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EDITORIAL

Selective mRNA Translation: A New Player in Ferroptosis After Myocardial Infarction

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Acute myocardial infarction (AMI) remains a leading cause of death worldwide.[1] Despite advances in reperfusion therapies and pharmacological interventions, effective strategies for preventing myocardial loss during AMI remain elusive. Reducing cardiomyocyte death and infarct size is critical for maintaining cardiac function and reducing the incidence and severity of lethal heart failure. Evidence indicates that multiple cell death pathways participate in ischemic injury, including apoptosis, necrosis, necroptosis, pyroptosis, autophagy, and ferroptosis.[2] Among them, ferroptosis, a newly identified iron-dependent programmed cell death, is characterized by lipid peroxidation, redox imbalance, and unique mitochondrial morphological changes such as increased membrane density and cristae destruction.[3] Compared with other cell death types, ferroptosis provides a unique metabolic perspective on AMI. Its hallmark feature, such as iron dysregulation, accumulation of lipid peroxides, and impaired antioxidant defenses further refine our understanding of the metabolic alterations that accompany AMI. We and others recently demonstrated that cardiomyocyte ferroptosis is involved in myocardial ischemia and reperfusion injury.[4,5] Ferroptosis inhibitors that either target iron ions or prevent lipid peroxidation have displayed cardioprotective effects in ischemic heart disease models,[6] indicating a novel avenue for AMI treatment to improve cardiac function. However, how the diverse biochemical and morphological features of ferroptosis are integrated and regulated in AMI and which patient populations may benefit most from therapeutic strategies targeting ferroptosis remain unclear.

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In this issue of *Circulation*, Chen and colleagues[7] provide novel insights by demonstrating that the aldehyde dehydrogenase 2 (ALDH2) genetic variant (ALDH2*2) exacerbates acute heart failure after AMI by promoting cardiomyocyte ferroptosis (Figure). ALDH2 is a mitochondrial enzyme critical for detoxifying ethanol-derived acetaldehyde and lipid aldehydes generated during lipid peroxidation. A single-nucleotide polymorphism in ALDH2, ALDH2*2 (rs671), results in a glutamate-to-lysine substitution at position 504, which restricts substrate access to the catalytic site and markedly reduces enzymatic activity. The present study found that ALDH2*2 carriers showed a ferroptotic plasma signature after AMI and that ALDH2*2 knock-in mice recapitulated this phenotype and displayed worsened cardiac function after myocardial infarction. Mechanistically, ALDH2 mutation or deficiency selectively enhanced the translation of ferroptosis-related mRNAs through ribosome remodeling. Two main advances make this study particularly notable: It identifies selective translation as a key mechanism of cardiomyocyte ferroptosis, and it uncovers the nonenzymatic role of ALDH2 in repressing this process.

The overall rate of protein synthesis is tightly orchestrated and plays a critical role in regulating cell metabolism. In response to stress or developmental cues, cells prioritize the translation of specific mRNAs to rapidly reshape their proteome,[8] a process known as selective translation. This study identified selective mRNA translation as a novel and critical regulatory mechanism in cardiomyocyte ferroptosis.[7] ALDH2*2 knock-in mice exhibit more severe MI, and targeted plasma metabolomics revealed ferroptosis-associated lipid signatures. An interesting finding was that ALDH2 mutation increased the protein levels of

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EDITORIAL

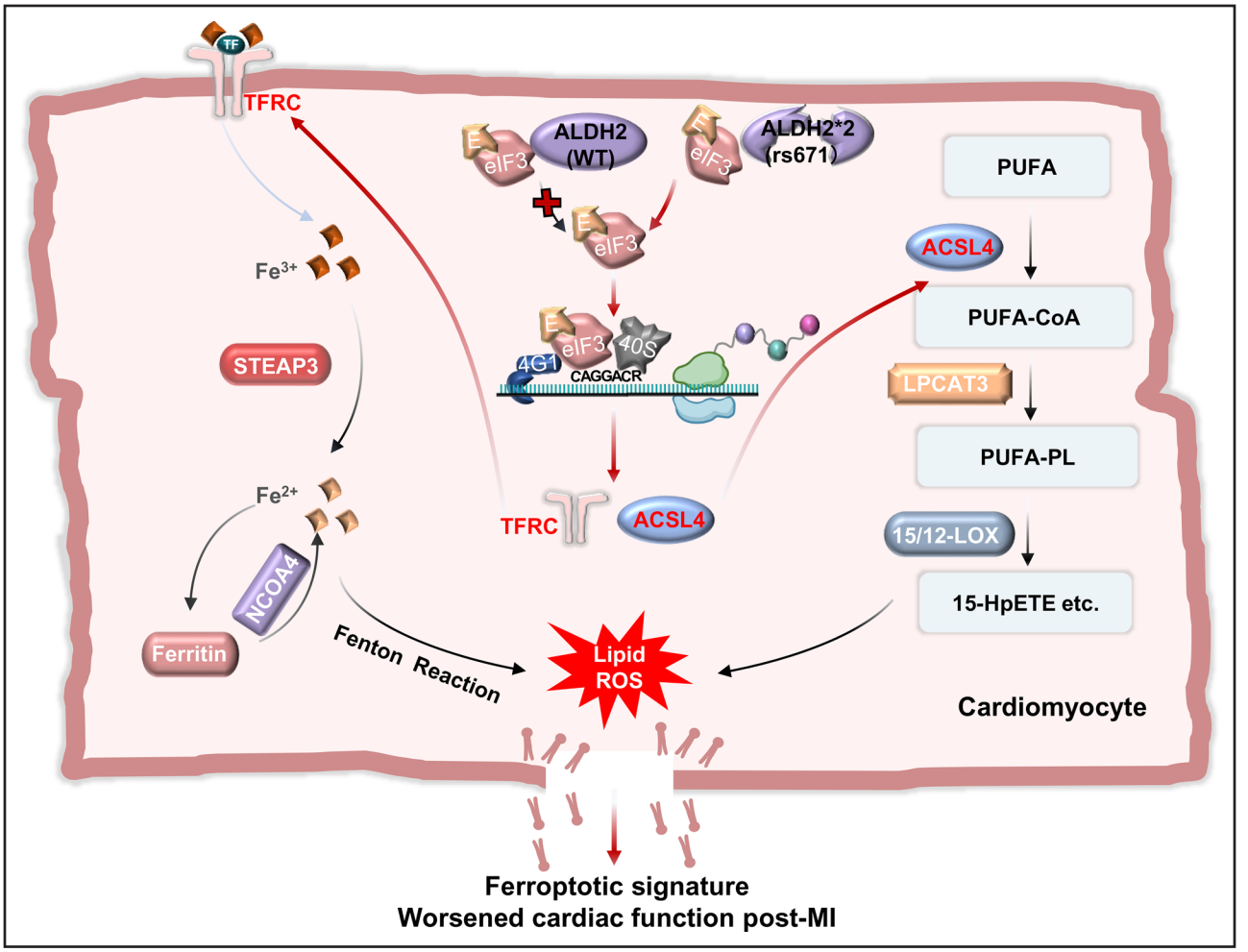

Figure. ALDH2 mutation promotes selective translation of ACSL4 and TFRC and exacerbates heart failure post-AMI. The aldehyde dehydrogenase 2 (ALDH2) genetic variant (ALDH2*2; rs671) releases eukaryotic translation initiation factor (eIF) 3E from its interaction with ALDH2, allowing eIF3E to assemble with eIF4G1 and facilitate the selective translation of GAGGACR-containing transcripts such as ACSL4 (acyl-CoA synthetase long-chain family member 4) and TFRC (transferrin receptor). This enhanced translation promotes cardiomyocyte ferroptosis under ischemic stress and contributes to worsened cardiac function after acute myocardial infarction. PUFA-PL indicates phospholipid-containing polyunsaturated fatty acid chain; ROS, reactive oxygen species; and WT, wild type.

ACSL4 (acyl-CoA synthetase long-chain family member 4) and TFRC (transferrin receptor), 2 well-established ferroptosis markers. After excluding transcriptional regulation and protein degradation, the authors hypothesized that altered translation efficiency might be a key driver. Through ribosome profiling, the authors showed that ALDH2 deficiency globally suppresses translation but selectively enhances the translation of mRNAs containing a conserved GAGGACR motif, thereby fueling ferroptosis. It is important to note that this motif-dependent translational control has been observed in ferroptosis-related and metabolic genes, indicating a master regulatory mechanism for ferroptosis. Mutation of the GAGGACR motif within the 5′ untranslated region abolished this preferential translation and reduced ferroptosis-associated protein synthesis. Selective translation is often governed by dynamic changes in the translational machinery, and the authors demonstrated that ALDH2 deficiency enhances the eukaryotic translation initiation factor (eIF) 3E–eIF4G1 interaction to selectively modulate the translation of genes containing the GAGGACR motif. This mechanism expands our understanding of how cellular stress programs can bypass global translational inhibition to promote cell death, positioning ferroptosis as a precisely coordinated process that integrates metabolic rewiring, iron homeostasis, and translational control.

In the East Asian population, nearly 560 million individuals carry the ALDH2*2 variant. Carriers typically exhibit facial flushing after alcohol consumption and have increased risks of various diseases, including cardiovascular, neurological, dermatological, and oncological disorders.[9] In a cohort of >8000 subjects, ALDH2*2 was associated with a 48% higher risk of coronary artery disease.[10] Traditionally, this elevated risk has been attributed to aldehyde accumulation and loss of detoxification

capacity. Supporting this view, the small-molecule ALDH2 activator Alda-1, which enhances the activity of both ALDH2 and ALDH2*2, demonstrated striking cardioprotective effects by reducing ischemic injury in rat models.[11] Subsequent studies have confirmed the essential role of ALDH2 in ischemic heart disease and highlighted the therapeutic potential of Alda-1.[9] Beyond its well-established effects in cardiomyocytes, enhancing ALDH2 activity with Alda-1 promotes angiogenesis in coronary endothelial cells,[12] whereas ALDH2 deficiency facilitates the mobilization and recruitment of fibroblast progenitor cells in pressure-overloaded heart failure, thereby exacerbating cardiac fibrosis.[13] Thus, these findings indicate that ALDH2 exerts broad cardioprotective effects across multiple cardiac cell types, highlighting the promising therapeutic value of Alda-1 in cardiovascular diseases. However, the authors found that, in the clinical cohort, ALDH2*2 carriers exhibited lower alcohol consumption and, in animal experiments, the ALDH2 agonist Alda-1 failed to alter lactate dehydrogenase levels in either wild-type or ALDH2*2 knock-in mice, highlighting an alcohol-independent effect and important function of the ALDH2 protein besides its enzymatic detoxification activity. Through a series of elegant mechanistic studies, the authors further demonstrated that ALDH2 physically interacts with the eIF3 complex through eIF3E, thereby preventing the formation of the eIF3E-eIF4G1-mRNA ternary complex. Loss of ALDH2 in ALDH2*2 conditions liberates eIF3E, enabling it to assemble with eIF4G1 and promote the selective translation of mRNAs. Consequently, ALDH2 acts as an endogenous translational repressor of ferroptosis-related genes, and its mutation or deficiency primes cardiomyocytes to ferroptosis under ischemic stress. These findings provide new insight into the role of ALDH2 in ischemic heart disease and suggest that preserving ALDH2 expression while enhancing its activity might further amplify its cardioprotective effects. In addition, identifying the full spectrum of GAGGACR-containing transcripts selectively regulated by ALDH2 will deepen our understanding of the ALDH2*2 phenotype and may help explain the reason that this mutation confers a higher risk of coronary artery disease.

It is important to note that AMI is a dynamic, time-dependent process involving coordinated changes in both infarcted and remote myocardium.[14] Necrotic cardiomyocytes release danger signals that activate resident cardiac cells and recruit leukocytes, initiating inflammation that evolves from an early inflammatory phase, dominated by neutrophils and M1 macrophages, to a reparative phase, marked by anti-inflammatory macrophages and tissue repair. Although ferroptosis has been implicated in AMI pathogenesis, an intriguing and clinically relevant question is, "At which stage would targeting ferroptosis yield the maximal therapeutic benefit?" Consistent with this concept, we previously found that apoptosis and necrosis may predominate during the acute ischemia/reperfusion phase, whereas ferroptosis is the dominant mode of cardiomyocyte death ≈24 hours after reperfusion in mice.[5] In this study, the authors found that ALDH2*2 knock-in mice developed accelerated heart failure after MI, accompanied by elevated leukocyte and neutrophil counts, suggesting aggravated neutrophil-driven inflammation. The balance between fatty-acid–derived proinflammatory mediators and specialized proresolving mediators critically determines the duration and resolution of post-AMI inflammatory response.[15] Given that lipidomic analyses indicated profound alterations in ferroptosis-related lipid profiles in ALDH2*2 mice, it is reasonable to hypothesize that ferroptosis inhibition might offer dual benefits in myocardial protection and inflammation resolution. Future time-course intervention studies are warranted to determine the optimal therapeutic window for ferroptosis inhibition in patients with AMI.

From studies such as the present one in *Circulation*, it is evident that defining the specific forms of cardiomyocyte death and their precise regulatory mechanisms during AMI represents the following frontier in therapeutic discovery and clinical translation. This study makes an important contribution by uncovering a novel nonenzymatic role for ALDH2 in repressing the translation of ferroptosis-related genes, thereby establishing selective mRNA translation as a central regulatory mechanism in cardiomyocyte ferroptosis. Elucidating how ALDH2 orchestrates this translational control will refine our understanding of myocardial injury, clarify its temporal complexity after infarction, and open new avenues for protecting the ischemic heart and improving outcomes in patients with AMI.

ARTICLE INFORMATION

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Disclosures

None.

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