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Research Paper

miR-200a-5p regulates myocardial necroptosis induced by Se deficiency via targeting RNF11

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ABSTRACT

Necroptosis has been discovered as a new paradigm of cell death and may play a key role in heart disease and selenium (Se) deficiency. Hence, we detected the specific microRNA (miRNA) in response to Se-deficient heart using microRNAome analysis. For high-throughput sequencing using Se-deficient chicken cardiac tissue, we selected miR-200a-5p and its target gene ring finger protein 11 (RNF11) based on differential expression in cardiac tissue and confirmed the relationship between miR-200a-5p and RNF11 by dual luciferase reporter assay and real-time quantitative PCR (qRT-PCR) in cardiomyocytes. We further explored the function of miR-200a-5p and observed that overexpression of miR-200a-5p spark the receptor interacting serine/threonine kinase 3 (RIP3)-dependent necroptosis *in vivo* and *in vitro*. To understand whether miR-200a-5p and RNF11 are involved in the RIP3-dependent necroptosis pathway, we presumed that oxidative stress, inflammation response and the mitogen-activated protein kinase (MAPK) pathway might trigger necroptosis. Interestingly, necroptosis trigger, z-VAD-fmk, failed to induce necroptosis but enhanced cell survival against necrosis in cardiomyocytes with knockdown of miR-200a-5p. Our present study provides a new insight that the modulation of miR-200a-5p and its target gene might block necroptosis in the heart, revealing a novel myocardial necrosis regulation model in heart disease.

1. Introduction

Selenium (Se) is an essential trace element for the internal environment in the body during homeostasis and pathogenesis [1]. The current issue of Se deficiency in the environment is attracting increasing attention globally, as this deficiency may lead to many diseases, including heart disease, cancer and diabetes. Se deficiency in humans and animals can cause severe myocardial injury, such as Chagas disease in humans [2], Keshan disease [3], mulberry heart of swine [4], chronic heart failure in rats, myocardial hemorrhage and necrosis [5], accompanied by myocardial fiber sarcoplasmic edema and vacuolization of mitochondria in avian species. Research during the last decade of myocardial injury has mainly focused on apoptosis and inflammation. The related literature confirmed that heart disease induced by Se deficiency is mainly due to cardiomyocyte injury caused by oxidative stress and inflammation [6]. Cellular responses to Se deficiency often lead to the induction of inflammation and oxidative overload involving multiple signaling pathways. Jie Y et al. reported that an Se-deficient diet increased the apoptosis of chicken heart *in vitro* and *in vivo*, and other researchers have shown that Se deficiency enhances the main pro-apoptotic factors (Bax and p53) in a mouse model [7,8].

Comprehensive heart disease is intricately connected to myocardial cell death, and the main form of myocardial cell death induced by Se deficiency is necrosis [9]. Necroptosis is a type of non-apoptosis programmed cell death, which is emerging as a new target in inflammation disease and heart disease [10]. Accumulating evidence has revealed that necroptosis is carried out by complex execution pathways and activators, such as TNF-α. Most of our knowledge of necroptosis comes from studies of receptor interacting serine/ threonine kinase 3 (RIP3)-dependent necroptosis, which is mediated by the activation of TNF-α and suppression of Caspase 8 involving receptor interacting serine/ threonine kinase 1 (RIP1) and RIP3 complex with the recruitment and phosphorylation of mixed lineage kinase domain-like (MLKL) [11]. MicroRNAs (miRNAs), as non-coding RNAs, can post-translationally modify mRNA by binding to its target sequence to block mRNA translation and protein production, followed by the regulation of different

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biological reactions, such as cell survival and cell death [12]. Recent studies have shown that miRNA can control necroptosis by modulating related genes [13]. miR-155 can target RIP1 to activate the Akt survival pathway and prevent the occurrence of programmed necrosis of human cardiac progenitor cells after transplantation [14]. In addition, miR-874 plays a key role in cardiomyocyte necrosis and myocardial infarction. miR-874 can mediate necroptosis by targeting Caspase 8 and disable the ability of Caspase 8 to repress the necrotic program [15].

Oxidative stress and cell death occur in the imbalance of reactive oxygen species (ROS) generation, and the high level of ROS production may damage the organelle and DNA and induce necroptosis [16]. Oxidative stress and inflammation have been considered a driving force for RIP3-dependent necroptosis [17]. A related study demonstrated that many ROS produced in mitochondria can activate RIP1 serine residue 161 (S161) autophosphorylation, and this specific process modifies RIP1 to recruit RIP3 to form the necrosome, a key controller of TNF-induced necroptosis [18]. In addition, the importance of excessive inflammation in inducing necroptosis has also been confirmed *in vivo* in children with inflammatory bowel disease [19]. The ubiquitin-editing enzyme A20 prevents apoptosis induced by the TNF-α pathway as an anti-inflammatory protein. Onizawa et al. reported that A20 restricted necroptosis by limiting the ubiquitination of RIP3 in mouse T cells [20]. As an essential component of the A20 ubiquitin-editing protein, ring finger protein 11 (RNF11) has been implicated in inflammation induced by TNF-α signaling [21]. A specific PPXY motif of RNF11 could bind to the Itch WW domain to facilitate Itch ubiquitination of target proteins, such as RIP1.

In this setting, the present experiment was designed to investigate whether miRNA can regulate myocardial necrosis induced by Se deficiency. In the proteomics and miRNA genomics detection, miR-200a-5p was identified to be up-regulated under Se-deficient stimulation, and its target gene RNF11 was found by regulating the expression of miR-200a-5p *in vitro*. We elaborated that the specific Se-deficient-responsive miRNAs likely modulate the target gene RNF11 involved in necroptosis. Thus, through the inhibition of necroptosis and induction, we can suppress necroptosis with knockdown of miR-200a-5p in cardiomyocytes. Our results reveal a novel myocardial necrosis induced by an Se-deficient model composed of miR-200a-5p and RNF11 and new insights for the understanding of heart syndrome treatment.

2. Results

2.1. Se deficiency induces necrotic cell death in the heart

We observed myocardial tissues stained by hematoxylin and eosin (H&E) in the control group and Se-deficient group. The histopathological changes in myocardial tissues are shown in Fig. 1. The myocardial tissues in the control group displayed normal morphologies. However, many typical myocardial necrosis features appeared in the tissues of the Se-deficient group, including myocardial fiber fracture disintegration, myofilament implication and muscle fiber bundles accompanied by inflammatory cell infiltration. All these observations confirmed that Se deficiency induces necrosis in the heart. We reproduced the necrotic model.

2.2. miR-200a-5p is involved in Se deficiency-induced cardiac necrosis in the chick through targeting RNF11

Se deficiency is well known as an important factor inducing necrosis. To determine the effect of Se deficiency on the miRNA expression levels, we performed high-throughput sequencing with Se-deficient chicken cardiac tissue in the miRNA genomics group. Based on miRNA genomics group analysis, we selected the in Se-specific miRNA-miR-200a-5p, which is up-regulated in the Se-deficient cardiac group compared with that in the control group (Fig. 2**A**, Table. S1). To confirm the genomics group result, we carried out quantitative reverse transcription-polymerase chain reaction (qRT-PCR) to verify the miRNA levels *in vivo*. Consistent with the predicted results, miR-200a-5p was substantially elevated 3 times in the Se-deficient cardiac compared with the control cardiac (Fig. 2**B**).

To discovered how miR-200a elicits its effect on cardiac necrosis triggered by Se deficiency, we selected downstream target genes of miR-200a-5p. Using the website-based miRNA target prediction databases, we defined several targets of miR-200a-5p. Some of the predicted targets are implicated in the modulation of inflammation and cell death. We defined target genes through running qRT-PCT in vivo and in vitro (Fig. 2**C**, Fig. 2**D**, Fig. 2**E**). The mRNA expression of RNF11 was reduced by ~ 50% in Se-deficient cardiomyocytes compared with control cardiomyocytes. Additionally, the expression of RNF11 was reduced in response to the increasing level of miR-200a-5p and elevated in response to the decreasing level of miR-200a-5p in cardiomyocytes cultured *in vitro*. Using the 3'UTR-mediated luciferase activity assay, we found that the miR-200a-5p mimic markedly modulated the luciferase activities driven by RNF11 mRNA 3′UTR plasmids. However, the miR-200a-5p mimic failed to inhibit the luciferase activities driven by the 3′UTR plasmids whose miRNA target sequences were mutated (Fig. 2**F**, Fig. 2**G**). These results suggest that RNF11 is a specific downstream target gene of miR-200a-5p and may be involved in cardiac necrosis triggered by Se deficiency.

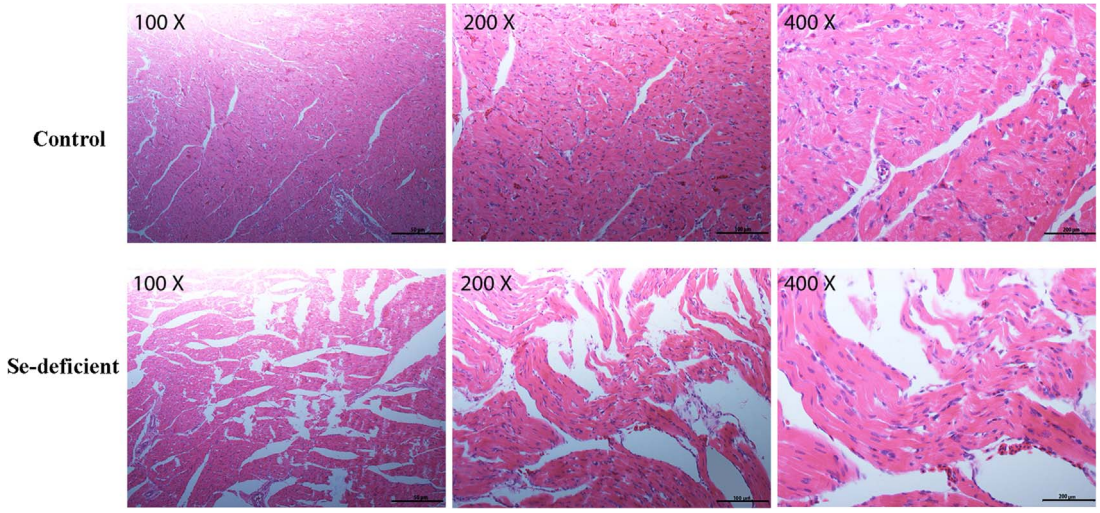

Fig. 1. HE staining for myocardial tissues in the control group and Se-deficient group. Histopathological analysis of the heart in the control group and Se-deficient group.

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