Review

Mechanism of Long Non-Coding RNAs in Autophagy and Inflammation of Vascular Endothelial Cells: A Review

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Abstract: Increasing researches have highlighted the properties of long non-coding RNAs (lncRNAs) regulating gene transcription, epigenetics, stem cells differentiation and other biological processes. Vascular endothelial cells have been implicated in the process of angiogenesis since they comprise the morphological basis of cardiovascular system. Vascular endothelial cell dysfunction in vascular endothelial cells affects the occurrence and progression of various cardiovascular diseases while secretion of inflammatory factors can induce vascular endothelial cells dysfunction. Autophagy has been widely regarded as an inflammation-related defensive mechanism in cardiovascular diseases. Emerging studies have addressed the involvement of lncRNAs in vascular endothelial cells. As vascular endothelia cells exert great effects on the cardiovascular system, this review discusses the correlations between lncRNAs and vascular endothelia cells with emphasis on regulation of lncRNAs on both autophagy and inflammation in vascular endothelial cells.

Keywords: long non-coding RNAs; vascular endothelial cells; autophagy; inflammation; mechanism; review

1. Introduction

As a monolayer covering the vascular lumen, vascular endothelial cells could integrate into the vascular endothelium [1]. The vascular endothelium plays a key role in maintaining the balance of various physiological mechanisms as well as trafficking immune cells [2]. Besides, the endothelium involves in management of vascular permeability and angiogenesis, and retention of an anti-coagulant and anti-adhesive surface and its possesses notable functional diversity and plasticity, constitutively, in response to soluble, cellular, and physical factors [3]. The disruption of endothelial barrier function occurs as a result of pro-inflammatory factors, such as vascular endothelial growth factor (VEGF, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and lipopolysaccharide (LPS), consequently leading to the rise of endothelial permeability [4]. Emerging evidence has illustrated that the senescence of vascular endothelial cells plays pivotal roles in the pathogenesis of atherosclerosis, thrombosis as well as other vascular dysfunctions [5].

Published data have recently identified that circulating long non-coding RNAs (lncRNAs) could function as valuable diagnostic and prognostic biomarkers of cardiac remodeling and cardiovascular death [6]. Noncoding RNAs (ncRNAs), a group of RNA molecules typically not coding for proteins, generally can be assigned into two types: housekeeping ncRNAs and regulatory ncRNAs. More specifically, housekeeping ncRNAs consist of transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs ( snoRNAs) while regulatory RNAs are comprised of piwi-interacting RNAs (piRNAs), microRNAs (miRNAs) and lncRNAs [7]. LncRNAs represent a series of transcripts with important biological functions. Existing literature has previously suggested the correlations of aberrant expression of lncRNAs and the related dysregulation of mRNAs with a variety of diseases [8]. Owing greatly to the development of next generation sequencing techniques (especially RNA sequencing), a great deal of lncRNAs are detected and annotated each year. On the basis of NONCODE database (http://www.noncode.org), which covers the most comprehensive number of transcripts to date, 56018 lncRNA genes are counted for human beings and 46475 genes for mouse, which is about two times more than the current published human protein-coding genes (20345 in total) [9].

LncRNAs has been identified to exert crucial roles in many diseases via their diverse functional activities and specific mechanisms. The dysregulation of lncRNAs has potentiality to affect inflammatory response, demonstrating their associations with various inflammatory conditions [10]. Dysfunction of endothelial cells related to stimulation of inflammatory factors is implicated in the development of a variety of vascular diseases [1]. For example, simulated by
inflammatory cytokines, endothelium will become active, which in turn increases cellular inflammation, whereby promoting the occurrence and development of atherosclerosis plaque. In the field of vascular biology, the current investigation of IncRNA in inflammation has focused on other cell types, such as macrophages [9], yet the role of IncRNA in mediating the inflammatory response of endothelial cells remains to be elucidated. Autophagy and inflammation are two closely related biological processes engaged in the progression of a diversity of vascular diseases. Interestingly, autophagy regulates the inflammatory response, and in turn inflammatory factors affect autophagy, suggesting their crucial interaction [11]. In this thesis, we have systematically reviewed the role and molecular mechanism of IncRNAs related to endothelial cell autophagy and inflammation in human cardiovascular diseases.

2. Definition, Classification and Functional Mechanisms of IncRNAs

2.1. Definition of IncRNAs

Different from small regulator RNAs, IncRNAs generally refer to transcripts longer than 200 nucleotides without protein-coding capacity [12]. These IncRNAs exert crucial roles in epigenetic regulation through chromatin remodeling and have been widely reported to regulate gene expression by means of diverse mechanisms [13]. After the long-term studies in miRNAs, IncRNAs have attracted increasing attention due to the findings that almost all of the mammalian genome is transcribed, and that only about 2% of the genome sequences encodes proteins [14].

2.2. Classification of IncRNAs

There are no uniform criteria for the classification of IncRNAs. According to different features such as molecular functions/effects, mechanisms/modes of action and genomic location, IncRNAs can be classified into different subtypes. Traditionally, on the basis of locations of transcripts from genome, IncRNAs consisted of five types including sense, antisense, bidirectional, intronic and intergenic, respectively [15]. In the recent study, one of the widely accepted criterion to group IncRNAs is based on the corresponding genomic context (the position in the chromosome wherein the IncRNA is transcribed) through which the IncRNAs were classified into five different categories: (1) Natural antisense transcripts; (2) Pseudogenes; (3) Large intergenic noncoding RNA (lincRNA); (4) Long intronic ncRNAs; and (5) Other uncharacterized and divergent transcript [16]. In the aspects of mode of action, IncRNAs are sorted according to their targeting mechanisms which mainly include (1) signal: IncRNAs exhibit in a type-specific manner and give response to enormous stimuli; (2) decoy: IncRNAs bind and titrate away a protein target without any additional functions; (3) guide: IncRNAs bind proteins and subsequently direct the localization of ribonucleoprotein complex to specific targets; (4) scaffold: IncRNAs serve as central platforms to bring together multiple proteins to form ribonucleoprotein complexes. It is necessary to establish a systematic and effective classification, which is conducive to the function and mechanism research of IncRNAs [17].

2.3. Functional Mechanisms of IncRNAs

IncRNAs are involved in a battery of cellular molecular functions via diverse mechanisms. According to the distinct mechanisms, IncRNAs are approximately sorted to three groups that affect transcriptional regulation, post-transcriptional regulation or other functions [16].

2.3.1. Epigenetic Regulation

Epigenetic regulation of gene expression is an increasingly well-known mechanism which is responsible for the influence of an organism's environment and experience on its biology [18]. Epigenetic modulation contributes to relatively stable changes which may be influenced by many other components, such as age, diet, life style to disease and environment. Several types of epigenetic regulation have been widely addressed in recent decades, including DNA methylation, histone modifications, and non-coding RNAs. Each of them has ability to modulate gene expression under the condition that DNA sequences are not altered [19]. Numerous preceding studies have demonstrated that epigenetic processes contribute to the differential expression of key genes in different types of malignancies [20]. For example, in the context of hepatocellular carcinoma (HCC), IncRNAs exerts their regulatory effects on gene expression via binding as well as recruiting epigenetic modifiers on specific genomic loci [21]. Additionally, lung adenocarcinoma transcript 1 (LUADT1) can not only suppress the growth of lung adenocarcinoma cells, but also modulate cell cycle progression by epigenetically suppressing the expression of p27 [22]. In addition, epigenetic regulation has also been implicated in the pathogenesis of heart failure, leukemia, and cardiac fibrosis [23–25].

2.3.2. Transcriptional Regulation

Increasing studies have argued the points that IncRNAs are transcriptional noise and have proved that IncRNAs play regulatory roles in a wide range of biological processes, and the their dysregulation is closely linked with the occurrence
or development of many types of disease [26]. Many lncRNAs that are extensively explored, including XIST and HOTAIR, all exert their crucial effects through recruitment of the Polycomb repressive complex 2 (PRC2) by binding to PRC2 component histone-lysine N-methyltransferase EZH2. As a result, the local enrichment of H3K27me3 contributes to transcriptional repression. Nevertheless, BORDERLINE lncRNAs and other lncRNAs may exhibit to inhibit repressive histone modifications in two different manners. One is relying on transcription and the other is through binding to and removing the heterochromatin protein 1 (HP1/Swi6) from the locus [27]. By recruiting activating factors or remodelling nucleosomes, the process of transcription itself is likely to contribute to gene regulation [28]. Then this is followed by transcriptional regulation via lncRNA interaction with chromatin-modifying enzymes, leading to gene activation or silencing either in cis or in trans [29].

2.3.3. Other Functions

Nuclear genes can be upregulated or downregulated at both transcriptional and post-transcriptional levels. Among them, post-transcriptional regulations of gene expression is required for pre-messenger RNA (mRNA) processing (including three steps: capping, splicing, and polyadenylation), mRNA stability, and mRNA translation [30]. Alternative splicing is a typical post-transcriptional regulation which is suggested in a recent study that this regulation is possibly involved in plant responses to high widely-spread cadmium stress [31]. LncRNAs have been demonstrated to play important regulatory roles in gene expression, from histone modification to protein stability [32]. Furthermore, several post-transcriptional regulatory processes, including pre-mRNA processing, RNA turn-over and surveillance, and regulation of translation, have been investigated in plants [33]. Moreover, a prior study has illustrated the post-transcriptional regulatory network connecting to epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial (MET), which was supported by the finding that several lncRNAs are capable of regulating EMT [34].

LncRNAs can also function as endogenous decoys for miRNAs as they contain miRNA-binding sites which communicate with and co-regulate each other by competitively binding to shared miRNAs. For instance, a long intergenic noncoding RNA linc-MD1 with two miRNA bonding sites can act as sponge of miR-135 and miR-133, thus regulating the expression levels of MEF2C and MAML1 which are target genes of miR-135 and miR-133 [35].

3. Evaluation of Vascular Endothelial Cells Function

Vasculature spread around the whole body and it occurs accompanied by the arrangement of diverse types of cells throughout the development process and later during growth into adulthood. Endothelial cells contribute to the formation of the luminal side of a blood vessel while pericytes or mural cells promote to the development of the outer surface [36]. This endothelial cell layer possesses a wide variety of properties. Specifically, it serves as a selective mechanical barrier between blood and tissue, as a biochemically highly active cell layer that is responsible for the control of blood clotting processes and also as a key modulator of vascular smooth muscle tone [37]. Vascular endothelial cells, located in a monolayer on the luminal surface, can control the blood coagulation-fibrinolytic system by synthesizing and secreting two main physiological factors (von Willebrand factor and tissue factors) that promote blood coagulation and prostacyclin, leading to suppression of platelet aggregation [38]. As the wall of blood vessels and the blood stream, the pathophysiology of endothelium is complicated that involves diverse mechanism. Endothelial dysfunction is capable of promoting inflammation and platelet adhesion which may lead to severer cardiovascular injury [39].

4. Association Between Autophagy and Inflammation

Autophagy, a dynamic process, not only manages the turnover of cellular organelles and long-lived proteins, but also has function in cellular homeostasis and adaptation to adverse environments [40]. Autophagy only initiates at a low basal level and it can involve in the maintenance of tissue homeostasis so as to give response to a series of physiological and pathological stresses, such as solar ultraviolet B radiation [41]. It should be noted that excessive autophagy triggers muscle catabolism and therefore result in atrophy while reduced autophagic flux becomes a distinctive feature of several muscle diseases [42]. In addition, autophagy is indispensable if mammals is lacking of nutrition as the evolutionarily conserved intracellular catabolic process will be activated under starvation conditions. Otherwise such lower organisms with deficient autophagic will die during starvation, suggesting the significance of autophagy in survival. Of note, autophagy is also activated in mammalian tissues experiencing prolonged starvation [43]. However, autophagy plays dual roles in tumors, acting either as a tumor suppressor or as a survival mechanism. Inhibition of autophagy will cause disruption to neuronal differentiation and increases the number of tumor cells, consequently leading to shorter life span of tumor-bearing animals, while induction of autophagy will prolong their life span by inhibiting tumor cell proliferation [44].

Vascular endothelial inflammation is a key event in vascular diseases [45]. Upon stimulation by pro-inflammatory cytokines, endothelial cells function in the adhesion and extravasation of circulating leukocytes into inflamed tissues [46]. Chen et al in their study on vascular endothelial inflammation and autophagy reported that inflammation participates
centrally in all stages of atherosclerosis, beginning with inflammatory changes in the endothelium, which are characterized by expression of the adhesion molecules [47].

Autophagy may be induced by stress from starvation, pathogens, or cytokine signals, wherein cytokines are gradually determined to be important regulators of autophagy that are capable of both activating and inhibiting it during inflammation. Cytokine regulation of autophagy emerges as an important part of the immune response to pathogens or in noninfectious disorders such as atherosclerosis or malignancy [48]. Autophagy plays a critical role in regulating cell damage evoked by excessive inflammation. At least two ways have been reported for autophagy to protect the cells from excessive long-term inflammation damage that are to indirectly remove damaged organelles or intracellular pathogens, and to directly inhibit the development of proinflammatory complexes. Inflammatory factors that affect the autophagy includes innate immune receptors (recognizing highly conserved pathogen-associated molecular patterns as well as damage associated molecular patterns), cytokines (an important mechanism for the organism to remove invading pathogens), reactive oxygen species (an early inducer of autophagy under deficiency of nutrition) and autophagy-related transcription factors. In addition, autophagy functions as an modulator of inflammation as it regulates the inflammation nodules, secretion of inflammatory factors and polarization of macrophages.

5. Mechanisms Between IncRNAs and Vascular Endothelial Cells

Recently, with the development of high-throughput sequencing technologies, IncRNAs have been demonstrated to be regulators of gene transcription in cancers and many other diseases, including vascular diseases [35]. Vascular injury-induced endothelial dysfunction is one of distinctive characteristics of many diseases, such as chronic renal disease, diabetes mellitus, and systemic inflammatory conditions, and predisposes to apoptosis and atherogenesis [3]. Here, we will explore the mechanisms of IncRNAs in the pathogenesis of vascular diseases such as atherosclerosis, coronary artery disease, ischemic stroke and etc.

5.1. IncRNAs in Atherosclerosis

Atherosclerosis represents the leading cause of cardiovascular disease, accounting for high rate of mortality in the population [49,50]. Atherosclerosis, a chronic inflammatory arterial disease, is influenced by either innate or adaptive immune responses to modified lipoproteins and components of the injured vascular wall [51]. Endothelial dysfunction is a critical early process in atherosclerosis that can be observed in patients with diabetes mellitus, renal impairment, and systemic inflammatory diseases [3]. It is actually a systemic disorder and a key variable in the pathogenesis of atherosclerosis and even its complications [52]. The potential mechanisms that affect endothelial function and atherosclerosis for flow have been reviewed previously. Specifically, disturbed laminar blood flow (D-flow) induces endothelial dysfunction and atherosclerosis while sustained laminar blood flow (S-flow) prevents both of them, partly attributable to the alterations of gene expression and the epigenetic landscape. Vascular endothelial cells respond to blood flow through mechanical sensors, which transduce the mechanical force associated with flow (also known as shear stress) into cell signaling events and ultimately, alter gene expression [53]. Vascular endothelial cells covering the luminal surface of blood vessels contribute to the antithrombogenic properties of the vascular endothelium by synthesizing and secreting anticoagulant and fibrinolytic substances, such as anticoagulant heparin sulfate proteoglycans, thrombomodulin and tissue plasminogen activator, finally prevent atherosclerosis [54].

It has been claimed that in animal studies, some anti-miRs targeting mecano-miRs such as miR-712, miR-205, or miR-155, and athero-miRs such as miR-33 have potential of functioning as anti-atherogenic therapies [55]. Moreover, a study has implicated autophagy as a protective mechanism during atherosclerosis development, and pharmaceutical approaches through inducing autophagy have recently been developed to stabilize vulnerable, rupture-prone lesions [47]. Hence, we will discuss the role and mechanism of IncRNAs in atherosclerosis from the perspectives of endothelial cells, vascular smooth cells and macrophages based on a fact that endothelial cells, vascular smooth cells and macrophages are primary contributors to atherosclerotic lesion formation [35].

LncRNAs regulate the angiogenesis of endothelial cells. Endothelial cells is one of the main cell types within the vasculature and the endothelium forms the inner thin layer that represents an interface between circulating fluid in the lumen and the rest of the vessel wall. Endothelial cells mainly function in the regulation of vascular tone, fluid filtration, neutrophil recruitment, hormone trafficking, and hemostasis [55]. Proper tissue vascularization is a vital process for cellular function due to its function of delivering oxygen, nutrients, hormones, and immune cells and clearing cellular debris and metabolic waste products. Tissue angiogenesis initiates to satisfy energy requirements and cellular sensors of metabolic imbalance coordinate vessel growth [56]. Several biological processes are implicated in pathological angiogenesis, such as cell proliferation, cell motility, immune response, and inflammation. LncRNAs have emerged as key players in these biological processes [57]. For example, IncRNAs n342419 (termed MANTIS) exerts positive effects on endothelial angiogenic function by functioning as a scaffolding IncRNA within a chromatin remodeling complex, mediating and directing efficient key endothelial gene transcription. Specifically, MANTIS acts in trans through the SWI/SNF chromatin remodeling factor BRG1 to facilitate the interactions with angiogenic genes and with the BRG1 stimulating factor BAF155. SOX18, SMAD6 and COUP-TFII are target endothelial genes of MANTIS and they attract
attention for their functions in angiogenesis. BRG1 is known to be a critical mediator of Coup-TfII expression in the cardiovascular system and BRG1 acts on SOX18 and SMAD6. MANTIS directly interacts with BRG1, and increases its ATPase activity by promoting BAF155 interaction. Uppregulation of MANTIS in Macaca aortae in the regression phase after atherosclerotic diet can manifest an involvement of this lncRNA in vascular regeneration \[58\]. This is further supported by a study on the potential role of lncRNAs for angiogenesis that lncRNAs act as molecular switches in cellular differentiation, movement, apoptosis and in the reprogramming of cell states by altering gene expression patterns \[59\].

lncRNAs also function in vascular smooth cells. Vascular smooth cells are able to contract or relax in response to various stimuli, and are therefore responsible for the redistribution of the blood within the body to areas, including tissues with temporarily enhanced oxygen consumption. Their main function is to regulate the caliber of the blood vessels: excessive vasoconstriction possibly leads to hypertension while excessive vasodilatation induces hypotension \[55\]. Disordered vascular smooth cell proliferation, cell growth, migration, and inflammatory signaling are certain contributors to cardiovascular diseases \[60\]. Gengze et al have reported that lincRNA-p21 regulates vascular smooth cell proliferation and apoptosis in atherosclerosis by promoting the activity of p53 a well-established factor involving in atherosclerosis. Mechanistically, lincRNA-p21 directly binds to Murine Double Minute 2 (MDM2), an E3 ubiquitin-protein ligase, resulting in p53 releasing from MDM2 and binding to p300, whereby enhancing p53 activity. \[61\]. Analysis of the RNA-seq data pinpointed smooth muscle-induced lncRNA enhances replication (SMILR) as an IL1α/PDGFr-responsive lincRNA located on chromosome 8, 750 kbp from the closest protein-coding gene, on the same strand. This gene, HAS2, encodes an enzyme that synthesizes hyaluronic acid (HA), a critical component of the extracellular matrix which accumulates in human restenotic and atherosclerotic lesions. Knockdown of SMILR reduces HAS2 expression and therefore attenuates VSMC proliferation \[62\]. Moreover, in a study of angiotensin II-mediated lincRNAs in vascular smooth muscle cells, Amy et al have demonstrated initially that Inc-Ang362 is proximal to miR-221 and miR-222 and these two miRNAs are involved in VSMC proliferation and are upregulated in response to Ang II in endothelial cells to promote inflammation and migration. Hence, Inc-Ang362 affects cell proliferation and expression of a critical component of cell cycle progression \[63\].

lncRNAs exerts important regulatory effects on macrophages. Classically or alternatively activated macrophages (M1 and M2, respectively) play distinct and crucial roles in micro-biocidal activity, inflammation and tissue homeostasis \[64\]. The differentiation of monocyte/macrophage is controlled by a complicated process including the coordinated expression patterns of stage-specific transcription factors, various cytokines and ncRNAs \[65,66\]. Gain- and loss-of-function experiments demonstrate that long noncoding monocytic RNA (Inc-MC) promotes monocyte/macrophage differentiation of THP-1 cells and CD34 + hematopoietic stem/progenitor cells (HSPCs). Mechanistic investigation reveals Inc-MC acting as a competing endogenous RNA to sequester miR-199a-5p (miR-199a-5p) to alleviate miR-199a-5p-induced repression of activin A receptor type 1B (ACVR1B), an important regulator of monocyte/macrophage differentiation \[67\]. In addition, not only has lincRNA-Cox2 been indicated to function as a critical component of the inflammatory response, but also has lincRNA-p21 been suggested as a repressor in the p53-dependent transcriptional response \[68\].

### 5.2. LncRNAs in Coronary Artery Disease

Coronary artery disease is one of the leading causes of death with an increasing prevalence worldwide \[69\]. There are numerous widely accepted risk factors for coronary artery disease, such as hypertension, hyperlipidemia, diabetes, family history, and tobacco use. Over the past 10-15 years, achievements in gene expression profiling have opened new arenas for the discovery of biomarkers in the pathogenesis of numerous diseases, including coronary artery disease \[70\].

According to Matsuzawa Y et al, coronary endothelial dysfunction mainly consist of epicardial endothelial dysfunction and microvascular endothelial dysfunction, independent predictors of acute cardiovascular events irrespective of presence or absence of angiographically detectable coronary lesions. Endothelial dysfunction in epicardial and/or microcirculatory coronary arteries causes myocardial ischemia. Coronary microcirculatory endothelial dysfunction has been suggested as an important feature of the pathophysiology of apical ballooning syndrome, and impaired left ventricular relaxation in patients with normal ejection fraction in the absence of occlusive coronary artery disease and cardiomyopathy \[71\].

The Wellcome Trust Case Control Consortium (WTCCC) study (which involved 1926 case subjects with coronary artery disease and 2938 controls) has demonstrated the association of chromosome 9p21.3 with coronary artery disease \[72\]. A IncRNA located at human chromosome 9p21.3, ANRIL (also known as CDKN2BAS), shares an association with increased coronary artery disease risk \[73\]. This locus is adjacent to the last exon of a lncRNA named antisense noncoding RNA in the INK-4 locus (ANRIL), whereas the 2 other protein-coding genes (cyclin-dependent kinase inhibitors 2A and 2B; CDKN2A and CDKN2B, respectively) lie >100 kb from associated single nucleotide polymorphisms (SNPs), suggesting that SNPs on ANRIL are more likely to contribute to the susceptibility of coronary artery disease \[9\]. Indeed, subsequent studies have reported that ANRIL expression is associated with the risk for carotid atherosclerosis, peripheral artery disease and other vascular diseases \[74,75\]. Primary cultures of vascular smooth muscle cells (VSMCs) from mice with the deletion of the orthologous interval exhibited excessive proliferation, presumably due to altered CDKN2A and
CDKN2B expression [76]. Since VSMCs play important roles in atherosclerosis, these findings suggested a possible mechanism for the association of the 9p21 locus with susceptibility to CAD in humans [77], but the underlying mechanism between ANRIL and coronary artery disease warrants further investigation in the future.

A microarray analysis in the plasma from patients with coronary artery disease identified CoroMarker to be a stable, sensitive and specific biomarker for coronary artery disease [78]. Another functional enrichment analysis demonstrated CoroMarker to be clustered with genes positively correlated with signal transduction, transmembrane transport, synaptic transmission, and innate immunity and negatively correlated with inflammation [79].

5.3. LncRNAs in Diabetes Mellitus/Hyperglycaemia

Diabetes mellitus is complex disease that involves primary metabolic changes followed by immunological and vascular pathophysiological adjustments [80]. Diabetes exerts major effects on the cardiovascular system via many mechanisms. Endothelin, angiotensin, and tissue factor activity are increased, whereas nitric oxide and prostacyclin production is reduced [81]. Endothelial dysfunction represents one of the most frequent features in diabetic macroangiopathy, while Oxidative stress and eNOS uncoupling are also essential constituents for endothelial dysfunction in patients with diabetes [82]. Furthermore, it has been proved that biomarkers of inflammation and endothelial dysfunction were positively associated with incident type 2 diabetes [83].

The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), alternative named nuclear-enriched transcript 2 (NEAT2) and masrcRNA, is a lncRNA consisting of more than 8700 nt located on chromosome 11q13 [84]. Overexpression of MALAT1 has been witnessed to confer an oncogenic function in renal cell carcinoma [85]. In addition, Liu et al have suggested that knockdown of MALAT1 on the one hand ameliorates retinal function, retinal vessel impairment and retinal inflammation in diabetic rats, and on the other hand affects endothelial cell migration and tube formation in vitro and prevents hyper-proliferation of retinal endothelial cells through p38 mitogen-activated protein kinase (MAPK) signaling [86]. Additionally, lncRNAs-MIAT regulates microvascular dysfunction by functioning as a competing endogenous RNA [57]. Taken all these together, it is reasonable that we conclude MALAT1 to be one of lncRNAs responsible for the endothelial dysfunction in Diabetes mellitus.

It has also been reported that maternally expressed gene 3 (MEG3) participates in diabetes mellitus-related microvascular dysfunction. MEG3 is an imprinted gene, located on human chromosome 14q32.3 [87]. Growing evidences suggest MEG3 as a tumor suppressor in several tumors, including glioma, hepatocellular cancer, bladder cancer, and menigioma [88]. Furthermore, Kamlesh et al have reported that knockdown of MEG3 in macrophages gives rise to induction of autophagy and then promotion in eradication of intracellular Mycobacterium bovis BCG [89]. Hepatic insulin resistance is a major characteristic of type 2 diabetes mellitus and hepatic gluconeogenesis is a major contributor to the overproduction of glucose in patients with type 2 diabetes mellitus. Hence, inhibition of the gluconeogenesis pathway may be a possible strategy against hyperglycaemia associated with type 2 diabetes mellitus. Strikingly, lncRNA MEG3 has properties to promote hepatic insulin resistance via increasing Fork-head box protein O1 (FoxO1) expression [90]. Meanwhile, lncRNA MEG3 has similar influences on diabetic retinopathy via PI3K/Akt signaling which is an important signaling pathway in the regulation of endothelial cells by regulating angiogenesis, proliferation, microvascular permeability [91]. Therefore, it can be concluded that MEG3 up-regulation may serve as a therapeutic target for treating diabetes-related microvascular complications.

5.4. LncRNAs in Ischemic Stroke

Ischemic stroke occurs when the blood flow to the brain is blocked by a blood clot (http://www.stroke.org/understand-stroke/but-stroke/ischemic-stroke). Occlusion of a cerebral blood vessel can result in an physiologically dysfunctional area but non-infarcted tissues surrounding an infarcted core [92]. The body's natural response to ischemia is a reparative mechanism termed neovascularization which consists of angiogenesis, arteriogenesis, and vasculogenesis [93]. The World Health Organization has been estimated that 15 million patients suffer stroke worldwide each year [94]. Stroke is increasingly recognized as a significant cause of morbidity and mortality in children, and as a financial burden for families and society [95]. Ischemic stroke, one subtype of stroke, is a complex genetic disorder caused by complex multiple genetic and environmental factors [96]. Conventional factors such as hypertension, dyslipidaemia, diabetes and smoking are well-established, while genetic factors accounting for 30–40% of risk and are poorly understood [97]. In addition, brain endothelium is an important therapeutic target for the inhibition of cerebrovascular dysfunction in ischemic stroke [98].

A prior RNA-seq analysis, Zhang et al has profiled lncRNA expression signatures in primary brain microvascular endothelial cells (BMECs) and has documented the expression patterns for 362 of the 10,677 lncRNAs. As a result, they found a total of 147 lncRNAs increased and 70 lncRNAs decreased. Among them, the most highly upregulated lncRNAs include Snhg12, Malat1, and Inc-OGD 1006, whereas the most highly down-regulated lncRNAs include 281008D09Rik, Peg13, and Inc-OGD 3916 [98]. Moreover, a recent study has reported that downregulation of MEG3 can promote angiogenesis after ischemic brain injury by activating notch signaling pathway. During the processes, MEG3 regulates endothelial cell function and vessel growth in vitro, whereas knockdown of MEG3 activates the Notch pathway in
endothelial cells to promote angiogenesis while reducing brain lesions after ischemic stroke [99]. The concerning introduction on MEG3 have been illustrated in the diabetes mellitus/hyperglycaemia.

5.5. LncRNAs in Hypertension

Hypertension, a leading cause of morbidity and mortality worldwide, affects at least one third of the adult general population [100,101]. Hypertension represents the most commonly diagnosed condition in persons aged 60 and older and is the single most important risk factor for cardiovascular disease (ischemic heart disease, heart failure, and stroke), kidney disease, and dementia [102]. Also, 80 % of patients with chronic kidney disease are hypertensive [103]. A key role in the etiology of hypertension is played by endothelial dysfunction and the inflammatory reaction in the vascular wall, wherein the low molecular weight proteins so called chemokines are implicated [104]. Hypertension induces endothelial dysfunction and inflammation by elevating levels of soluble adhesion molecules and inflammatory cytokines [105].

The prominence of endothelium-dependent contractions has been observed in arteries of aging animals and humans, in particular, in subjects with essential/spontaneous hypertension [106]. A preceding study has linked endothelial dysfunction in hypertension to decreases in nitric oxide (NO) bioavailability [107]. NO is a gas generated from the metabolism of L-arginine by constitutive endothelial NO synthase (eNOS) [108]. The main alteration ascribable to endothelial dysfunction is an impaired (or absent) availability of NO, essentially as a consequence of increased oxidative stress. Indeed, in addition to its relaxing activity, NO inhibits platelet aggregation, proliferation and migration of vascular smooth cells, release of adhesion molecules, and production of endothelin-1, thus protecting the blood vessel wall from the initial events [109].

Zhang has reported that through inhibiting the expression of LncRNA sOne, Lycium barbarum L., a traditional Chinese medicine used for preventing and treating various diseases, such as diabetes, hyperlipidemia, thrombosis, immunodeficiency and cancer. LncRNA sOne is a lncRNA derived from a transcription unit (NOS3AS) on the opposite DNA strand of human eNOS [110]. According to an article published in 2016, growth arrest specific 5 (GAS5) functions as a novel regulator of hypertension-induced vascular remodeling, as GAS5 knockdown exerts effects on both the functions of endothelial cells and vascular smooth muscle cells in vitro and in vivo [111]. The GAS5 gene is encoded at locus 1q25 and has up to 12 exons and 10 box C/D snoRNAs within its alternative introns together with conserved 5’-terminal oligopyrimidine tract (5′ TOP) [112]. In addition, decreased GAS5 levels are found in serum of diabetic patients, which suggests a correlation of GAS5 level with the prevalence of type 2 diabetes mellitus [113].

Besides, four targeted lncRNA-mRNA related genes including Ankyrin Repeat and SOCS Box-Containing 3 (Asb3), cation transport regulator homolog 2 (Chac2), peroxisomal membrane 11B (Pex11b) and Sp5 transcription factor (Sp5) are critical regulators for blood pressure in hypertensive rats. [82]. These four genes encompassing several unique features are candidate genetic determinants of blood pressure that are associated with cardiovascular traits [114].

5.6. LncRNAs in Myocardial Infarction

Myocardial infarction is a leading cause of death among all cardiovascular diseases [115]. A study has suggested that peripheral vascular endothelial dysfunction in rats with myocardial infarction can be prevented by using pyridostigmine, an acetylcholinesterase inhibitor to improve vagal activity and ameliorate cardiac dysfunction following myocardial infarction [116]. It has further been demonstrated that endothelial dysfunction 4 weeks to 6 weeks after primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction does not predict future clinical events [117].

Although recent data suggest the possible association between LncRNAs and cardiac diseases, little is known about the potential mechanisms [118]. By performing a microarray analysis among the 31,423 LncRNAs in ischemia, only 151 differentially expressed (64 up- and 87 down-regulated) LncRNAs are documented in the infarct region. Among them, AK035396, ENSMUST00000156081, AK005401, ENSMUST00000118172 and ENSMUST00000118702 are identified to be the first five up-regulated LncRNAs with largest fold changes, while the first five down-regulated most are LncRNAs uc007prv.1, AK080112, ENSMUST0000170410, AK156124 and ENSMUST0000166777 [119]. Given these limited information, we hold that the interplay between endothelial dysfunction and LncRNAs in myocardial infarction should be devoted more efforts.

6. Conclusion and perspectives

Endothelial dysfunction is requisite in the pathogenesis of cardiovascular events [120]. Improvement of endothelial function has been emerged as a promising therapeutic approach for vascular diseases [121]. Identification of LncRNAs provides candidates delaying the progression of cardiovascular diseases and aids in the development of novel therapeutics in cardiovascular medicine.

Insights into the roles of LncRNAs in cardiovascular diseases have been identified over the past 10 years. However, the functionality of LncRNAs as biomarkers for endothelial dysfunction in cardiovascular diseases is yet poorly understood. A big challenge is that LncRNAs are generally found to be poorly conserved, thus limiting the clinical translation from
IncRNAs in animal models to humans. Moreover, IncRNAs have various transcripts and targeted multiple genes, which may increase the obstacle to determine specific actions of IncRNAs in cardiovascular diseases. Another problem is that investigations on epigenetic regulations of IncRNAs and endothelial dysfunction are also limited in number.

In the future, increasing studies are necessary to solve the aforementioned problems. As for drug therapy, endothelium-specific small molecules and antibodies targeting LOX-1 are recently proposed novel therapeutics, which is evolving to be a major endothelium-damaging ox-LDL receptor.

Cardiovascular risk can be reduced by optimal risk factor management and lifestyle changes. Smoking cessation is a cornerstone of cardiovascular disease prevention and represents a public health problem due to the effect of passive smoking. All smokers should be encouraged to quit smoking by various smoking-cessation therapies. Furthermore, a healthy diet and regular exercise are also two of general cardiovascular prevention measures applicable to the entire population. Thus, around half of the reduction in deaths from coronary heart disease is attributable to better management of cardiovascular risk factors and the other half to advances in medical treatments [122]. Hence, IncRNA-targeted therapies and management of cardiovascular risk factors are the two important perspectives to be investigated for the treatment of cardiovascular diseases.

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