MINI-REVIEW



The role of metabolomics in myocardial infarction: a recent mini-review

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Abstract

Myocardial infarction (MI) is one of the most common and important causes of heart failure in critical care and emergency medicine. Incidence of MI and MI-related mortality have been on the rise in the recent past. Metabolomics is a new field that entails analysis of profiles of metabolites (<1250 Da) in living organisms. Currently, several studies have extensively explored the application of metabolomics in medical field. In the current article, the emerging applications of next-generation metabolomics on MI in the previous 10 years were reviewed. The present article thus provides references for further use of metabolomics to guide clinical treatment and provides a basis for prevention of cardiovascular events.

Keywords

Myocardial infarction; Metabolomics; Metabolic biomarkers; Occurrence prediction; Molecular mechanisms

1. Introduction

Myocardial infarction (MI) is a state of acute critical condition in which the coronary artery and its main branches occluded and are characterized by severe stenosis, causing significant decrease and interruption of blood flow. Long-term myocardial ischemia leads to irreversible myocardial necrosis, which can be accompanied by cardiogenic shock and malignant arrhythmia, and can be life-threatening in severe cases. The common risk factors for MI include age, smoking, obesity, diabetes, hyperlipidemia, genetics, and psychological factors. Various methods such as drug thrombolysis, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) are used for clinical treatment of MI. However, MI is still one of the leading causes of death and disability all over the world [1]. Currently, the clinical diagnosis of MI mainly through clinical symptoms of the patient, electrocardiogram, myocardial necrosis markers, or coronary angiography and other auxiliary examinations. However, these diagnostic strategies are not effective because many patients have no or only present with mild clinical symptoms in the early stage of MI, and the electrocardiogram (ECG) results may not be specific to MI. Moreover, the current clinical biomarkers used for MI, such as troponin and creatine kinase, require detection several hours after the onset of the disease [2]. In addition, the cost of coronary angiography which is an invasive examination is too high, resulting in high economic burden to patients. Therefore, there is a need to develop biomarkers that can offer timely, non-invasive, and reliable prediction of the occurrence of MI thus improving clinical diagnosis and prognosis of MI.

Metabolomics is a new omics technology developed after genomics, transcriptomics, and proteomics. Metabolomics involves study of small molecules (with a molecular weight <1250 Da) in organisms, as well as their responses to internal and external factors [3]. Several metabolites have been explored through metabolomics, and the molecular structures have been elucidated, providing a basis for further studies on metabolites. In addition, the study of metabolites can directly reflect the physiological or pathological state of the organism compared with studying the function of genes or proteins. The main methods and effects of different omics technologies are presented in Table 1. The main techniques used in metabolomics include mass spectrometry (MS) (including Gas Chromatography-Mass Spectrometry (GC-MS), Liquid Chromatograph-Mass Spectrometry (LC-MS), and capillary electrophoresis-Mass Spectrometry (CE-MS)) and nuclear magnetic resonance (NMR). Metabolomics can be divided into targeted metabolomics and non-targeted metabolomics based on the type of metabolites. Traditional targeted metabolomics involves analysis of a list of specific metabolites and related metabolic pathways, and is characterized by high precision and accuracy. On the contrary, non-targeted metabolomics focuses on all the metabolites in the biological samples and can provide an overall metabolic profiling of a biological system [4]. Previous studies developed a novel targeted metabolomic method for quantification of hundreds of metabolites simultaneously in a single run [5-7]. This broad-spectrum targeted metabolomic platform transformed traditional assays to the next generation, and is similar or even better compared with non-targeted approach. Metabolomics studies can effectively reflect the pathophysiological process of various disease.

Omics	Research content	Main tools and methods	Application
Genomics	The structure, function, evolution, posi- tioning, editing of the genome, and their impact on organisms	Bioinformatics, genetic analysis, gene expression measurement, gene function identification	Study the genetic basis of disease
Transcriptomic	To situation of gene transcription and the regulation of transcription at an overall level	Full-lengthcomplementaryDNA(cDNA)library,ExpressedSequenceTags(EST)library,cDNA chip, gene expression cluster	Infer the function of unknown genes and reveal the mechanism of action of specific genes
Proteomics	Composition, expression and modifi- cation of the dynamically changing proteins of the body at an overall level, and the interactions and connections between proteins	Protein separation technology, identification technology (biological mass spectrometry), protein interaction analysis technology	Search for and identify disease- related proteins as early clinical diagnosis markers, and explore disease pathogenesis and treat- ment approaches
Metabolomics	Small molecules in the body (<1250 Da), and the changes in the expression of metabolites, as well as the relationship between the physiological and pathological changes of metabolites	NMR, GC-MS, LC-MS, CE-MS	Diagnose diseases by detecting changes in metabolite levels and explore the metabolic mechanism of disease occurrence

TABLE 1. Details on the technical methods and applications of different omics.

Application of metabolomics in medical research has become more in-depth and extensive in recent years, and key breakthroughs have been made in disease diagnosis and drug development, especially in cardiovascular diseases [8–12]. Studies have identified several metabolic biomarkers that can predict the occurrence of MI or guide the prognosis of MI. This article comprises a review of advanced in metabolomic research achieved in the previous 10 years, with the aim of providing a reference for future clinical applications of metabolite markers in diagnosis and treatment of MI.

2. Metabolic markers predict the occurrence of MI

An ideal marker for prediction of MI should be able to indicate changes of the metabolites in the sample which can be easily accessible before MI occurs. This will allow screening of the individuals who may have MI, or directly predict risk of MI occurrence.

Studies have revealed the roles of L-homocysteine (L-HCSA) and cysteine (CA) in predicting cardiovascular risk events [13, 14]. L-HCSA is a sulfur-containing amino acid. Like methionine, it cannot be synthesized in the human body and is only formed through enzyme activity on methionine. L-HCSA is implicated in various metabolic pathways in the body including: (1) it can be methylated under the catalysis of methionine synthase in the presence of vitamin B12 as a coenzyme, and (2) it can utilize vitamin B6 to generate CA through the transsulfuration pathway. A prospective study conducted by Khan et al. [15] reported that the concentration of acidic homocysteine derivatives L-HCSA and CA in the patient's serum showed a significant increase before the occurrence of MI. High concentration of L-HCSA can promote oxidative stress responses and lead to mitochondrial dysfunction through the infect of inflammatory mediators such as reactive oxygen species (ROS). Moreover, L-HCSA can damage cell endothelium and stimulate the proliferation

of vascular smooth muscle cells. In addition, high L-HCSA levels can promote dissolution and destruction of the elastic material in the arterial wall, thus exerting atherosclerotic effect on the arterial wall [16]. Studies report that patients with high L-HCSA levels present with a relative deficiency of vitamin B family [17]. Therefore, folic acid and B vitamins are clinically administered to increase utilization of L-HCSA in the body thus improving cardiovascular symptoms caused by high serum levels of L-HCSA.

Tryptophan (Trp) level in serum had been reported as a potential marker for predicting occurrence of MI [15]. Yoon et al. [18] observed that elevated urine Trp levels were correlated with the risk of coronary heart disease. Trp is an essential amino acid in the human body and can only be ingested exogenously. Metabolism of Trp in the body is mainly through the serotonin pathway and the kynurenine pathway. Trp is mainly metabolized through the kynurenine pathway, and low levels can be directly absorbed in the large intestine. The kynurenine pathway plays an important role in modulation of oxidative stress responses, immune activation, and inflammatory response. Tryptophan-2,3-dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) are key rate-limiting enzymes in kynurenine pathway. Kynurenine (Kyn) is an effective vasodilator and expression of TDO and IDO is significantly upregulated during myocardial ischemia. In addition, the body increases the uptake of free Trp by the kynurenine pathway, reduces the plasma Trp level, increases the Kyn level, and blood vessels vasodilate to increase the blood supply. Studies reported that through exogenously intake can inhibit the expression of IDO, thus reducing the production of Kyn [19]. The ratio of Kyn to Trp (KTR) in plasma can be used as a reference index for evaluating inflammation and cardiovascular events in clinical practice [20]. Low levels of Trp can be converted to 5-hydroxytryptamine (5-HT) under the action of tryptophan decarboxylase and tryptophan hydroxylase enzymes. 5-HT is a neurotransmitter mainly distributed in the human brain and gastrointestinal tract. The peripheral serotonin pathway is involved in vasoconstriction, and regulation of body temperature. Platelet secretes high levels of 5-HT during the activation process when the inner wall of the blood vessel is damaged. 5-HT then promotes the aggregation of platelets and the contraction of smooth muscle, which promotes the formation of vascular plaque and the occurrence of MI to a certain extent [21].

Previous studies report significant correlations between the serum levels of phosphatidylcholine and sphingomyelin concentration, and MI occurrence. Floegel et al. [22] found that levels of diacyl-phosphatidylcholine C38:3, C40:4 and acyl-alkyl-phosphatidylcholine C36:3 in human serum are correlated with risk of MI occurrence. Zhu et al. [23] observed that lysophosphatidylcholine (Lyso-PC) (C18:2), Lyso-PC (C16:0), Lyso-PC (C18:1) are significantly associated with pathogenesis of MI. Wang et al. [24] proposed that the metabolites of dietary phosphatidylcholine can be used for accurate prediction of the risk of cardiovascular disease. The human body releases free fat acids under the action of sphingomyelinase and phospholipase enzymes. Phospholipase is a marker that reflects the inflammation state of blood vessels and is highly associated with atherosclerosis. Endothelial cell membrane ruptures under the action of phospholipase and the production of phosphatidylcholine (PC) is reduced [25]. Notably, Cui et al. [11] reported that plasma phosphatidylcholine diacyl C36:0, C34:2, C36:4, phosphatidic acid C34:1, ceramide, and sphingomyelin diacyl 18:1/20:1 play significant roles in promoting in-stent restenosis (ISR) after percutaneous coronary intervention (PCI). Sphingomyelins in the endoplasmic reticulum are catalyzed and degraded by sphingomyelinase to produce ceramide. Ceramide is involved in the transmission of cell signals, the activation of inflammation, and induction of oxidative stress [26]. In addition, ceramide reduces activity of vasoactive factors such as Nitric Oxide (NO) [27], increases the thickness of arterial lumen, modulates diastolic function of blood vessels, thus causing decrease in vascular blood flow, vascular endothelial damage and dysfunction. Ceramide is a precursor for formation of sphingosine-1phosphate (S1P) through the sphingosine-ceramide pathway. S1P is an important bioactive molecule which can promote dilation of blood vessels, protect cells and effectively prevent myocardial ischemia-reperfusion injury [28].

Secretory phospholipase A2 (sPLA2) can be hydrolyzed to arachidonic acid (AA). Floegel et al. [22] reported a correlation between high serum AA levels and high risk of MI, which has also been confirmed by Nielsen et al. [29] and Sun *et al.* [30]. AA is a type of ω -6 polyunsaturated fatty acid, and is the direct precursor for synthesis of prostaglandins, leukotrienes, and other inflammatory factors. Leukotrienes and their metabolites play a vital role in vascular inflammation and atherosclerosis. AA is implicated in various metabolic pathways in the body, and its accumulation in peripheral tissues aggravates effects of instability factors in blood vessels. AA are converted to 20-hydroxy eicosatetraenoic acid (20-HETE) through cytochrome 450. 20-HETE can act on calcium channels to induce vasoconstriction [31, 32]. Moreover, 20-HETE is associated with vascular endothelial dysfunction and cardiomyocyte necrosis [33]. AA is converted to prostaglandin

(PGF1 α) and thromboxane A2 (TXA2) through activity of various enzymes. PGF1 α inhibits platelet aggregation and promotes vasodilation, whereas TXA2 is implicated in promoting platelet aggregation and inhibition of vasodilation. Under physiological conditions, PGF1 and TXA2 antagonize each other and modulate dynamic balance to maintain normal blood flow. However, this balance is broken under the action of cyclooxygenase (COX) when MI occurs, causing platelet aggregation and increasing blood viscosity, leading to lipid deposition and thrombosis [34]. Notably, studies report a fat-specific phospholipase in adipose tissue associated with obesity, which can activate prostate receptors to produce prostaglandins, reduce Cyclic adenosine monophosphate (cAMP) levels, and promote accumulation of fat [35]. Furthermore, the polymorphism of AA-related genes is a major cause cardiovascular disease [36, 37].

Hence, biological fluids such as plasma, serum, and urine from patients with MI can be collected and analyzed using metabolomic techniques to identify potential markers. We summarize the metabolic markers in biological fluids that predict the occurrence of MI, and their changes compared to controls in Table 2 (Ref. [15, 18, 20, 22, 23, 29]).

3. Metabolic markers decipher the molecular mechanisms of MI

Smoking, hypertension or abnormal lipids panel are key risk factors for cardiovascular events such as atherosclerosis and MI. Several advances have been reported on diagnosis and treatment of MI. However, the pathological mechanism of MI has not been fully elucidated that the potential metabolic pathways involved in pathogenesis of MI are mainly included: (1) oxidative stress and (2) energy metabolism disorders caused by ischemia and (3) abnormal amino acid metabolism [38, 39]. Use of metabolomics to study the changes of metabolites after MI can provide comprehensive information on the metabolic characteristics and pathological mechanisms of MI, and provide a reference for discovering therapeutic targets for MI. Potential metabolic pathways implicated in pathogenesis of MI are presented in Fig. 1.

3.1 Energy metabolism

The main energy source for human cardiomyocytes under normal physiological conditions is aerobic oxidation of fatty acids and glucose. Although aerobic oxidation is the primary energy source for the myocardium under MI conditions, the level of free fatty acids in the heart is reduced. This can be attributed to downregulation of fatty acid oxidase gene expression thus aerobic oxidation is reduced. A study by Zhang et al. [40] proved that lipid metabolism is the most significant change observed after PCI surgery. Blood flow through the heart decreases sharply in a short period of time, thus myocardial cells exhibit hypoxia state, and anaerobic oxidative glycolysis is mainly involved in replenishment of certain energy during this state [41]. Latic acid generated during glycolysis can be used as a substrate for myocardial metabolism by being channeled to the tricarboxylic acid (TCA) cycle. Hypoxia inhibits synthesis of reduced coenzymes re-

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Metabolite	Sample type	Changes in MI compares to controls
L-homocysteine Sulfinic acid, Cysteic acid, Carnitine [15]	Serum	Increased
Tryptophan [18]	Urine	Increased
Tryptophan (Trp), kynurenine (Kyn), 5-hydroxytryptamine (5-HT) [20]	Plasma	Trp and 5-HT were increased, Kyn was decreased
acylalkyl-phosphatidylcholine C36:3 and diacyl-phosphatidylcholines C38:3 and C40:4 [22]	Serum	Increased
Phosphatidylserine, C16-sphingosine, N-methyl arachidonic amide, N- (2-methoxyethyl) arachidonic amide, lyso-phosphatidylcholine (lyso- PC) (C18:2), lyso-PC (C16:0), lyso-PC (C18:1), arachidonic acid, and linoleic acid [23]	Plasma	N-methyl arachidonic amide was increased; Others biomarkers were decreased.
Arachidonic acid [29]	Gluteal adipose tissue	Increased

TABLE 2. Metabolic biomarkers predict the occurrence of MI.



FIGURE 1. Metabolic pathways and relationships involved in biomarkers found in the blood (plasma and serum) of patients with myocardial infarction.

quired in the TCA cycle, thus TCA cycle is blocked. Hypoxia inducible factor-1 (HIF-1) is activated during MI. HIF-1 promotes a shift of energy acquisition from TCA cycle to glycolysis, which reduces oxygen consumption by inhibiting mitochondrial respiration thus helps in maintaining a balance in energy metabolism. Moreover, anaerobic glycolysis can provide some energy for biological processes. Accumulation of lactic acid produced during glycolysis [42] can cause various symptoms such as angina pectoris and metabolic acidosis.

HIF-1 exerts a protective effect on the myocardium immediately after MI [43]. HIF-1 can increase the supply and delivery of oxygen by regulating levels of vascular endothelial growth factor and erythropoietin, and can effectively alleviate myocardial injury caused by ischemia-reperfusion [44]. Increase of total myocardial phosphate level after myocardial infarction indicates a decrease in synthesis of Adenosine-Triphosphate (ATP). However, activities of phosphorylase and glycolysisrelated enzymes are higher in the subendocardial region, implying that glycolysis mainly occurs in the subendocardial region during MI [45].

A significant correlation occurs between high serum-free Lcarnitine levels and MI [38, 46]. L-carnitine is a trimethylated amino acid, which can be synthesized endogenously from methionine and lysine, or can be exogenously supplemented through ingested food. Carnitine is implicated in energy production in the body and it plays an important role in human metabolism. It can be used as a carrier for transport of longchain fatty acids (LCFA) enter into mitochondria through formation of acyl carnitine, which is involved in β oxidation of fatty acids in mitochondria. Fatty acid oxidation in mitochondria provides high energy levels for the myocardium and skeletal muscle. Carnitine palmitoyltransferase is a key rate-limiting enzyme in fatty acid β oxidation. Increase in L-carnitine level in blood during MI can be attributed to hypoxia caused by ischemia. Fatty acid oxidation in cardiomyocyte mitochondria is thus blocked, and acylcarnitines are released into the bloodstream, resulting in dysregulated fatty acid metabolism [47]. Exogenous supplementation of L-carnitine can reduce oxidative stress damage, accelerate utilization of fatty acids, and can exert a protective effect on the heart [48]. Koeth et al. [49] reported that gut microbes have an atherosclerotic effect on carnitine metabolism in red meat. DiNicolantonio et al. [50] conducted a meta-analysis and the finding showed that administration of L-carnitine can reduce MI-related mortality.

3.2 Oxidative stress

[51] reported that serum levels of S-Nam *et al*. Adenosylmethionine (SAM) and the ratio of SAM to s-Adenosylhomocysteine (SAH) decreased were significantly low in a rat model of myocardial ischemia relative to the level in control rats. SAM and SAH are main products of the methionine cycle. SAM is converted to SAH through transmethylation, and the two compounds are implicated in metabolism of homocysteine [52]. Decrease in the ratio of SAM/SAH indicates that the methylation reaction is limited, and previous studies report that this dysregulation may be attributed to activity of coenzyme Q10 (COQ10). COQ10 is a fat-soluble ubiquinone, which is widely distributed in the myocardium. COQ10 is an important antioxidant in the human body [53], and plays a key role in process of ATP generation through mitochondrial oxidative phosphorylation. Notably, COQ10 is highly expressed in cardiomyocytes owing to the high ATP demand in these cells. Decrease in COQ enzyme protein activity after myocardial ischemia results in a decrease in synthesis of ATP. Biosynthesis of COQ10 gradually increases with age and tends to be stable in adults, however, the synthesis ability in the middle-aged and elderly population is low. Cytokines are related after MI thus inducing inflammatory response. Ischemic stress can promote the release of cytokines. The release of cytokines such as tumor necrosis factor- α (TNF- α), interleukin- 6 (IL-6), and interleukin- 1b (IL-1b) occurs as a response to ventricular remodeling [54]. Acute myocardial ischemia promotes production and accumulation of ROS. ROS can react with proteins and lipids in cells and blood vessels to

generate reactive nitrogen species. The reactive nitrogen species are implicated in aggravation of cell and blood vessel damage, and stimulation of cardiomyocyte proliferation and myocardial hypertrophy. In addition, reactive nitrogen species can combine with NO and inhibit induction of dilation blood vessels by NO [55]. COQ10 can inhibit binding of active nitrogen species to NO, thus reducing production of peroxides in mitochondria, and abrogate formation of lipid superoxide radicals. Moreover, COQ can promote production of platelet growth factor (PGF), relieve blood vessel pressure, and alleviate the damage caused by oxidative stress. In addition, studies report that COQ10 has a direct anti-atherosclerosis effect [56], which is attributed to ability of COQ10 to stabilize low-density lipoproteins and prevent its peroxidation. Exogenous supplementation of COQ10 can effectively reduce blood pressure [57], as well as the size of atherosclerotic lesions, thus reducing the incidence of cardiovascular events.

Succinic acid levels in the blood are significantly high in ischemic tissues. Succinic acid is an intermediate product of TCA cycle [58]. The accumulation of succinic acid increases the risk of reperfusion injury after myocardial infarction. Succinic acid can be formed from malic acid and fumaric acid during myocardial ischemia. Succinic acid generates fumaric acid under the action of succinate dehydrogenase when reperfusion occurs. In addition, high levels of 1,5-dihydroflavin adenine dinucleotide (FADH2) are generated which play a role in transfer of electrons and activation of mitochondrial complex I, thus promoting production of large amounts of superoxide, and causes myocardial ischemia-reperfusion (IR) injury [59].

3.3 Amino acid metabolism

TCA cycle is significantly limited during MI. TCA cycle is the common metabolic pathway of the three major nutrients (carbohydrates, lipids and proteins) in the body. Amino acids are important metabolites mainly derived from diet in the body. Myocardial infarction induces release and hydrolysis of proteins by necrotic tissue, thus differences in amino acid metabolism are observed before and after MI [60]. Previous studies reported that the level of branched-chain amino acids (BCAA) is significantly high in patients with myocardial infarction compared with controls [39, 61]. Dysregulated BCAA metabolism is highly associated with cardiovascular events. BCAA level in circulation is correlated with abnormal blood pressure, high level of blood lipids and glucose tolerance [62]. BCAA include leucine, valine and isoleucine, which are essential amino acids in the human body. These amino acids can be directly metabolized in the heart, brain, and muscle tissues to provide energy to the body organs. Branchedchain ketoacid dehydrogenase (BCKDH) is dephosphorylated under the stress condition of myocardial ischemia [63], leading to accumulation of BCAA. BCKDH is the key rate-limiting enzyme in catabolism of BCAA. In addition, the level of branched-chain ketoacid (BCKA) increases during myocardial ischemia, thus promoting production of high levels of peroxides in mitochondria [64], ultimately affecting respiratory function of mitochondria. A study by Dong [65] reported that BCKA rather than BCAA protects cells against oxidative stress and has a protective effect on acute myocardial ischemiareperfusion injury. However, the effect of BCKA on myocardial protection should be explored further.

McKirnan *et al.* [66] reported high level of taurine in rabbit ventricular muscle after MI. Taurine is a sulfur-containing β amino acid product, which is widely distributed in the human body and is synthesized from cysteine and methionine. Early compensatory remodeling of the ventricle after MI is manifested as enlarged ventricular cavity, whereas myocardial hypertrophy and progressive reduction of cardiac function are observed in the late stages. These processes may evolve into heart failure, and sudden death may occur in severe cases [67]. Taurine supplementation reduces serum triglyceride levels, prevents atherosclerosis [68], and reduces ventricular remodeling after MI [69].

4. Metabolic markers predict the prognosis after MI

Several markers have been identified that can be used for timely prediction of the occurrence of MI, However, good treatment and prognosis are more important for patients who have already developed MI. Prognosis of MI patients is often related to correlated with the age, lifestyle, and whether the patient receives effective therapies. Antithrombotic therapy, β blockers, and statins are widely used in secondary prevention of MI [70]. Metabolomics can be used to identify effective biomarkers for patients diagnosed with myocardial infarction for prognosis prediction.

Essential fatty acids (EFA) are a key part of phospholipids. EFA can maintain normal metabolism in the body and cannot be synthesized by the body. Supplement of EFA through exogenous food intake requires administration of an appropriate proportion to maintain the balance of metabolism in the body. In theory, unbalanced ratio of EFA in the body such as the ratio of ω -6 and ω -3 EFA, indicates that the body is under stress. Increase in serum ω -6 polyunsaturated fatty acids such as AA is positively correlated with occurrence of MI [22]. Masayuki [71] explored the relationship between the levels of AA and eicosapentaenoic acid (EPA), and the occurrence of adverse events after MI and the results showed a lower level of EPA in the group with adverse events relative to the control. This finding indicates that unsaturated fatty acids can be used to predict poor prognosis of patients with acute myocardial infarction (AMI). Moreover, Lazaro et al. [72] reported that eating foods rich in EPA and a-linolenic acid (ALA) can improve prognosis of patients with ST-segment elevation myocardial infarction (STEMI). High serum ω -6/ ω -3 ratio is correlated with cardiovascular disease, whereas low serum ω -3 EFA levels are associated with high risk of sudden death [73]. EPA prevents platelet aggregation and exhibits an opposite effect to that of AA in atherosclerosis. Increase of in EPA level increases anti-inflammatory effect in the body and reduces the effect of inflammatory factors such as IL-1.

Vignoli *et al.* [74] used metabonomic network analysis technology to analyze the serum of patients who died within two years of AMI (death group) and patients who survived more than two years (survival group). The findings showed a significant difference in serum creatinine level between the

two groups. The level of serum creatinine in patients who died within 2 years was higher relative to the level in patients who survived longer, implying that the level of serum creatinine is correlated with the prognosis of MI. Serum creatinine comprises endogenous creatinine and exogenous creatinine. Exogenous creatinine is mainly derived from food intake, whereas endogenous creatinine is mainly formed through metabolism of muscle tissue. High serum creatinine level is an independent risk factor for prognosis of MI [75]. Clearance of creatinine in the blood is carried out by the kidney. Therefore, myocardial infarction patients with kidney disease have a reduced clearance rate of creatinine. This results in increased accumulation of creatinine in blood, thus affecting the survival rate of MI patients [76].

Additionally, a previous study reports a relationship between elevated mannose levels and cardiovascular death [77]. Mardinoglu *et al.* [78] reported significant association between plasma mannose levels and cardiovascular disease, and type 2 diabetes. Mannose cannot be absorbed and fully digested in the human body. Therefore, mannose is mainly excreted in urine in unchanged form, whereas low levels are metabolized by hexokinase enzyme. Patients who die within two years after MI have higher levels of mannose in their plasma.

Patients who die within two years after MI diagnosis exhibit lower plasma histidine levels. Plasma histidine level decreases in patients with thrombotic MI, but not in patients with non-thrombotic MI [79], which is a pathological difference attributed to the presence of thrombotic metabolites. Histidine is an essential amino acid in children, whereas it can be synthesized from intermediates in adults. Histidine can be metabolized into histamine under the catalytic activity of histamine decarboxylase (HDC). Histamine plays a role in vasodilation of blood vessels and reduces platelet aggregation. Chen et al. [80] found that endogenous histamine derived from myeloid cells can inhibit occurrence of myocardial fibrosis after MI. Notably, knocking out decarboxylase related genes increases MI-related mortality. Immune response is activated after occurrence of MI, resulting in increasing the levels of inflammatory factors such as IL-6 and fibrosis factor transforming growth factor- β (TGF- β). Moreover, HDC knockout mice have higher levels, and activates proliferation of fibroblasts indicating that histamine has exerted an inhibitory effect on fibroblast proliferation and myocardial fibrosis, thus exhibiting a protective effect on the myocardium. In addition, exogenous histamine supplementation can alleviate the damage caused by MI. Isoproterenol is a β -adrenoceptor agonist which can activate β-adrenoceptor in the myocardium, increase heart rate and oxygen consumption, decrease activity of antioxidant enzymes. Furthermore, it and cause severe oxidative stress, inflammatory reaction, and further promote platelet aggregation. Moradi-Arzeloo et al. [81] reported that histidine and vitamin C can inhibit production of ROS and prevent myocardial damage.

5. Limitations of metabolomics and prospective

Current metabolomic research has limitations which can be circumvented through following suggestions: (1) Most metabolomics studies are based on small sample sizes and larger populations or multi-center studies have not been performed, thus reducing the credibility of identified biomarkers. Therefore, research based on multiple centers and large populations should be conducted to validate these findings. (2) Different research teams are involved in identification of different markers, thus the sample processing methods, and data analysis methods used are different. Use of unified standards can improve credibility and validate application of detected biomarkers. In addition, a metabolomics library can be established to facilitate future metabolism-related research based on published literature on metabolic markers [82]. (3) Biological significance and function of identified markers should can be verified in animal models, to explore the molecular function and pathological mechanism underlying the function of selected metabolites. Metabolomics can be combined with other omics to supplement and improve the findings owing to the correlation between different omics fields. (4) Simple and rapid detection methods for verified biomarkers can be further developed, such as enzyme-linked immunosorbent assay (ELISA) kit methods. Moreover, these detection methods can be combined with elucidation of the pathological mechanism to achieve early intervention for MI.

6. Conclusions

Myocardial infarction significantly affects the quality of life of patients and is associated with high mortality rates. Metabolomics is an important technology for exploring the changes of metabolites in organisms in addition to genomics, transcriptome, and proteomics. Metabolomics can be used for timely prediction of risk, for MI and associated adverse cardiovascular events, including occurrence of for reinfarction after treatment, thus improving prognosis of MI patients. In conclusion, metabolomics is an emerging omics field highly effective in identification of differential metabolites before and after myocardial infarction. Metabolomics has high potential for early diagnosis and prediction, and play key roles in elucidating the mechanism and can be used identify prognosis for myocardial infarction.

AUTHOR CONTRIBUTIONS

CS and PZ contributed conception of this minireview. XM wrote the first draft of the minireview. All authors contributed to the revision, reading and approval of the manuscript for submission.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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