has recently been unveiled to protect against pressure-overload cardiac hypertrophy via an as-yet unclear mechanism of METTL3 downregulation.¹²⁸

FTO m⁶A eraser has also been observed with contrasting but tissue- and cell-type specific functions in hypertrophy. The first report assessing FTO in hypertrophy by Gan et al. pinpointed upregulated FTO in hypertrophic cardiomyocytes treated with leptin, a pro-satiety and prohypertrophic adipokine,²⁶⁹ through JAK-STAT3-cut-like homeobox 1 pathway p110 isoform (CUX1p110).¹¹⁸ Here, FTO silencing unveiled its prohypertrophic function *in vitro*,¹¹⁸ a finding later recapitulated with phenylephrine treatment,¹²¹ albeit the FTO-regulated downstream mRNAs responsible for the phenotype in these cell cultures remained veiled. As an interesting link, JAK-STAT3 signaling has been implicated in cardiac anti-apoptosis, cell-cycle re-entry, differentiation, regeneration, fibrosis, hypertrophy, MI, HF,^{270,271} and in the regulation of induced pluripotency by acting through m⁶A-YTHDF1/YTHDF2 and suppressor of cytokine signaling 3 (SOCS3).²⁷² Congruent with these prohypertrophic findings, Tanshinone IIA (TanIIA), an active compound from *Salvia miltiorrhiza*, was shown to inhibit pressure-overload-induced myocardial hypertrophy, the mechanism, as evaluated in AngII-stressed cardiomyocyte culture, of which was suggested to operate via downregulation of ALKBH5 to downregulate Galectin-3 via respective mRNA m⁶A methylation.¹⁴¹

Contrasting results have also been obtained, however. While FTO knockout in a model of pressure-overload-induced HFrEF decreases contractility and increases ventricular dilatation,¹²¹ its overexpression in a model of diabetic cardiomyopathy has been shown to inhibit

fibrosis and hypertrophy.¹²⁷ On the other hand, global knockout of FTO, unlike the above cardiomyocyte-targeted interventions, has been reported to result in promoted hypertrophy.¹¹⁹ This finding receives weak support from a positive correlation observed among a small case series of patients with congenital FTO deficiency and hypertrophic cardiomyopathy.²⁷³ Much like that for METTL3 m⁶A writer, the contrasting findings regarding m⁶A erasers may be explained by the diversity of the models and hypertrophic stimuli used, as these will yield distinct transcriptomes available for modification. Further, the expressed m⁶A reader profiles, concurrent with availability of needed functional subunits, cofactors, or substrates, all may affect how the m⁶A is interpreted by the cells. The use of standardized methodologies with broader concurrent consideration of m⁶A readers may help to crystallize this rapidly developing field.

Last, to identify conserved epitranscriptomic pathways in hypertrophy, Hinger et al. utilized a rat-to-human cross-species comparison approach from myocardium samples of human non-ischemic hypertrophy against that of isolated rat hypertrophied cardiomyocytes. Intriguingly, they found a set of 38 mRNAs with conserved m⁶A enrichment.¹³¹ Of these, five contained conserved m⁶A sequence loci, and only repressor element silencing transcription factor 1 (*Rest1*) and splicing factor 3b subunit 4 (*Sf3b4*) mRNAs were modified at their CDS. Moreover, the baseline comparison of non-hypertrophic human myocardium against rat cardiomyocytes revealed 11 m⁶A-enriched transcripts, of which only *coronin 6*, a transcript encoding an actin filament-binding protein,²⁷⁴ emerged as a conserved m⁶A-modified transcript at a specific sequence locus within its 3' UTR,¹³¹ a known critical RNA regulatory hub.²³² Intriguingly, while the function of coronin 6 has not yet been studied in the heart, its protein levels were shown to correlate with those of METTL3 and to be downregulated in hypertrophic cardiomyocytes.¹³¹

Ischemic and hypertrophic cardiomyopathy. Akin to hypertrophy, the roles of post-transcriptional regulation in hypertrophy in both murine HF models and human ischemic HF and DCM specimens are highlighted as the number of differentially m⁶A-methylated mRNA transcripts seem to outweigh up to 5- to 7-fold the differentially expressed genes.^{121,122} Further, mice-to-human cross-species-conserved m⁶A-altered transcripts in HF models have been associated with regulation of calcium fluxes, cardiac contraction, and VSMC differentiation.¹²²

Experimental studies targeting FTO expression suggest it to be cardioprotective against development of HF and fibrosis.^{107,122,127} While FTO expression has been described as either repressed^{107,116,131} or unaltered^{121,122} in HFrEF, it has been reported to be upregulated in HFpEF.¹⁵¹ Based on a combination of measurements from hypoxic cardiomyocytes, ischemic myocardium, and clinical HFrEF samples, such activity has been suggested, at least partially, to relate to demethylation of sarcoplasmic/ER Ca²⁺ATPase 2a (*Serca2a*) mRNA m⁶A, resulting in increases in the amount of SERCA2A protein and improved Ca²⁺ signaling.¹⁰⁷ Such findings link the m⁶A-mediated

regulation of mRNA translation and respective protein production to cardiomyocyte contraction kinetics and more generally with Ca^{2+} dynamics in HF.¹⁰⁷ According to lessons from neurons, FTO can also demethylate Ca^{2+} /calmodulin-dependent protein kinase II (*CaMKII*) mRNA, a key mediator of cardiomyocyte Ca^{2+} -dependent contraction,²⁷⁵ to increase its expression.²⁷⁶ In addition, decreased m⁶A methylation of both mouse and human *Calmodulin 1* mRNAs (a core member of the CaMKII pathway) lead to its reduced protein expression in the failing myocardium.¹²² On the other hand, hypermethylation of the high-conductance intracellular calcium channel ryanodine receptor 2 (*Ryr2*) and *RYR2* mRNAs has been observed in mice post MI and human ischemic HFrEF myocardial specimens, respectively. These modifications may thus also contribute to disturbances in intracellular calcium signaling during ischemia and proneness for arrhythmias, which is ameliorated with FTO overexpression in hypoxic cardiomyocytes *in vitro*.¹⁰⁷ Finally, FTO has recently been proposed to antagonize the development of pressure-overload cardiac dysfunction via duplex mechanism converging to promote glycolysis.¹⁷⁵ Namely, FTO was shown to upregulate phosphoglycerate mutase 2 (PGAM2) in cardiomyocytes, a key enzyme in glycolysis, via m⁶A hypomethylation of *Pgam2* mRNA, and promote AKT phosphorylation, which led to enhanced insulin-responsive glucose transporter type 4 (*Glut4*) gene transcription, GLUT4 expression, and glucose intake.¹⁷⁵

Despite varying ALKBH5 expressions in HFrEF,^{107,121,122,131,151} its overexpression has also been shown to be cardioprotective against the development of ischemic HF.⁵⁴ Taken together with the above notions also for FTO, akin to cardiac regeneration, upregulation of FTO and ALKBH5 emerges as a putative therapeutic handle to antagonize HF development and progression. However, mechanistic insights remain limited.

METTL3 levels have been observed to be repressed in both experimental HFpEF¹⁵¹ and pressure-overload hypertrophic HFrEF,¹²² but overexpressed¹³¹ or unaltered in clinical samples of ischemic HF¹⁰⁷ or DCM.^{121,122} In preclinical models, knockdown of METTL3 has been shown to reduce fibrosis,^{60,121} preserve cardiac function,^{60,140} and enhance both autophagy¹³⁴ and regeneration-associated markers.¹⁴⁰ In concert, METTL3 overexpression has been shown to drive progressive eccentric remodeling, ventricular ballooning, and ultimately systolic dysfunction.¹²⁰ Hence, the observed downregulation of METTL3 in murine HF models may act as an active, but insufficient, compensation mechanism. However, the measured both unaltered and upregulated METTL3 in many small sets of human HF samples^{107,121,122,131} highlight the need to keep in mind the probable species-specific differences.

Dominant hypomethylation of the m⁶A-methylomes in both experimental and human HFrEF have been reported.¹²² At the same time, the still-m⁶A-enriched transcripts were positively correlated with polysome occupancy and enhanced translation, an interesting finding not recapitulated in the baseline myocardium.¹²² Hence, it can be speculated that the downstream m⁶A reader milieu undergoes notable

reorganization within the failing myocardium with as-yet veiled functional consequences.

To date, only the YTHDF2 m⁶A readers have had their protein expression evaluated in failing myocardium in a targeted fashion. Namely, while human failing dilative cardiomyopathy samples upregulate YTHDF2 protein,¹²⁵ the *Ythdf2*, alongside *Ythdf1*, *Ythdf3*, and *Ythdc1*, mRNA levels have been measured unaltered in experimental models of HFrEF and human DCM.^{122,151} Moreover, YTHDF2 overexpression has been shown to be cardioprotective in pressure-overloaded failing myocardium.¹²⁵ As such, the dominating hypomethylation in failing murine and human myocardium¹²² may be a consequence of an active compensation mechanism where aberrantly m⁶A-modified transcripts are degraded by YTHDF2 to enable effective positive selection of a smaller subset of cardioprotective m⁶A-methylated mRNAs for recruitment to polysomes and enhanced translation by other m⁶A readers, such as YTHDF1.

Multiple mechanisms, most probably in a synergistic fashion, tend to promote m⁶A in mRNAs in failing myocardium. Indeed, as discussed later in future perspectives, hypoxic metabolism in general may hamper m⁶A eraser function, but FTO and ALKBH5 eraser levels have also been measured to downregulate in ischemic myocardium,^{107,131,135} and their overexpression—as well as METTL3 knockout—has proved beneficial against the development of HF.¹⁴⁰ Furthermore, the relationship between YTHDF1 protein and *Ythdf1* mRNA levels might be complex within the failing myocardium.¹²² For example, the post-MI cardioprotection of ALKBH5 against HF development seem to be conveyed by hypomethylation-dependent stabilization of *Ythdf1* mRNA, thus upregulating YTHDF1 protein without altering its transcription.⁵⁴ Moreover, recent evidence suggests most m⁶A to be non-functional enzymatic noise, also in myocardium.²⁷⁷ An *in vivo* HF model with YTHDF1 overexpression, in conjunction with YTHDF2 knockout, and vice versa, come with power to address such speculations.

Despite myocardial YTHDF3-targeted experimental studies remaining to be published, an intersection with HF exists, as bioinformatic reanalysis of published protein expression datasets has revealed YTHDF3 to be downregulated in human ischemic failing myocardium.¹³³ Interestingly, YTHDF3 seems to promote translation of m⁶A transcripts common also for YTHDF1 via recruitment to polysomes, but to also perform a contrasting role for other transcripts.²⁷⁸ Intriguingly, YTHDF3 has thus been suggested as a modulatory pivot for the effects of YTHDF1 and other m⁶A binders.^{278,279} Furthermore, YTHDF3 has been suggested to suppress YTHDF1 in ESC-derived differentiating cardiomyocytes *in vitro* with an as-yet veiled mechanism.¹⁶⁰ Finally, lessons from the fruit fly suggest that its single YTHDF orthologue binds Fmr1, an orthologue of the mammalian m⁶A reader FMRP, and consequently inhibit its translation.²⁸⁰ FMRP also associates to polysomes and negatively regulates bound transcript translation.^{281,282} As FMRP has protective effects against inflammatory cardiomyocyte injury²⁸³ and counteracts myocardial mitochondrial proton leak,²⁸⁴ as well as regulating several key

processes against development of cardiac dysfunction,^{285,286} namely RNA splicing and export,²⁸⁷ FMRP, as a relatively unexplored m⁶A reader, should be investigated in the failing heart.

Dilated cardiomyopathy. Various causes ranging from toxins and infections to hereditary mutations can disrupt myocardial architecture and develop a pathophenotype of DCM, which is hallmarked by outward enlarged and thin-walled, often poorly contracting, and ultimately failing ventricles.²⁸⁸ While the myocardial m⁶A content in clinical DCM samples has been reported to be increased, the expression levels of the major writers and the FTO eraser remain unaltered.¹²¹ However, yet another m⁶A reader, YTHDC1, has been assigned a key cardioprotective role against DCM development by controlling alternative splicing in mice.¹⁵⁰ Indeed, expression of Titin, a giant myofibrillar protein that serves as a molecular spring during cardiomyocyte contractions and encoded by a colossal 364 exon-containing *Titin* gene, was revealed to rely on the m⁶A reader YTHDC1 for the proper splicing of its m⁶A modified pre-mRNA.¹⁵⁰ While the m⁶A-dependent and YTHDC1-guided *Titin* pre-mRNA splicing produced a shorter and more rigid Titin isoform, N2B, cardiomyocyte-targeted conditional YTHDC1 knockout led to expression dominance of longer and less stiff N2BA isoform manifesting with DCM phenotype and ultimately HF.¹⁵⁰ Considering that *Titin* gene mutations, which disrupt its proper maturation, underlie nearly every fourth case of congenital DCM when the causative mutation can be identified,²⁸⁹ these findings appear to be of potential therapeutic interest. The N2BA isoform has also been reported to increase at the expense of the stiffer N2B isoform in human end-stage DCM.²⁹⁰ In sum, this discovery warrants evaluation of YTHDC1's role in human *Titin* pre-mRNA maturation and pathogenesis of DCM, which is often considered idiopathic.²⁸⁹ As YTHDC1 remains currently the only known helicase-domain-containing m⁶A reader,³⁸ the above findings may also prove to be a catalyst to broaden the epitranscriptomic considerations in CVDs toward RNA splicing control.

Metabolic cardiomyopathy. Most metabolic pandemics of our time, including obesity, hyperlipidemia, and type 2 diabetes, are increasingly being linked with both m⁶A and to its role in the heart. A mechanistic summary of these emerging molecular findings is presented in Figure 5. Interestingly, and in sharp contrast with ischemic HF, FTO inhibition appears to be therapeutic in hyperlipidemia- and palmitic acid (PA)-induced cardiomyopathy and cardiomyocyte inflammation, respectively, where its targeted pharmacological inhibition by a LuHui monomer derivative was reported to provide therapeutic benefit, likely via disrupted mRNA translation of cluster of differentiation 36 (*CD36*), alias scavenger receptor class B protein (*SR-B2*).¹⁵⁴ While METTL3 and ALKBH5 have been reported to be downregulated in PA-induced inflammation in human cardiomyocytes,¹⁵⁴ METTL3 was measured to be upregulated in mice myocardium with high-fat-diet-induced cardiomyopathy,¹⁵⁵ again highlighting methodological, cell-type-specific, and species-dependent differences.

While METTL14 appeared downregulated in a mouse model of diabetic cardiomyopathy,¹⁵² ALKBH5 was upregulated and, contrary to

its function in ischemia,¹³⁴ promoted cardiomyocyte apoptosis ultimately via YAP1 inactivation.¹⁵³ Mechanistically, in high-glucose-treated cardiomyocytes, ALKBH5 was unveiled to demethylate forkhead box O3 (*Foxo3*) mRNA m⁶A, upregulate the protein, and activate the transcription of circular RNA cerebellar degeneration-related protein 1 antisense RNA (*circ-CDR1as*), which enabled blockage of ubiquitination of mammalian sterile 20-like kinase 1 (*MST1*). This induced large tumor suppressor kinases 1/2 (*LATS1/2*), which ultimately inactivated YAP1 via phosphorylation.¹⁵³ This finding contrasts the results from ischemic regenerating⁵⁴ and reperfused¹⁴⁵ myocardium where ALKBH5 and FTO, respectively, were found to upregulate YAP1 via other mechanisms. Similarly, increasing m⁶A by METTL14 overexpression appeared therapeutic through suppression of nucleotide-binding oligomerization domain-like receptor (*NLR*) family pyrin domain containing 3 (*NLRP3*)-mediated cardiomyocyte pyroptosis, which was firmly linked with a m⁶A-dependent and YTHDF2-mediated degradation of lncRNA terminal differentiation-induced non-coding RNA (*TINCR*).¹⁵²

As cardiac insulin signaling converges in translocation of GLUT4 receptor to the cardiomyocyte plasma membrane, and its disturbance is a key etiologic factor in diabetic cardiomyopathy,²⁹¹ it is worthwhile to reiterate here the notion that FTO protects the murine heart from pressure-overload-induced dysfunction via Akt-mediated GLUT4 upregulation.¹⁷⁵ Hence, the therapeutic role of FTO in diabetic cardiomyopathy, perhaps via regulation of GLUT4 expression, warrants targeted attention. In sum, although metabolic disease causes alterations in the myocardial m⁶A epitranscriptomic landscape and its regulatory networks, further specific characterizations are required to unleash the therapeutic and biomarker potential of the epitranscriptomic modifications.

A-to-I editing

Cardiac hypertrophy. Reports directly investigating A-to-I editing in hypertrophy remain scarce. While ADAR1 protein levels have been reported to promptly decrease following murine induction of pressure overload and hypertrophy, the *Adar1* mRNA levels remain unaltered until the decompensated phase of hypertrophy with HF.¹³⁰ Moreover, conditional cardiomyocyte-specific ADAR1 knockout results in hypertrophy and interstitial fibrosis.¹³⁰ On the other hand, after ADAR2 knockout, Altaf et al. identified myocardial downregulation of the let-7 miRNA family,¹³² known regulators of cardiac hypertrophy,²⁹² as well as reduced levels of hypertrophy and fibrosis-associated miR-29b.^{293–295} However, ADAR2 has also been reported to be unrelated to the size regulation of unstressed cardiomyocytes when either silenced or overexpressed *in vitro*. While ADAR2 is reported to upregulate in milder exercise-induced physiological hypertrophy *in vivo*, the consequent functional assessments corroborated the findings from the cell culture.¹⁴⁶

Last, miR-1, an abundant and hypertrophy-limiting miRNA in the heart,^{296–299} has been shown to act as an ADAR repressor.^{300–301} As oxidative epitranscriptomic modification of miR-1 at its seed

sequence position 7 guanosine (7o⁸G-miR-1) changes miR-1 function and provides it with prohypertrophic properties,³⁰² further studies are required to discover links between A-to-I editing and miRNAs in cardiac hypertrophy. Notably, such functions for miRNA editing have been demonstrated for angiogenesis, as described later in a dedicated section for angiogenesis.

Heart failure. A-to-I editing appears to be critical in HF pathophysiology as forced cardiomyocyte ADAR1 knockout during pressure overload accelerated cardiac dysfunction and adverse dilatation, and resulted in massive lethality in an UPR-dependent manner.¹³⁰ Furthermore, and speculating an underlying mechanism, as the above seems consistent with the ADAR1's role to keep innate immune response within developing murine myocardium at bay via MDA5–MAVS–INF–(ER stress)–UPR pathway inhibition (described above in section “cardiogenesis and cardiac regeneration”), it appears interesting that case reports have described several unfortunate children with either congenital MDA5 gain-of-function³⁰³ or ADAR1 loss-of-function mutations,¹⁵⁶ both causing a class I interferonopathy, to develop severe cardiac valve calcifications, HF, and ultimately increased premature lethality.

Moreover, it is intriguing to consider the established role of A-to-I editing in control of angiogenesis—a key process in HF^{190,304,305}—via editing of miRNAs^{65–67} jointly with miR-1, which has been implicated in cardiogenesis,²⁹⁶ hypertrophy,^{297–299,306} cardioprotection,³⁰⁷ and atherosclerosis,³⁰⁸ as it represses ADAR1 non-cardiac tissues^{300,301} and acts oppositely in favor of hypertrophy when modified by oxidation.³⁰² Moreover, ADAR1 knockout downregulated multiple miRNAs within failing myocardium.¹³⁰ Hence, evaluation of an ADAR1-mediated A-to-I editing in controlling, perhaps via miRNA editing, angiogenic responses in myocardium appear an avenue, when better understood, that could ultimately provide feasible molecular targets to ignite therapeutic revascularization to repair the failing heart.

Atherosclerosis

Atherosclerosis, described as the fattening and hardening of arteries, is promoted by such factors as aging, hypertension, obesity, smoking, and renal failure.^{19,309,310} Mechanistically, endothelial shear stress, dysfunction, and inflammation drive atherosclerosis, the pathophysiology of which is characterized by subendothelial deposition of lipids—especially low-density lipoproteins (LDLs)—to arterial walls. The ensuing endothelial dysfunction and increased permeability promote adherence and translocation of immune and inflammatory cells that engulf the deposited lipids and turn into foam cells.³¹¹ The plaques calcify and grow over time, may rupture, and eventually obstruct blood flow causing tissue ischemia and MI when occurring in a coronary artery supplying the myocardium. If the patient survives, such infarction is a major risk factor for malignant arrhythmias as well as further infarctions and development of HF in the future.

Several molecular mechanisms in atherosclerosis and involving m⁶A and A-to-I editing have been discovered recently. A summary of these

molecular pathways is presented in Figure 3, and a detailed overview involving these modifications with respect to atherosclerosis pathophysiology is presented in Figure 6. In addition, Figure 7 summarizes currently discovered molecular interactions involving m⁶A during macrophage inflammation and formation of foam cells.

m⁶A modification

Disturbed flow, endothelial dysfunction. The endothelial stress response is considered as the initial step in the pathogenesis toward clinically manifest atherosclerosis.³¹² Notably, METTL3-mediated m⁶A RNA deposition has been suggested to have a key role in early atherosclerosis. Namely, oscillatory blood flow was found to increase METTL3 expression in endothelial cells predisposed to oscillatory flow and stress.⁹² The authors identified METTL3 to function as an upstream activator of nuclear factor kappa B (NF-κB), an enhancer of NLR family pyrin domain containing 1 (NLRP1) protein and repressor of Krüppel-like factor 4 (KLF4). They demonstrated NLRP1 mRNA stabilization (upregulating NLRP1) to occur via m⁶A-YTHDF1 and KLF4 mRNA degradation (downregulating KLF4) to be dependent on m⁶A-YTHDF2 interactions. NF-κB is an inflammatory master regulator and NLRP1 is crucial for inflammatory activation in endotheliocytes during atherosclerosis,³¹³ while KLF4 is a key regulator of vascular homeostasis and endotheliocyte function.³¹⁴ However, a contrasting effect for oscillatory-flow-induced endothelial dysfunction has also been described. With a considerably shorter period of oscillatory stimulus, rather than upregulation, Li et al. described endothelial METTL3 downregulation with consequent epidermal growth factor receptor (EGFR) mRNA m⁶A-hypomethylation-mediated EGFR upregulation, which was linked with promoted atherosclerosis both *in vitro* and *in vivo*.⁹⁵ As advocated further later in section “future perspectives”, these drastically contrasting effects for METTL3 require methodologically standardized validations and further profiling of the m⁶A reader expressions and interactions.

Endothelial and monocyte inflammation, manifest atherosclerosis. Increased expression of both METTL3 and METTL14 in endothelial cells activated by tumor necrosis factor alpha (TNF-α) have been associated with enhanced monocyte adherence and enhanced vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) expression.⁹⁰ Binding to METTL14 activates the forkhead box O1 (FOXO1) transcription factor, leading to increased transcription of VCAM-1 and ICAM-1 mRNAs, also independently of m⁶A.⁹⁰ METTL3/14-dependent m⁶A methylation of FOXO1 mRNA and subsequent binding by YTHDF1 further increase FOXO1 protein expression. Chen et al. linked the increased METTL14 expression with m⁶A-dependent degradation of vasculoprotective *Klotho* mRNA³¹⁵ in dysfunctional endothelium.¹⁰¹ Endothelial cells of human cerebrovascular plaques harbor increased METTL14 expression.⁹¹ Zhang et al. described a METTL14-DGCR8-m⁶A-miR-19a axis where METTL14 directly binds DGCR8 and enhances its interaction with pri-miR-19a. The resulting m⁶A-dependent maturation of miR-19a then drives proliferation and the invasive capacities of atherosclerotic endothelial cells.⁹¹

Interestingly, knockdown of cardiomyocyte-secreted miR-19a improves angiogenesis after MI via hypoxia-inducible factor 1 α (HIF-1 α) *in vivo*.³¹⁶ Hence, it can be speculated that a m⁶A-dependent miR-19a maturation regulates, via HIF-1 α , endothelial function within myocardium.³¹⁷

In addition to the endothelial inflammation and dysfunction, activation of the blood monocytes—especially their pro-inflammatory phenoconversion to endothelium- and plaque-penetrating atherosclerosis-promoting macrophages—is a critical atherosclerosis-promoting event recently shown to be influenced by the m⁶A methylation (Figure 7). Increased inflammatory activation of oxidized LDL (oxLDL)-stimulated monocytes was associated with METTL3-dependent hypermethylation and YTHDF2-dependent mRNA degradation of peroxisome proliferator-activated receptor gamma co-activator 1 α (PGC-1 α) protein, a mitochondrial biogenesis-regulating cofactor.¹⁰⁰ While pro-inflammatory ROS production was increased, the production of ATP and oxygen consumption decreased alongside downregulation of electron transport chain proteins cytochrome *c* (CYCS) and NADH:ubiquinone oxidoreductase subunit C2 (NDUFC2).¹⁰⁰ In line with the effect on m⁶A abundance and the adverse METTL3 upregulation, FTO has recently been assigned an anti-atherosclerotic role via inhibiting foam cell formation by controlling cholesterol efflux transporters and scavenger receptors, and suppressing both mature interleukin-1 β (IL-1 β) synthesis and secretion.⁹⁴ The suggested atheroprotective role of FTO was further shown *in vivo*, but the favorable effect interestingly occurred only in male mice.⁹⁴

However, in contrast to its role in atherosclerotic endothelium, METTL14 has been associated with anti-atherosclerotic activity. Namely, a bioactive metabolite mono-(2-ethylhexyl) phthalate (MEHP) has been shown to inhibit both mRNA m⁶A content and METTL14 expression to promote intracellular cholesterol accumulation and foam cell formation *in vitro* through disrupted cholesterol efflux accountable for an m⁶A-dependent scavenger receptor class B member 1 (*Sr-b1*) mRNA downregulation with consequent downregulation of SR-B1 protein.³¹⁸ Furthermore, Gong et al. recently promoted the putative therapeutic importance of METTL14-mediated modification of miR-654 in human atherosclerosis via regulating cholesterol efflux.⁹³ Specifically, they pointed out a putative pathway consisting of METTL14–m⁶A–(miR-654-3p)–lncRNA ZNF1 antisense RNA 1 (ZFAS1)–ADAM metallopeptidase domain 10/RAB22A, member RAS oncogene family (ADAM10/RAB22A). In brief, such a hypothesis stems from a notion that lncRNA ZFAS1, dependent on miR-654-3p, promotes inflammation and diminishes cholesterol efflux from the atherosclerotic plaques by regulating ADAM10/RAB22A.³¹⁹ Moreover, ZFAS1 is overexpressed in human atherosclerotic plaques³²⁰ and is subject to m⁶A methylation.³²¹

A-to-I editing

ADAR1-dependent editing and increased expression of vascular inflammation-associated cathepsin S (CTSS), an extracellular ma-

trix-cleaving protease,^{50,322,323} was found by Stellos et al. in patient samples from coronary and carotid atherosclerotic arteries and aortic aneurysms as well as in hypoxic and inflamed (TNF- α and interferon gamma [INF- γ]) endothelial cells. Moreover, based on a finding of reduced CTSS expression in atherosclerotic plaques of minipigs treated with anti-oxLDL antibody,³²⁴ its atherosclerotic plaque-stabilizing mechanism was hypothesized to be mediated by ADAR1 A-to-I editing of *Ctss* mRNA.¹⁰² In peripheral blood mononuclear cells (PBMCs), the editing of the lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) by ADAR1 led to its stabilization and increased expression, which then positively correlated with the level of atherosclerotic disease.¹⁰³ Further, in TNF- α -activated human umbilical vein endothelial cells (HUVECs), NEAT1 knockdown blunted the mRNA expression of proatherosclerotic chemokines C-C motif chemokine ligand 2 (*CCL2*), C-X-C motif chemokine ligand 8 (*CXCL8*), and adhesion molecules *ICAM-1* and *VCAM-1*.¹⁰³ Together with increased *Adar1* mRNA levels, the levels of *EndoV* mRNA and inosine have been reported to be upregulated in human carotid atherosclerotic plaques.⁷³ Moreover, as both reduced atherosclerotic plaque monocyte infiltration and size were observed in double *ApoE*^{-/-} *EndoV*^{-/-} knockout mice, the inhibition of the seemingly proatherosclerotic ENDOV might prove a therapeutic strategy.⁷³ Also, as the specific interplay between ADAR1, inosines within various RNAs, and ENDOV in atherosclerosis remains elusive, such targeted considerations would be of great interest in light of the above findings and the following notions. In fact, cluster of differentiation 47 (CD47), an important proatherosclerotic and antiphagocytic immunoglobulin,³²⁵ was measured as potentially downregulated in *EndoV*^{-/-} macrophages *ex vivo*, despite harboring no sites for A-to-I editing.⁷³ Hence, it justifiable to postulate RNA editing-independent functions for ENDOV in atherosclerosis. Indeed, rather than acting as an inosine-specific endonuclease, as established *in vitro*,⁵⁴ ENDOV has recently been suggested to preferentially bind RNAs to protect them from degradation *in vivo*.³²⁶

Atherosclerosis pathophysiology as a multiorgan systemic process

The emerging epitranscriptomic insight regarding atherosclerosis is justifiably heavily plaque focused. However, contributions of other organs and cells to the progression of the atherosclerotic lesions—alongside the emanated paracrine and endocrine signals from these disease foci—are needed to form a more comprehensive view of epitranscriptomic regulation in atherosclerosis. The organs shown to respond to such systemic signals of atherosclerosis are the liver, adipose tissue, bone marrow, and the lymphoid organs. Increased proliferation of the bone-marrow-residing hematopoietic stem cells^{327,328} and their splenic invasion³²⁹ establishing extramedullary hematopoiesis are such key extravascular processes. These processes then seed into circulation pro-inflammatory monocytes with plaque-invasive and plaque-promoting properties.^{328,329} Such a vicious cycle of atherosclerosis has recently been detailed in terms of causation so that the atherosclerotic process itself increases the proliferation rate of hematopoietic stem cells, thus accelerating the efflorescence of proatherogenic clonal hematopoiesis.³³⁰ As accumulating research

also indicates both m⁶A^{331–334} and A-to-I⁶⁹ pathways to play crucial roles in regulating the proliferation and differentiation of hematopoietic stem cells, studies focusing on the role of epitranscriptomics within these systemic aspects of atherosclerosis are warranted.

Myocardial hypoxia, infarction, and fibrosis

Although m⁶A has been associated with hypoxia-reoxygenation (H/R) injury, myocardial hypoxia, ischemia, ischemia-reperfusion (I/R) injury, and post-ischemic fibrosis, reports specifically addressing A-to-I editing in these conditions remain very scarce. Stable expression of ADAR2 has been recently reported, however, both shortly and 3 weeks after MI.¹⁴⁶ Remarkably, ADAR2 overexpression unveiled a phenotype of improved cardiac healing after MI.¹⁴⁶ Namely, abolished functional deterioration, infarct size, fibrosis, and necrosis, as well as cardiomyocyte-specific increase in proliferative markers, were demonstrated.¹⁴⁶ As detailed above (section “cardiogenesis and cardiac regeneration”), the underlying mechanism was suggested to operate via an A-to-I editing-dependent inhibition of pri-miR-34a maturation.¹⁴⁶

m⁶A modification

Reduced myocardial FTO expression has been reported after MI both in humans and mice,^{107,133} and cardiomyocyte-targeted FTO overexpression in mice has been shown to reduce myocardial ischemic damage.¹⁰⁷ In hypoxic cardiomyocytes, FTO overexpression counteracted dysfunctional intracellular Ca²⁺ oscillations, increased contractility, reduced arrhythmic events, and increased both *Serca2* mRNA and protein expression. FTO expression reversed the hypermethylation observed in failing cardiomyocytes.¹⁰⁷ Interestingly, Mathiyalagan et al. also showed that the hypermethylation of *Ryr2* mRNA, a major mediator of cardiac sarcoplasmic calcium-induced calcium release that is imperative for proper propagation of electrical impulses, was attenuated by FTO overexpression in infarcted myocardium.¹⁰⁷ However, the subsequent impact on the respective protein levels remained elusive.

In response to AngII-induced activation of cardiac fibroblasts, reduced expression of circular RNA CUGBP Elav-like family member 1 (circCELF1), also seen in plasma samples of MI patients,³³⁵ was reported to drive the downregulation of FTO.¹⁴⁹ It was mechanistically further revealed that the FTO downregulation led to m⁶A hypermethylation of Dickkopf WNT signaling pathway inhibitor 2 (*DKK2*) mRNA, which enhanced its miR-636-mediated degradation and promoted a profibrotic cellular phenotype. The therapeutic effect of this pathway was confirmed by *DKK2* and miR-636 antagonism overexpression during experimental MI.¹⁴⁹ To identify novel m⁶A-based post-MI angiogenesis-promoting and fibrosis-restricting therapies, it will be of great interest to assess this FTO-dependent molecular pathway, perhaps with an additional focus on the m⁶A-regulated angiogenic Wnt/ β -catenin signaling pathway (see discussion in section “angiogenesis”) in myocardial vasculature.³³⁶ Moreover, finer dissection of the revealed positive upstream regulation of FTO by circCELF1, including, for instance, identifying *FTO* targeting miRNAs sponged by this circRNA, could offer novel druggable targets.

In line with the observed beneficial effects of FTO for ischemic cardiomyocytes, cardiac fibroblasts, and myocardium, similar to the above discussions on hypertrophy and HF, Shen et al. identified FTO to reduce cardiomyocyte apoptosis after H/R injury via demethylation of a lncRNA myosin heavy-chain-associated RNA transcript (Mhrt).¹³⁵ Of further therapeutic interest, Mhrt, alongside another myocardium-specific lncRNA cardiac hypertrophy-associated transcript (CHAST), has earlier been measured hypermethylated in a murine infarcted myocardium and to demethylate after local myocardial FTO silencing yielding a beneficial phenotype.¹⁰⁷ Indeed, Mhrt is a cardiac-specific lncRNA transcribed from the antisense strand of *Myh7* gene with a protective role against hypertrophy by sequestering the brahma-related gene-1 (*Brg1*) mRNA to consequently blunt the prohypertrophic transition from myosin heavy chain 6 (MYH6) to myosin heavy chain 7 (MYH7) expression dominance.^{337,338} Interestingly, triiodothyronine upregulates Mhrt in I/R-injury³³⁹ and has been linked to predict MI³⁴⁰ and HF.³⁴¹ Other m⁶A-modified lncRNAs expressed in ischemic myocardium, such as long-chain non-coding RNA metastasis-related lung adenocarcinoma transcript 1 (*MALAT1*), have also been suggested as future therapeutic targets for myocardial reperfusion injury.³⁴²

A functional intersection for the METTL3 writer and ALKBH5 m⁶A eraser was established by Song et al. in cardiomyocyte H/R and I/R injuries.¹³⁴ The authors reported increased m⁶A levels and expression of METTL3 to adversely associate with decreased autophagic flux and increased apoptosis.¹³⁴ Furthermore, a master regulator of apoptosis, transcription factor EB (TFEB), was shown not only to be regulated by METTL3 but also to regulate METTL3 and ALKBH5 in cardiomyocytes and myocardium after I/R injury. Specifically, a negative-feedback loop with two arms was discovered, where first METTL3-mediated m⁶A-methylation of *Tfeb* pre-mRNA attracts the indirectly m⁶A-binding heterogeneous nuclear ribonucleoprotein D (HNRNPD, alias AUF1 [ARE/poly(U)-binding/degradation factor 1], measured overexpressed in human failing heart³⁴³) to increase its translation and consequently TFEB protein expression. The consequent binding of TFEB to *Alkbh5* gene promoter is enhanced, resulting in enhanced *Alkbh5* gene transcription and ALKBH5 protein expression. Second, rather than controlling transcription, TFEB was discovered to destabilize *Mettl3* mRNA, thus downregulating its own positive upstream regulator.¹³⁴

METTL3 therefore appears to be a detrimental agent in murine hypoxic cardiomyocytes *in vitro* and in infarcted myocardium, akin to the earlier discussion for cardiac hypertrophy. These findings support a rationale that METTL3 inhibitors may act as putative therapeutic agents in IHD.^{344,345} Such postulation is strengthened by the findings that (1) METTL3 knockout before mice MI preserves cardiac function and structure afterward,¹⁴⁰ and (2) METTL3 promotes cardiomyocyte pyroptosis and myocardial I/R injury in rats via an m⁶A-dependent DGCR8-mediated pri-miR-143-3p maturation to yield miR-143-3p to finally suppress protein kinase C epsilon type (PRKCE).¹⁴² However, myocardial METTL3 overexpression has also been implicated with cardioprotective ability by (1) inducing

therapeutic myocardial angiogenesis in mice shortly after MI,⁵⁶ (2) lessening post-MI damage in rats by promoting cardiomyocyte proliferation via stimulated pri-miR-17-3p maturation,¹⁴⁷ and (3) its non-catalytic METTL14 subunit protecting mice heart from extensive I/R injury by activating Wnt1/ β -catenin signal pathway via an m⁶A-dependent enhanced Wnt family member 1 (*Wnt1*) mRNA translation.¹⁴³ Hence, it can be postulated that the resulting final effect on the cardiac phenotype depends considerably on the relative weights of METTL3 activity within the distinct cardiac cell types, ischemic models, as well as the expression profile of the m⁶A readers and transcribed transcriptome available for methylation at a given time, as discussed above (see section “cardiac hypertrophy and failure”).

Hypoxia-inducible m⁶A deposition by METTL3 was recently described to operate specifically in cardiomyocytes, which could possibly provide an operating rationale for some of the above speculations.¹⁴⁴ Namely, a hypoxia-inducible, cardiomyocyte-enriched, and mesoderm-restricted upregulation of a nuclear cap-binding subunit 3 (NCBP3) protein was identified to occupy the 5' UTRs of 85 distinct mRNAs in hypoxic cardiomyocytes with a striking 87.6% congruency to a previously published hypoxic cardiomyocyte dataset of transcripts with incongruent translation activity to their transcriptomic expression.³⁴⁶ NCBP3 was shown to recruit METTL3, promoting the bound mRNA m⁶A methylation and eukaryotic translation initiation factor 4A2 (eIF4A2) to initiate their translation.¹⁴⁴

Furthermore, ALKBH5 overexpression has also been shown beneficial by enhancing cardiac regeneration and salvage myocardial function after MI in both neonatal and adult mice (see section “cardiogenesis and cardiac regeneration”) via m⁶A demethylation-dependent increase in *Ythdf1* translation and consequent YTHDF1-dependently enhanced *Yap1* translation to YAP1.⁵⁴ This YTHDF1-m⁶A-*Yap1* interaction was confirmed operative irrespective of ALKBH5 activity when YTHDF1 was overexpressed, suggesting incapability of ALKBH5 to demethylate *Yap1*. FTO, in addition to its anti-apoptotic effects in H/R-treated cardiomyocytes,¹³⁵ has also been indicated with an age-dependent waning and consequently propagated ischemic myocardial injury.¹³⁸ In H/R-injured neonatal cardiomyocytes, FTO overexpression upregulated YAP1 via m⁶A-demethylation-mediated protection of *Yap1* mRNA from degradation.¹⁴⁵ While the phenotype of these H/R-injured neonatal cardiomyocytes appears analogously therapeutic with ALKBH5 overexpression,¹⁴⁵ the distinct epitranscriptomic pathways converging at *Yap1* translation suggest FTO selectivity as an m⁶A eraser for *Yap1* with simultaneous m⁶A reader milieu that promotes the degradation of m⁶A-methylated *Yap1*. Hence, it will be of interest to assess the capacity of FTO to demethylate *Ythdf1* mRNA and consequently regulate the protein.

On the other hand, WTAP, a METTL3 writer complex subunit,¹³⁶ has been associated with adverse effects in ischemic myocardium. Namely, an ischemic damage and ER-stress-promoting pathway was identified, where WTAP, via activating transcription factor 4

(*Atf4*) mRNA m⁶A methylation, upregulates ATF4 and promotes cardiomyocyte injury.¹³⁶ Therapeutically, WTAP knockout effectively restricted the injuries.¹³⁶ Moreover, the WTAP overexpression-induced cardiomyocyte ER stress and apoptosis during H/R injury was effectively ameliorated *in vitro* with administration of 4-phenylbutyric acid (4-PBA), an ER stress inhibitor.¹³⁶ Interestingly, in global *Mettl114*^{+/-} mice with worsened I/R-injury phenotype compared with controls, WTAP was identified as the only differentially expressed, i.e., upregulated, m⁶A writer subunit.¹⁴³ Finally, based on bioinformatic reanalysis of up to 108 ischemic, 16 non-ischemic, and 86 idiopathic human myocardium specimens, WTAP was also identified as the most consistently upregulated of the m⁶A governing enzymes.¹³³ Hence, WTAP might be unveiled as a biomarker in human ischemic cardiac pathologies.

Aortic valve calcification

Aortic valve calcification is the most common progressing cause of aortic stenosis in the industrialized world.³⁴⁷ In Europe and North America, aortic stenosis is estimated to affect up to 12.4% of the population over 75 years of age with a staggering prevalence of 3.4% for such critical disease that surgical intervention is guideline-mandated.³⁴⁷ Macroscopically, progressing stenosis narrows the valve orifice and drives cardiac hypertrophy.³⁴⁸ Microscopically, the valve calcification is characterized by osteoblast-like phenotype conversion of the valve interstitial cells, ROS production, calcium deposition, and activation of resident valve endotheliocytes as well as leukocyte diapedesis.³⁴⁹

m⁶A and A-to-I modifications

Only two studies have addressed m⁶A and A-to-I modifications in the pathophysiology of aortic valve calcification. In the first, the m⁶A modification was described to control the phenotype conversion of human aortic valve interstitial cells to osteoblast-like cells via METTL3-mediated methylation and consequent YTHDF2-dependent degradation of twist family basic helix-loop-helix (bHLH) transcription factor 1 (*Twist1*) mRNA, which ultimately downregulated the protein.¹⁵⁷ The other case study has described three children, all with tricuspid aortic valves and biallelic loss-of-function mutations in the *ADARI* gene, who developed systemic class I interferonopathy with pronounced early-age-onset aortic valve calcification, stenosis, and HF.¹⁵⁶

Angiogenesis

Angiogenesis has been heavily implicated in epitranscriptomic control of both m⁶A and A-to-I editing. Especially modifications of miRNAs and their altered targetome have been unveiled as important. An overview of the key results from the field of non-malignant angiogenesis is offered below. For more detailed insight into epitranscriptomic control of neovascularization, the reader is directed toward recent reviews for m⁶A³⁵⁰ and A-to-I editing.⁶⁸

m⁶A modification

Corneal angiogenesis is inhibited in FTO knockout mice.⁵⁸ Alike, the tube formation of HUVECs in either unstressed or H₂O₂-stressed

conditions shrinks via a putative focal adhesion kinase (FAK)-m⁶A-YTHDF2 axis.⁵⁸ Accordingly, FTO overexpression has been associated with enhanced post-ischemic myocardial angiogenesis, albeit with light methodological evidence (see the next paragraph).¹⁰⁷ On the other hand, silencing of the other m⁶A eraser, ALKBH5, promoted angiogenesis in a hindlimb ischemia model.¹⁰⁴ The angiogenesis-repressing function of ALKBH5 was associated with increased m⁶A methylation and stability of Wnt family member 5A (*Wnt5A*) mRNA in hypoxia-treated cardiac microvascular endothelial cells (CMECs).¹⁰⁴ No responsible m⁶A readers were identified, however. Moreover, as the role of WNT5A in angiogenesis remains controversial,³⁵¹ it is plausible to speculate the molecular network to be more complex. Increased expression of ALKBH5 has also been reported in HUVECs and human microvascular endothelial cells (HMVEs) after lipopolysaccharide and hypoxia, consistent with results for hypoxic CMECs.¹⁰⁴ However, rather than disrupting angiogenesis, upregulated ALKBH5 was shown to sustain it. In detail, ALKBH5 was found to maintain sphingosine kinase 1 (SPHK1) expression by reducing *SPHK1* mRNA m⁶A methylation, and to preserve both endothelial nitric oxide synthase (eNOS) and protein kinase B (PKB), alias AKT, phosphorylation.¹⁰⁹ Here, it is worth noting the methodological differences. Indeed, with the above lipopolysaccharide and hypoxia protocol,¹⁰⁹ the authors could not replicate the well-established vascular endothelial growth factor (VEGF)-A induction in these cells when singly stimulated by these stressors.^{352,353} At the same time, such findings also suggest a relatively conserved endothelial hypoxia response to upregulate ALKBH5. Such dynamics appear distinct from the measured downregulation of FTO¹⁰⁷ and ALKBH5⁵⁴ in infarcted myocardium.

Regarding the role of m⁶A writers, overexpression of METTL3 *in vitro* has been shown to increase angiogenic parameters in both HUVECs and human CMECs (HCMECs) during basal conditions,⁵⁶ and endothelial progenitors under hypoxia.¹⁰⁸ Namely, in HUVECs and HCMECs, METTL3 increased the m⁶A methylation of let-7e-5p and miR-17-92 clusters, which were subsequently shown to downregulate antiangiogenic thrombospondin 1 (TSP1).^{56,354-355} METTL3 overexpression was also reported to increase angiogenesis in experimental models of MI and hindlimb ischemia *in vivo*.⁵⁶ As the authors pointed out, with regard to general effects on m⁶A in RNA, their findings are contradictory to the increased myocardial angiogenesis observed with FTO overexpression following MI.¹⁰⁷ However, the robust methodological variation limits the interpretation of the results. Specifically, with the FTO overexpression, angiogenesis was assessed with a single-antibody staining against platelet endothelial cell adhesion molecule (PECAM-1), alias cluster of differentiation 31 (CD31), positive endotheliocytes 4 weeks after MI, a time point at which post-MI healing and angiogenesis have mostly taken place already. Notably, HIF-1 α has been pinpointed as a positive upstream regulator of proangiogenic METTL3 expression in hypoxic endothelium *in vitro*.⁵⁷ Specifically, METTL3 was identified to mediate its proangiogenic role in a YTHDF1-dependent manner by enhancing the translation of m⁶A-methylated low-density lipoprotein receptor-related protein 6 (*LRP6*) and disheveled segment

polarity protein 1 (*DVLI*) mRNAs.⁵⁷ Both targets, alongside the discussed *Wnt5a* mRNA,¹⁰⁴ encode proteins that are part of the Wnt signaling pathway, a core regulator pathway of angiogenesis in endotheliocytes.^{356,357}

Interestingly, decreased METTL3¹⁰⁶ and WTAP¹⁰⁵ expression has been associated with larger diameters of human cerebral arteriovenous malformations. Regarding m⁶A writer METTL3, Wang et al. pinpointed two putative mechanistic pathways for promoting angiogenesis *in vitro*. The first pathway involves METTL3-mediated stabilization of deltex E3 ubiquitin ligase 3L (*DTX3L*) mRNA in an m⁶A-IGF2BP1/3-dependent manner to enable the respective DTX3L protein to heterodimerize with deltex E3 ubiquitin ligase 1 (DTX1) to form a Notch E3 ubiquitin ligase, which suppresses Notch signaling and further downstream hes-related family bHLH transcription factor with YRPW motif 2 (HEY2).¹⁰⁶ In the second suggested mechanism, METTL3 represses the transforming growth factor β 1 (TGF- β 1) pathway via SMAD (homologs of the *Drosophila melanogaster* protein 'mothers against decapentaplegic' (MAD) and *Caenorhabditis elegans* 'small body size' (SMA)) family member 6 (SMAD6) downregulation and increases phosphorylation of its other members, including SMAD1-3, SMAD5, and SMAD9.¹⁰⁶ WTAP deficiency was noted also to increase free WT1 expression, which led to Wnt signaling inhibition and increased degradation of β -catenin.¹⁰⁵ WTAP has also been reported to maintain angiogenic desmoplakin (DSP)³⁵⁸⁻³⁶⁰ expression in endothelial cells in an m⁶A-IGF2BP1/3-dependent manner.¹⁰⁵

A-to-I editing

van der Kwast et al. discovered that miR-487b, previously known to maintain the integrity of hypertensive artery walls and post-ischemic blood flow recovery,³⁶¹ was increasingly edited from its seed sequence in hindlimb ischemia.⁶⁵ The edited form, miR-487b-ED, was unveiled to have unique proangiogenic functions and a near-completely altered targetome compared with the unedited miR-487b. In addition, four other vasoactive and vascular-cell-expressed miRNAs have been established to be the targets for notable A-to-I editing: miR-376a-3p, miR-376c-3p, miR-381-3p, and miR-411-5p.^{66,67} These miRNAs were shown to contain inosine edits in their seed sequence at the maturation stage and to respond to hypoxia by increased editing. These targetomes of these edited forms acted to promote angiogenesis.^{66,67} Collectively, these findings delineate a novel layer of ischemic angiogenesis regulation and elucidate avenues for epitranscriptomics-based angiogenic miRNAs to be tested as therapeutic handles.

Arterial aneurysms

Arterial aneurysms represent a set of conditions with variable risk factors and etiologies.³⁶²⁻³⁶⁴ All are characterized by the disruption of the structural and mechanical properties of the arterial wall.³⁶⁵⁻³⁶⁷ This leads to local ballooning of an artery with concurrent thinning of its wall rendering the artery prone to dissection³⁶⁸ and rupture.³⁶⁹⁻³⁷⁰ In general, aneurysm ruptures are associated with extremely high mortality rates.

A-to-I editing

Increased expressions of the A-to-I editor *ADAR1* and *CTSS* mRNAs have been described in human aneurysmatic thoracic aortas. The authors identified the RNA-stabilizing HuR to bind the newly formed inosine.⁵⁰ Importantly, *CTSS* has many matrix remodeling functions and participates in both collagenolysis and elastolysis,^{371–373} which are processes also heavily implicated in aneurysm pathophysiology,^{362–364,367} and could provide a pharmacologically targetable molecular pathway. Based on the discovery for A-to-I editing to control diastolic blood pressure via *Flna* mRNA editing,¹¹⁶ thus producing an actin crosslinking *FLNA*, heavily implicated in arterial wall integrity (see also section “hypertension”),²⁵² further investigations regarding A-to-I editing in also controlling aneurysm pathophysiology are warranted and rational.

m⁶A modification

Aging has been shown to downregulate *METTL3* expression in the aorta.¹⁵⁶ The development and progression of abdominal aortic aneurysm has been suggested to be induced through *METTL3*-mediated maturation of miR-34a and decreased Sirtuin 1 (*Sirt1*) mRNA expression.⁸⁶ Accordingly, knockdown of *METTL3* protects from development of abdominal aortic aneurysm, and this therapeutic effect is inhibitable by either miR-34a silencing or SIRT1 overexpression.⁸⁶ Interestingly, a recent study highlighted the SIRT1-melatonin axis in a murine thoracic aortic aneurysm model.³⁷⁴ The authors noted that melatonin administration prevented thoracic aortic aneurysm formation via acting on SIRT1 in a melatonin-receptor-dependent manner.³⁷⁴ Yang et al. reported melatonin to inhibit *METTL3* expression and m⁶A in ESCs specifically via melatonin receptor 1 (MT1) and further through the MT1–Janus kinase 2 (JAK2)–STAT3–zinc-finger protein 217 (*Zfp217*) pathway,³⁷⁵ all members of which are implicated to be regulated by m⁶A in CVDs.^{118,376} Moreover, melatonin has been shown to downregulate VEGF in hypoxic retinas,^{377–379} inhibit hypoxic angiogenesis by repressing the HIF-1 α -VEGF-ROS axis,³⁸⁰ and upregulate HIF-1 α targeting miR-3195 and miR-374b, thus downregulating VEGF.³⁸¹ These findings are of interest considering the upstream roles of melatonin and MT-1 in inhibiting *METTL3*,³⁷⁵ since *Vegf* mRNA has been shown to be m⁶A modified by *METTL3*, thus modulating a TEK receptor tyrosine kinase (TEK)–PI3K–VEGF axis via increasing its stability and enhancing angiogenesis.³⁸² Furthermore, the m⁶A-reader IGF2BP3 has been shown to bind m⁶A in *Vegf* mRNA, increasing its translation.³⁸³ To summarize, as VEGF inhibition has been shown to prevent aortic aneurysm progression,³⁸⁴ melatonin might, via *Vegf* mRNA m⁶A methylation, act on aneurysm development.

Dissected aortas were reported to have decreased KIAA1429 (alias *VIRMA*) and miR-143-3p levels while ALKBH5 was reported upregulated.⁸⁸ KIAA1429 was shown, via its increasing m⁶A methylation effect, to enhance pri-miR143-3p maturation by interacting with the important miRNA molecular processor DCGR8 to consequently downregulate its downstream target gene, responsible for observed phenotypes, DEAD-box helicase 6 (DDX6). On the other hand, ALKBH5 was shown to repress such interaction and thus, contrary

to the phenotypes observed in KIAA1429 overexpression, promote aortic dissection, suppress human aortic smooth muscle cell (HASMC) proliferation, and promote apoptosis in human aortic endothelial cells (HAECs).⁹¹

He et al. demonstrated increased m⁶A content and expressions of YTHDF2 and YTHDF3 in abdominal aortic aneurysm,⁸² of which YTHDF3 positively correlated with the aneurysm diameter. Another similar associative study has linked reduced *METTL14* expression with higher risk of aneurysm rupture.⁸⁴ Like ALKBH5,⁹¹ FTO is also upregulated in dissecting and stable aortic aneurysms.⁸⁷ Moreover, increased angiotensin-II-induced FTO levels and gain-of-function methods in VSMCs were shown to mediate pathologic phenotype switching.⁸⁷ Mechanistically, the FTO-driven demethylation of Krüppel-like factor 5 (*KLF5*) mRNA and downregulation of glycogen synthase kinase 3 β (GSK3 β) signaling, leading in combination to upregulated *KLF5* protein, were unveiled as the responsible pathways.⁸⁷ Interestingly, the adverse role of *KLF5* has also been shown in atherosclerosis as a part of oxLDL–*KLF5*–miR-29a–F-box and WD repeat domain containing 7 (FBW7) positive feedback loop. Specifically, oxLDL-induced upregulation of *KLF5*, further accelerated via miR-29a accumulation-mediated and FBW7-repression-dependent reduction of *KLF5* ubiquitination, increases VSMC proliferation and progression of atherosclerosis, thus stressing miR-29a suppression as a possible therapeutic strategy.³⁸⁵ Epitranscriptomically, it is interesting that miR-29a has been shown to undergo m⁶A methylation and to be consequently repressed by the HNRNPA2/B1 m⁶A reader.³⁸⁶ *KLF5* has been implicated as a key hub for vascular-injury-induced proliferative responses of VSMCs, neointima formation, as well as both angiotensin II-induced cardiac hypertrophy and fibrosis response.³⁸⁷ Combined, targeted hypermethylation of either the *KLF5* mRNA or miR-29a might prove therapeutic in conditions where VSMC hyperproliferation holds a central pathophysiologic role, including atherosclerosis, arterial aneurysms, and both pulmonary and systemic hypertension.

FUTURE PERSPECTIVES

Taken together, both the m⁶A and A-to-I modifications have emerged as dominant regulators of CVDs. Some future perspectives are discussed below.

Drugging the m⁶A- and A-to-I-related pathways in cardiovascular diseases

A number of compounds targeting m⁶A writers^{345,393} and erasers^{394–396} have been identified. A summary of these small molecules is provided in Table S5. As many of these well-characterized molecules remain untested in cardiovascular models (excluding the FTO inhibitors FB23-2 and Rhein;¹¹⁷ see section “hypertension”) and, based on the above discussions, the function of the m⁶A regulators varies across tissues, cell types, and diseases (as well as their models), their testing within the cardiovascular field appears to be a promising avenue to extend our evolving understanding. Pharmacological evaluation could reveal insightful sum effects of these regulators; for example, for *METTL3* in the context of cardiac hypertrophy, MI, and flow-induced

endothelial dysfunction. Consequently, coupled with accumulating new evidence, validations, and methodological standardization, such insights could help us to detangle these currently complex, even controversial, mechanistic landscapes currently hallmarked by simultaneous and extensive involvement of METTL3-mediated m⁶A methylation within multiple—even opposing—molecular pathways. Moreover, as these epitranscriptomic regulators have demonstrated both driving and suppressing roles in some of these pathologies, these compounds may also provide novel therapeutic benefits. For example, as a METTL3 inhibitor is emerging a handle to treat acute leukemia,³⁴⁵ and while YTHDF2 also appears another such target,³⁹⁷ testing this METTL3 inhibitor, STM2457, during MI or hypertrophy might produce therapeutic effects. Moreover, as upregulation of FTO and ALKBH5 has most consistently proved to be therapeutic during various models of myocardial ischemia, development of activating compounds for these m⁶A erasers could hold translational therapeutic value to mend ischemic hearts. Finally, the additional discovery of such compounds for the m⁶A readers and A-to-I editors is awaited.

m⁶A readers as a key to clarify the role of epitranscriptomics in CVD pathologies?

Many of the numerous readers of m⁶A remain uncharacterized.^{388–392} Due to the nature of these readers, responding to upstream stimuli to initiate the molecular, cellular, and ultimately systemic responses, it is probable that they will prove to be centrally important in CVD epitranscriptomics. Encouragingly, studies exploring the role of these readers in CVDs are being constantly reported (Figures 3, 4, 5, 6, and 7).

Although the YTHDF family of m⁶A readers has recently attracted considerable scientific interest, the redundancy of their targets and downstream functions remains a matter of recent controversy. Namely, two research groups, led by Jaffrey et al.²⁶⁴ and Hanna et al.,³⁹⁸ have recently called into question the canonical scheme where YTHDF1 stabilizes the m⁶A-bound transcripts, YTHDF2 degrades them, and YTHDF3 can act in both directions. According to this view, the YTHDF family shares a virtually identical set of modified target RNAs and functions in unity to promote their degradation. However, many both m⁶A- and YTHDF1-dependently stabilized mRNAs, as measured in cardiovascular tissues, seem to be in contradiction with such a scheme stemming from HeLa cells²⁶⁴ and ESCs.³⁹⁸ These include *NLRP1*,⁹² *FOXO1*,⁹⁰ *Myl2*,¹²¹ *Atf4*,¹³⁶ *MAGED1*,⁸⁰ and *Wnt5a*.¹⁰⁴ In addition, YTHDF2, but neither YTHDF1 nor YTHDF3, has been described to bind m⁶A-modified *Acvr2a* mRNA in hypertrophic skeletal muscle.²⁶² Notably, a recent preprint by Zou et al.⁴⁰⁰ has brought up major experimental controversies in the original paper published by Zaccara and Jaffrey.²⁶⁴ Also, based on revised and additional experiments, YTHDF1 was demonstrated to promote translation of its target mRNAs in HeLa cells and to harbor a low-complexity domain notably distinct from that of YTHDF2, which was found to account for their capacity to form different condensates and to act in a paralog-specific manner.⁴⁰⁰

Elucidation of the upstream control of m⁶A readers may also help to explain the possible discrepancy between YTHDF family members.

For example, post-transcriptional YTHDF2 SUMOylation considerably increases its affinity to m⁶A, thus stimulating the m⁶A-bound RNA degradation in cancer cells.³⁹⁹ Also, the importance of post-transcriptional regulation of METTL3,²⁶⁷ METTL14, WTAP,⁴⁰¹ and YTHDFs in a paralog-specific manner³⁸ by phosphorylation has been described in non-cardiovascular systems. Finally, to truly unravel the functions YTHDF paralogs, the importance of paralog-specific expressions according to given tissue, cell, and cell state, or even specific molecular signals, cannot be overemphasized. For example, the knockdown of YTHDF1 or YTHDF3 in ESC-derived cardiomyocytes, contrary to ESCs, does not accumulate m⁶A in RNAs,¹⁶⁰ and tumor protein 63 (p63) seems to upregulate just YTHDF3 in skin.⁴⁰² Hence, it is critical that the functions of YTHDF paralogs are also meticulously examined in the cardiovascular system. Such an approach could also provide clarification to the contrasting findings for METTL3-mediated m⁶A methylation in controlling the cardiac hypertrophy and oscillatory flow-induced endothelial dysfunction discussed above.

Revealing the upstream control of ADARs in cardiovascular systems

While the understanding of the role of A-to-I editing in cardiovascular diseases remains limited in general, overall highlighting the need for future investigations, deciphering its upstream control might provide avenues for novel considerations. For example, miR-1 has been shown to target ADARs by repressing their expression in non-cardiac cells.^{300,301} However, although this miRNA is highly expressed in heart²⁹⁶ and has an established role in many CVDs or related processes,^{298,299,302,305–307} its role from an epitranscriptomic viewpoint remains to be established in heart.

Cardiometabolism is a putative modulator of the cardiac m⁶A methylome

As oxygen and α -ketoglutarate are needed to erase m⁶A, and the reaction yields succinate (Figure 1),³⁸ the metabolic state of the myocardium can be expected to affect its RNA m⁶A content. Indeed, in hypoxic myocardium, α -ketoglutarate depletes downstream in the Krebs cycle into succinate,⁴⁰³ while it acts to produce high-energy phosphates as substituents for the deteriorating oxidative metabolism.⁴⁰⁴ In addition, α -ketoglutarate acts upstream in the cycle to produce citrate, thus circumventing the tormented mitochondrial respiration to produce lipids for energy. While originally described in hypoxic cancer cells,⁴⁰⁵ such a process may also alter myocardial epigenomes.⁴⁰⁶ Last, as α -ketoglutarate levels are supplemented endogenously in hypoxia only via either glutamine or glutamate deamination, it seems consistent that exogenous supplementation of these metabolites protects heart from ischemia.^{407–409}

Hence, epitranscriptomically, it appears congruent that m⁶A levels rise as α -ketoglutarate depletes in myocardial ischemia.^{107,134} Taken together, as overexpression of m⁶A erasers protects myocardium from ischemic insults,^{54,107} FTO is upregulated in cardiomyocytes by leptin adipokine¹¹⁸ and conveys cardioprotection also via stimulation of glucose metabolism,¹⁷⁵ the role of hypoxic cardiometabolism

in controlling cardiac RNA m⁶A dynamics, and vice versa, emerges as being worthy of future study.

CONCLUSIONS

An epitranscriptomic era is unfolding in translational RNA biology and medicine.⁴¹⁰ Here, we have reviewed the fast-growing body of evidence available regarding both initial associative and experimental findings to establish a firm link for the two most common epitranscriptomic modifications, m⁶A and A-to-I, to mirror as well as partake in the onset and development of multiple common cardiovascular diseases. As our current mechanistic understandings can be expected to further crystallize in the future, the potential of modified endogenous RNAs as targets for future cardiovascular pharmacologic development will increase. In addition, as exquisitely positioned at the intersection of our transcribed genome and its ultimate interpretation as functional proteins, these relatively stable, yet dynamic,⁴¹¹ modifications also hold potential for biomarker discovery. Prospective controlled observational cohort studies, such as the The Ischemic Heart Disease Epitranscriptomics and Biomarkers (IHD-EPITRAN) study (www.ihd-epitrans.com), help us to shed light into this fascinating development.⁴¹²

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.omtn.2022.07.018>.

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AUTHOR CONTRIBUTIONS

V.S. collected the related papers, drafted and wrote the manuscript, and drew illustrations. E.K. wrote and revised the manuscript and provided supervision. A.V. revised the manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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