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Review Article

The Role of MicroRNAs in Hyperlipidemia: From Pathogenesis to Therapeutical Application

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Hyperlipidemia is a common metabolic disorder with high morbidity and mortality, which brings heavy burden on social. Understanding its pathogenesis and finding its potential therapeutic targets are the focus of current research in this field. In recent years, an increasing number of studies have proved that miRNAs play vital roles in regulating lipid metabolism and were considered as promising therapeutic targets for hyperlipidemia and related diseases. It is demonstrated that miR-191, miR-222, miR-224, miR-27a, miR-378a-3p, miR-140-5p, miR-483, and miR-520d-5p were closely associated with the pathogenesis of hyperlipidemia. In this review, we provide brief overviews about advances in miRNAs in hyperlipidemia and its potential clinical application value.

1. Introduction

Hyperlipidemia is a metabolic disorder with high morbidity and high mortality, usually characterized by lipid dysfunction and oxidative stress [1]. Hyperlipidemia is one of the recognized risk factors for cardiovascular disease (CVD) [2], where elevated low-density lipoprotein cholesterol (LDL-C) is considered a major factor in the development of atherosclerosis [3] and coronary heart disease [4]. It is estimated that the reduction of LDL-C by 10 mmol/L is associated with a 22% reduction in cardiovascular mortality and incidence rate, while the triacylglycerol (TG) concentration greater than 10 mmol/L is associated with a significant increase in risk of acute pancreatitis and cardiovascular disease [5, 6]. With the increasing use of miRNA microarrays and gene expression microarrays for hyperlipidemia gene expression profiling in recent years, we have gained a deeper understanding of the molecular biological mechanisms underlying the occurrence and development of hyperlipidemia. MicroRNAs are short (~21 nucleotides) noncoding RNA molecules that play an important role in the posttranscriptional regulation of gene expression in eukaryotes [7]. miRNAs are found in most eukaryotes [8] and commonly aberrantly expressed in human diseases [9]. Many studies have shown that miRNAs are involved in the regulation of a range of human diseases, including cancer, hepatitis, and cardiovascular diseases [10–12]. miRNAs have also been found involving in the pathogenesis of many allergic diseases, including asthma, eosinophilic esophagitis, allergic rhinitis, and eczema [13–15]. miRNAs are stable in the peripheral blood circulation and exhibit good physiological properties and can tolerate different temperatures, pH, storage times, and even repeated freezing and thawing [16]. It is well demonstrated that miRNAs play an important role in lipid metabolism and are important posttranscriptional regulators of genes that related with lipid homeostasis [17]. For example, previous studies identified miRNAs, such as miR-128 and miR-144, are regulators of plasma lipoprotein and

cholesterol levels [18, 19]. Thus, discovery of specific hyperlipidemia-associated miRNAs may be a viable way to design miRNA-based therapies or obtain new prognostic markers in lipid metabolism-related diseases [20]. With the progressive research on the mechanism of small nucleic acids [21], it will greatly promote the translation of basic research into clinical practice and bring new opportunities for the development of drugs for the treatment of hyperlipidemia.

2. Hyperlipidemia

Hyperlipidemia is a disorder of lipid metabolism [22], usually with high levels of lipids in plasm because of the abnormal lipids transport and disturbed lipid metabolism [23]. Hyperlipidemia is characterized by elevated serum levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) or reduced levels of high-density lipoprotein cholesterol (HDL-C) [24]. LDL-C is responsible for transporting fat molecules into cells, and if they are oxidized during transport, they can easily form plaques within the arterial walls, driving the progression of atherosclerosis. HDL-C helps the body to remove LDL from the arteries and brings it back to the liver to break it down, thus preventing cardiovascular disease [25, 26]. Hyperlipidemia is a serious health risk. Studies have shown that hyperlipidemia is involved in a range of diseases such as stroke, atherosclerosis, coronary heart disease, myocardial infarction, diabetes, and pancreatitis [22, 27–31] and is also closely associated with the development of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) [32]. Hyperlipidemia has a high prevalence in China, there were approximately 160 million patients with dyslipidemia in 2002, and this number is increasing [33]. In the United States, according to the 2011-2012 National Health and Nutrition Examination Survey, about 12.9% of adults over the age of 20 had excess total cholesterol [34]. More than 100 million people (about 53% of adults) have elevated LDL-C levels [35].

Hyperlipidemia can be divided into primary hyperlipidemia and secondary hyperlipidemia. Primary hyperlipidemia is characterized by a familial predisposition. Familial hypercholesterolemia (FH) is one of the most common monogenic dyslipidemias with a heterozygous prevalence of 1 : 250, which causes atherosclerosis and increases the risk of premature coronary artery disease (CAD) [36, 37]. An unhealthy diet and less physical activity are considered the most critical risk factors for hyperlipidemia [38]. Secondary hyperlipidemia is a dyslipidemia caused by other diseases, such as diabetes and hypertension. According to the Guidelines for the Prevention and Treatment of Dyslipidemia in Chinese Adults, when meeting one of the following criteria can be diagnosed as hyperlipidemia: $TC \geq 5.2$ mmol/L, $TG \geq 1.7$ mmol/L, $LDL-C \geq 3.4$ mmol/L, $non-HDL-C \geq 4.1$ mmol/L, or $HDL-C < 1.0$ mmol/L. Clinically, hyperlipidemia can be classified as hypercholesterolemia, hypertriglyceridemia, hyper-LDL-C, and mixed hyperlipidemia according to the difference of clinical indicators.

3. MicroRNAs

MicroRNAs (miRNAs) are endogenously transcribed non-coding RNAs, approximately 22 nt long, which are key regulators involving in many biological processes [39]. The first miRNA was identified in 1993 as a small RNA transcribed from the Caenorhabditis elegans lin-4 locus [40], and 7 years later, the first human miRNA let-7 was identified [41]. In humans, miRNAs involve in the expression of protein-coding genes and considered to be a complex gene expression modifier [42]. By binding to the 3′UTR of mRNA, miRNAs can posttranscriptionally inhibit mRNA translation into proteins or promote mRNA degradation [43, 44]. Based on such principles, scientists at the Sanger Institute established the microRNA Registry database to facilitate miRNAs research, later renamed miRbase in 2002 [45]. During the past decades, the number of discovered miRNAs increases year by year, and miRNAs have become a hot topic in medical research. Since miRNAs are negative regulator of genes, any change of the expression level of a certain miRNA may affect its corresponding target gene expression, even cellular homeostasis [46, 47]. Although many studies have shown changes in the expression levels of miRNAs in diseased states, their application as clinical biomarkers is still in its infancy [48, 49].

The biogenesis of miRNAs can be divided into multiple processes (Figure 1). First, synthesis of pri-miRNA is a large structure containing sequences of miRNAs and forms in the nucleus under the action of RNA polymerase II enzyme. The sequence of pri-miRNA may be an independent miRNA gene or parts of introns of protein coding for RNA polymerase II transcripts [50]. Then, the pri-miRNA transcript is cleaved in the nucleus by microprocessor, a catalytic complex composed of Drosha and Di George critical region 8 (DGCR8) [51, 52]. After that, the exportin 5 exports pre-miRNA to the cytoplasm where it is cleaved by Disher near the loop into small double-stranded RNAs [53]. This double-stranded RNA has a structure of 3′overhangs and strands that were named as guide strand and passenger strand according to their function, respectively, [54]. The guide strand, that is mature miRNA, was identified by AGO protein and forms the RNA-induced silencing complex (RISC) [55], while the passenger strand of the miRNA duplex is degraded [56, 57]. The RISC directs the miRNA to bind to its corresponding target mRNA and blocks gene expression by translational repression or mRNA degradation. This process is associated with the action of *a* about 8 nucleotides in length seed region of miRNA. The seed region will recognize the binding site of 3′UTR of mRNA by the way Watson-Crick complementary and lead to mRNA instability and finally translational repression [58, 59].

4. The Relationship between Hyperlipidemia and miRNA

It was demonstrated that miRNAs have important role in the development and progression of hyperlipidemia, which will open a new field for the study of hyperlipidemia [60].

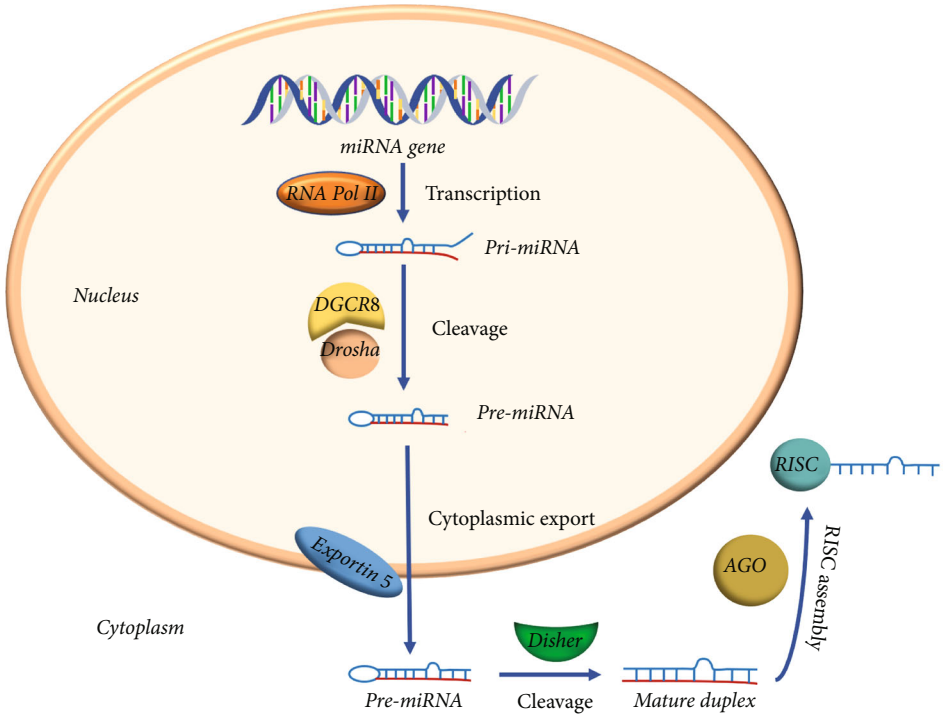

Figure 1: Overview of the miRNA biogenesis.

Several miRNAs in patients with hyperlipidemia were found undergone altered, such as miRNA-191-3p, miRNA-933, miRNA-425-3p, and miR-208a [61]. This suggested that miRNAs may involves in the pathogenesis of hyperlipidemia. In vitro and in vivo studies have revealed that miRNAs play roles in controlling plasma LDL-C by regulating the expression of LDLR, such as miR-199a and miR-140 [62, 63]. Emerging evidence demonstrates that miRNAs involve in multiple processes of hypercholesterolemia, such as lipid synthesis (miR-122), fatty acid biosynthesis (miR-33), and lipoprotein formation and secretion (miR-27a) [64]. In addition, miRNAs involve in multiple processes of HDL metabolism, from synthesis to clearance [65]. Due to the key roles of miRNAs in lipid and lipoprotein metabolism, miRNAs have been considered as new therapeutic targets for lipid metabolism diseases [66, 67]. In fact, therapies based on miR-34 and mir-122 drugs are already in phase 2 clinical trial development [68, 69]. Thus, with the proliferation of human genomic and proteomic data and new delivery vectors development, miRNAs as therapeutic agents or therapeutic targets for hyperlipidemia will become a clinical reality.

4.1. miRNA Has Important Roles in the Pathogenesis of Hyperlipidemia

4.1.1. miRNA and PCSK9. Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in cholesterol metabolism by targeting LDLR [70, 71]. PCSK9 binds to LDLR on the cell surface to form the LDLR-PCSK9 complex, which hinders the endocytic recycling of LDLR for lysosomal degradation [72, 73]. This effectively reduces LDLR cell surface presentation and LDL-C endocytosis in hepatocytes, thereby increasing circulating LDL-C levels [74]. Previous studies have found that miRNAs involve in the process of formation of LDLR-PCSK9 complex, such as miR-191, miR-222, miR-224, miR-520d-5p, and miR-483, can suppress the expression of PCSK9 by directly binding to its 3′ UTR and resulting in reduction of LDL-C levels [74–76] (Figure 2). Among them, miR-483 was one of the widely studied ones. In hyperlipidemic mice and humans, serum total cholesterol and LDL-C levels were found negatively correlated with miR-483-5p levels. The overexpression of miR-483 greatly reduced serum total cholesterol and LDL-C levels in mouse. In HepG2 cells [74], the high expression of miR-483-5p significantly inhibited the PCSK9 expression and led to LDLR upregulation and enhanced LDL-C uptake. In addition, it is reported that miR-337-3p could ameliorate the elevation of plasma LDL-C in mice feed with high-fat diet by inhibiting the expression of PCSK9 [77].

4.1.2. miRNA and Sort1. In addition to the PCSK9 pathway, miRNAs, such as miR-122, miR-30c, and miR-140-5p, also have been reported to be negative regulator of some key factors in LDL-C metabolism and involve in the regulation of plasma LDL-C [78–80]. Sortilin 1 functions as an intracellular sorting receptor for apoB100 and was encoded by Sort1 gene [81]. Plasma ApoB100 levels are one of the strongest risk factors for coronary artery disease [81]. Previous studies have found that the increase of hepatic Sort1 can reduce hepatic apolipoprotein B (APOB) secretion and increase LDL catabolism, resulting in reduced plasma LDL-C and TG levels in mice [63, 82]. Emerging evidence has shown that miRNAs were involve in the expression regulation of

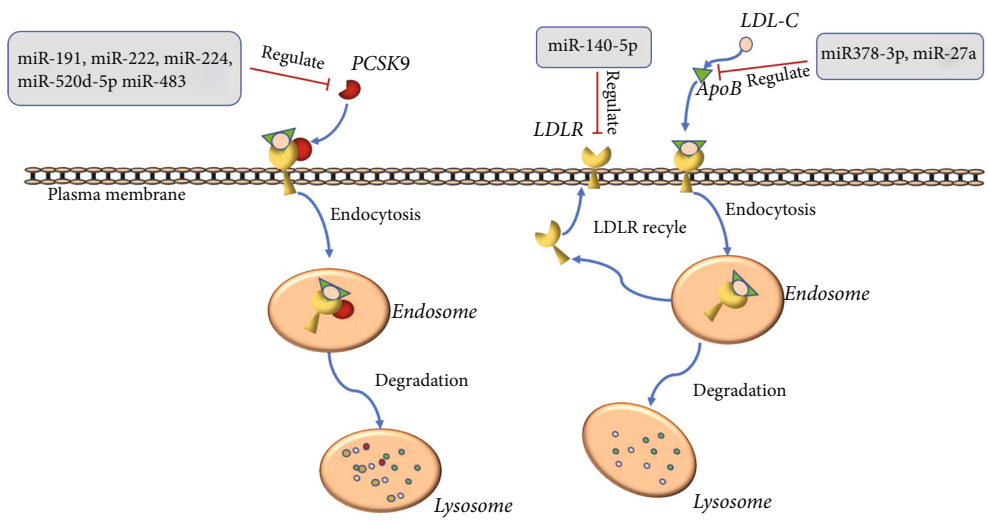

Figure 2: A schematic view of miR-mediated regulation of hyperlipidemia.

Table 1: The relationship between miRNAs, targets, and disease.

miRNAs	Target	Disease or pathophysiological process	References
miR-122, miRNA-33, and miRNA-206 miR-142a-5p	SREBP-1c	Fatty acid metabolism	[64, 117, 122]
miR-34a	PPARα	Hepatic steatosis	[109]
miR-223	NLRP3	Cholesterol metabolism	[116]
miR-128-3p	abca1, abcg1, and retinoid X receptor alpha (RXRA)	Hypercholesterolemia	[93, 94]
miR-27	(FASN), SREBP-1, SREBP-2, PPARα and PPARγ, and ApoA1, ApoB100, and ApoE3	Cholesterol metabolism	[92]
miR-33	ABCA1, ABCG1	Cholesterol metabolism	[88]
miR-337-3p, miR-191, miR-222, miR-224, miR-520d-5p, and miR-483	PCSK9	Lipid metabolism	[74–77]
miR-199a and miR-140	LDLR	Lipid metabolism	[64]

ApoB100/Sort1 axis in animals. One of the miRNAs is miR378a-3p. In the study conducted by Zhang et al., they have demonstrated that the miR378a-3p expression is significantly increased in livers of hyperlipidemic mice. By targeted inhibit Sort1 expression, miR378a-3p can stabilize ApoB100 and promote its secretion, thereby facilitate VLDL secretion in the liver and exacerbate the pathogenesis of hyperlipidemia and hypolipoproteinemia [83]. Consistently, the overexpression of miR378a-3p increased the lipid droplet size and resulted in triglyceride accumulation in mice, while knockdown decreased triglyceride accumulation [84].

4.1.3. miRNA and Cholesterol Metabolism. miRNAs also involve in cholesterol metabolism.

miR-33 was reported that it plays an important role in a variety of biological processes such as cholesterol homeostasis, HDL-cholesterol formation, and fatty acid oxidation [85]. miR-33a and miR-33b were significantly upregulated in the plasma of 28 hypercholesterolemia children compared to 25 healthy subjects, and both miRNAs were positively associated with the levels of TC and LDL-C. In the study by Price et al., they have demonstrated that inhibition of miR-33 increases HDL levels via promoting reverse cholesterol transport, and macrophage-specific loss of miR-33 decreases lipid accumulation and inflammation under hyperlipidemic conditions. This suggested that miR-33a is an important regulator of macrophage cholesterol efflux and HDL biogenesis and is a promising target for treatment of atherosclerosis [86, 87]. miR-33 also downregulates cholesterol efflux and HDL biogenesis by targeting ABC transport proteins (ABCA1: ATP-binding cassette subfamily A member 1, ABCG1: ATP-binding cassette subfamily B member 11) [88]. In a nonhuman primate model of dyslipidemia, miR-33 antagonism significantly reduced plasma VLDL-associated triglyceride levels, which was associated with the regulation of fatty acids (from synthesis to oxidation) [89].

miR-27 was demonstrated that it involves in hepatic lipid deposition, triglyceride synthesis, and lipoprotein uptake [90]. Studies have found that miR-27a can accelerate

lipolysis by releasing more glycerol and free fatty acids from adipocytes and inhibit lipid storage in cells [91]. Accumulated evidences have shown that miR-27a inhibits the expression of many lipid metabolism genes, including fatty acid synthase (FASN), SREBP-1, SREBP-2, PPARα, and PPARγ, and ApoA1, ApoB100, and ApoE3 [92]. Therefore, miR-27a is an important regulator of lipid metabolism.

miR-128-3p has important roles in cholesterol efflux. In the study by Chandra et al., they have found that anti-miR-128-3p (AM-128) treatment inhibited the expression of miR-128-3p in hypercholesterolemic mouse and resulted in a significant reduction in circulating total cholesterol levels [93]. Consistently, in vitro studies [94] have demonstrated that miR-128-3p can promote cellular cholesterol accumulation by targeted inhibiting abca1, abcg1, and retinoid X receptor alpha (RXRA) and thereby inhibition of cholesterol efflux [94]. These data suggested that inhibition of microRNA-128-3p can attenuate hypercholesterolemia in animals.

In addition, there are evidences shown that miR-96/182/183 can targeted inhibit MED1/FBXW7 in hepatocytes [95, 96], and miR-122a antagonism [97] can inhibit cholesterol synthesis and reduce plasma cholesterol levels. This suggested that these miRNAs involve in lipid synthesis.

4.2. miRNA Involves in the Pathogenesis of Other Hyperlipidemia-Related Diseases. It is reported that miR-21a [98] is one of the first identified mammalian miRNAs involved in many physiological processes and multiple diseases, and one of its most representative roles is the regulation of lipid metabolism. Previous studies shown that the expression level of miR-21a-5p is downregulated in patients diagnosed as nonalcoholic fatty liver or in mice fed with high-fat diet, and knockdown of miR-21a-5p leads to hepatic steatosis, accelerated atherosclerosis, plaque necrosis, and vascular inflammation [99]. miR-200, miR-34a, miR-217, and miR-146a were reported to be highly expressed in endothelial cell senescence characterized by uncontrolled apoptosis, severe inflammation, and reduced endothelial nitric oxide synthesis and release, which was associated with endothelial dysfunction, atherosclerosis, and its complications [100]. miRNA-153 was upregulated in the pancreas of hypertriglyceridemia (HTG) animal models and in the plasma of HTG- Acute pancreatitis (AP) patients. The increase of miR-153 worsens AP and delays pancreatic repair in LPL dysfunction-induced HTG mice and its molecular mechanism associated with the inhibition of tumor necrosis factor receptor-associated factor 3 (TRAF3) [101]. Upregulation of miR-103 will inhibit endothelial cell proliferation, promote endothelial cell DNA damage, and consequently affect inflammatory response and promote atherosclerosis. MiR29c-3p is a negative regulator of dishevelled 2 (Dvl-2), a key mediator of the wnt/β-catenin signaling pathway. By inhibiting the expression of Dvl-2, miR29c-3p plays important roles in osteoblast differentiation in the hyperlipidemic setting. For example, the high expression of miR29c-3p causes implant osseointegration deficits [102, 103]. Similarly, by negatively regulating the expression of Mafb (vmaf myofascial fibrosarcoma oncogene family protein B), miR-155-5p improves β-cell adaptation to hyperlipidemic stress and compensates for obesity-induced insulin resistance and consequently limits the progression of obesity and atherosclerosis [104].

4.3. miRNAs Have Values in Hyperlipidemia Treatment. Although PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (monoclonal antibody) bring a new era on hyperlipidemia treatment, however, low safety profile and high cost limit its application [105–107]. Therefore, developing new drugs for hyperlipidemia is urgent for basic and clinical study. miRNAs are promising agents for their stability, controllability, good specificity, and operation simplicity. The recent studies shown that miRNAs are negative regulator of some key factors related to lipid metabolism or cholesterol metabolism, such as SREBP-1c (sterol regulatory element-binding transcription factor 1c), PPARα, and NLRP3 (Table 1) [108–113]. Thus, miRNA as drugs or targets for hyperlipidemia therapy is theoretically possible. In fact, miRNAs as the action targets of drugs were studied broadly, such as grape seed proanthocyanidins, have an effect on the expression of miRNA-122 and miRNA-33 in rats, Averrhoa carambola free phenolic extract [114] has an effect on the expression level of miRNA-34a and miRNA-33 in db/db mice, paeonol (2′-hydroxy-4′-methoxyacetophenone, Pae) has an effect on the expression level of miRNA-223 in hyperlipidemic rats [115, 116], GNP (genipin) has an effect on the expression level of miR-142a-5p in rats [117], and diallyl trisulfide (DATS) has an effect on the miR-335 expression in obese rats [118]. In addition, even exercise has an effect on the expression of miR-21a-5p and exerts beneficial in hyperlipidemia [119, 120] [121]. Recently, therapies based on miR-34 and mir-122 drugs are already in phase 2 clinical trial development [68, 69]. These suggested that miRNAs attracted great attention by scientist and have potential values in hyperlipidemia treatment.

5. Summary and Outlook

The field of research on the use of miRNAs for hyperlipidemia is currently in its early stages. In most of the previous studies, the miRNA mimics were usually injected into target tissue sites and exert function. However, these methods cannot be used in clinic due to mimics easily be degraded by RNA enzymes in the blood. In addition, poor delivery of miRNA mimics to the target site makes it difficult to apply clinically. That is the reason why these studies of miRNAs successfully in animals cannot be translated into clinical applications [69, 123]. To overcome this above weakness of miRNAs, recently, scientists made some chemical modification of some nucleotide sequences of miRNAs to increase its stability and reduce its toxicity that it not essential for the intended function. As the advances in RNA chemical modification and delivery vector technologies have made continuously, several miRNAs have been entered into different clinical trials as therapeutic agents or therapeutic targets for human diseases. More and more studies have found that miRNAs play important roles in the pathogenesis of

hyperlipidemia via regulating some key genes of lipid metabolism and are important biomarkers or target of hyperlipidemia. Thus, people paid great attention to using miRNAs for hyperlipidemia therapy. With the depth of miRNA research on hyperlipidemia and the advance of related technologies, such as delivery technology and materials science, we believe that it will be a success that miRNAs used for hyperlipidemia therapy clinically in the near future.

Data Availability

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

Yu Xiang, Mei-Ling Zuo, Li Mao, Gui-Lin Song, Li-Ming Tan, and Zhong-Bao Yang wrote the main manuscript. All authors reviewed the manuscript. Yu Xiang and Li Mao contributed equally to the work.

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