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Post-transcriptional gene regulation by RNA-binding proteins in vascular endothelial dysfunction

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Endothelial cell dysfunction is a term which implies the dysregulation of normal endothelial cell functions, including impairment of the barrier functions, control of vascular tone, disturbance of proliferative and migratory capacity of endothelial cells, as well as control of leukocyte trafficking. Endothelial dysfunction is an early step in vascular inflammatory diseases such as atherosclerosis, diabetic vascular complications, sepsis-induced or severe virus infection-induced organ injuries. The expressions of inflammatory cytokines and vascular adhesion molecules induced by various stimuli, such as modified lipids, smoking, advanced glycation end products and bacteria toxin, significantly contribute to the development of endothelial dysfunction. The transcriptional regulation of inflammatory cytokines and vascular adhesion molecules has been well-studied. However, the regulation of those gene expressions at post-transcriptional level is emerging. RNA-binding proteins have emerged as critical regulators of gene expression acting predominantly at the post-transcriptional level in microRNA-dependent or independent manners. This review summarizes the latest insights into the roles of RNA-binding proteins in controlling vascular endothelial cell functions and their contribution to the pathogenesis of vascular inflammatory diseases.

endothelial dysfunction, vascular inflammation, RNA-binding proteins, microRNAs, post-transcriptional gene regulation

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The endothelium is the monolayer of endothelial cells (ECs) lining the lumen of blood vessels in every organ system. These cells form a protective barrier between all tissues and the circulating blood. Normal EC function is critical for all aspects of vascular homeostasis (i.e., control of blood vessel development, growth and differentiation; control of leukocyte trafficking; control of vascular tone; control of vascular barrier; control of platelet function, coagulation and fibrinolysis) [1–3]. EC dysfunction disrupts the balance between vasoconstriction and vasodilation and initiates a number of events that trigger EC activation and predispose the vessel wall to increased endothelial permeability, leukocyte adherence, endothelial proliferation, pro-oxidation and thrombosis. Endothelial dysfunction has been implicated in several diseases including atherosclerosis, diabetes, tumor metastasis, sepsis and severe virus infectious diseases [4–6]. Importantly, the expressions of inflammatory cytokines and vascular adhesion molecules are significantly involved in the processes of EC activation, which is regulated by the transcriptional regulation programs, as well as post-transcriptional and post-translational modifications that fine-tune this response [7,8]. microRNA (miRNA) is a key transcriptional regulator. In this regard, miRNAs have emerged as critical regulators of gene expression, acting predominantly at the post-transcriptional level [9–11]. RNA-binding proteins have also emerged as critical regulators of gene expression at the post-transcriptional level. They can act in a miRNA-dependent or independent way.

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Since the functions of miRNAs in vascular endothelial dysfunction have been comprehensively reviewed elsewhere [12–15], in the present review we summarize the latest insights into the roles of RNA-binding proteins in controlling vascular endothelial cell functions and their contributions to the pathogenesis of vascular inflammatory diseases.

1 Endothelial dysfunction in human diseases

The endothelium maintains normal vascular homeostasis with no or little expression of proinflammatory factors under normal homeostatic conditions. However, both traditional and novel cardiovascular risk factors including smoking, aging, hypercholesterolemia, hypertension, hyperglycemia, and a family history of premature atherosclerotic disease are associated with alteration in endothelial function [4–6]. In addition, infections with bacteria and viruses also impair the blood-tissue barrier and result in tissue/organ injuries [16,17]. This results in a chronic or acute inflammatory process accompanied by loss of antithrombotic factors and an increase in proinflammatory cytokines and prothrombotic products, in addition to abnormal vasoreactivity, therefore elevating risk of cardiovascular events and organ injuries.

1.1 Endothelial dysfunction and atherosclerosis

Atherosclerosis is characterized by the thickening of the arterial wall and is the primary cause of coronary artery disease and cerebrovascular disease, two of the most common causes of illness and death worldwide [18]. A crucial step in atherogenesis is the arterial recruitment of inflammatory cells from the circulation and their trans-endothelial migration into the sub-endothelial space of large arteries where they differentiate into macrophages and become functionally active. The endothelial activation is the first step in the development of atherosclerosis [19]. In response to inflammatory stimuli, such as tumor necrosis factor α (TNFα), interleukin 1β (IL-1β), and interferon gamma, ECs undergo inflammatory activation, resulting in an increased surface expression of cell adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, and E-selectin, which contributes to the recruitment of inflammatory cells to arterial wall and their transmigration across the wall. The activated ECs also release cytokines and chemokines such as monocyte chemotactic protein 1 (MCP-1), which is a potent inducer for monocyte attachment to ECs and migration into subendothelial space. Endothelial activation represents a switch from a quiescent phenotype toward a proinflammatory and prothrombotic phenotype. Indeed, most cardiovascular risk factors induce the expression of chemokines, cytokines, and adhesion molecules designed to interact with leukocytes and platelets in endothelium [20,21]. The molecular regulation of the gene expression program in endothelium is an intensively studied area.

1.2 Endothelial dysfunction and metabolic syndromes

Metabolic syndrome is a cluster of metabolic abnormalities that includes visceral obesity, dyslipidemia, hypertension, and impairment of glucose metabolism, which has been related to both endothelial dysfunction and increased risk for cardiovascular diseases and type 2 diabetes. Insulin resistance has been recognized as a common cause for clustering of these risk factors, whereas endothelial dysfunction may contribute to the progression of metabolic syndrome and the development of adverse outcome [22,23]. A growing body of evidence suggests that endothelial dysfunction may precede the development of insulin resistance or further promote the occurrence of manifest diabetic mellitus [24]. For example, eNOS-deficiency not only results in endothelial dysfunction, but also causes the development of insulin resistance and metabolic abnormalities, similar to those observed in diabetic mellitus [25]. The prospective investigations have also linked the increased levels of circulating markers of endothelial damage (i.e., plasminogen activator inhibitor-1 and von Willebrand factor) to the risk of incident diabetic mellitus [26].

1.3 Endothelial dysfunction and septic shock

Septic shock poses a serious public health problem worldwide with an overall mortality rate of 30%. Now it is recognized that a major contributor to septic morbidity and mortality is the breakdown in the function of the blood/tissue barrier due to intravascular or extra-vascular infections [27,28]. This breakdown is caused by a cascade of inflammatory events resulting in severe endothelial dysfunction which leads to systemic vascular leakage and irreversible multi-organ failure. Blood and vascular systems that respond to sepsis-associated microbial virulence factors encompass innate and adaptive immune cells, platelets, and the plasma proteins that represent antibody, complement, coagulation and fibrinolysis networks. These blood systems are enclosed by the enormous surface of the microvascular endothelium forming organ-specific vascular beds. It is vital that the blood/tissue barrier formed by this microvascular endothelium and the adjoining structures maintain their structural and functional integrity in order to support normal physiological functions of key organs. During sepsis-causing infections, the vasculature is profoundly altered by the combination of microbial virulence factors and proinflammatory mediators released from activated blood cells that gain access to surrounding tissue by crossing the leaky endothelial boundary. Severe endothelial dysfunction then results from the loss of homeostatic function of the microvascular endothelium and contributes to hypoxic injury of multiple organs. It is therefore clear that breakdown of the

blood/endothelial tissue barrier is one of the major contributors to sepsis morbidity and mortality. By preventing vascular leakage through reinforcement of the endothelial barrier, it is likely that mortality from sepsis can be reduced [30,31].

1.4 Endothelial dysfunction and severe virus infectious diseases

It is increasingly evident that endothelial dysfunction also contributes to the pathogenesis of a variety of potentially serious virus infectious diseases and syndromes, including dengue hemorrhagic fever, severe acute respiratory syndrome (SARS) and H1N1 influenza [32–34]. The development of severe virus infection-caused organ injury, for example, acute lung injury, has been attributed to a heightened innate immune response. Recent evidence suggests that endothelial activation, loss of barrier function, and consequent microvascular leak may also serve important mechanistic roles in the pathogenesis of severe virus infection. Shock syndrome is a dangerous complication of dengue infection and is associated with high mortality [35]. Severe dengue occurs as a result of secondary infection with a different virus serotype. Increased vascular permeability, together with myocardial dysfunction and dehydration, contribute to the development of shock, with resultant multi-organ failure [36]. The pathogenesis of shock in dengue is complex. It is known that endothelial dysfunction induced by cytokines and chemical mediators occurs. Understanding the regulatory mechanisms of endothelial dysfunction under severe virus infection may help to develop novel therapeutic strategies to cure these severe diseases.

2 Post-transcriptional gene regulation

Gene expression is a highly regulated process that begins with transcriptional initiation and ends with translation of a mature mRNA into protein. Between these two points, there are a series of events including processing and splicing of the pre-mRNA, export of the message from the nucleus to the cytoplasm, quality control assessment of the mRNA through the pioneer round of translation, message decay and stabilization, and translational repression and de-repression [37]. All of these events from initiation of transcription by transcription factors to the stability of the message to effective translation of the message are controlled by the presence of specific nucleotide sequences which are bound by specific RNA-binding proteins [38]. As a message is transcribed, proteins bind to form a messenger ribonucleo protein complex (mRNP) and the composition of the mRNP controls all aspects of the life of the mRNA, from pre-mRNA processing to mRNA localization to translation and degradation. Transitions between these events are accompanied by mRNP remodeling and exchange of mRNP proteins. Posttranscriptional control of gene expression, particularly mRNA stability and translation, allows for rapid changes in mRNA levels. Dysregulated mRNA stability and translation underlie a number of diseases, directly contributing to the overexpression of many genes encoding growth factors, inflammatory cytokines, and proto-oncogenes. microRNAs are an important layer that control gene expression at post-transcriptional level, which has been extensively reviewed elsewhere [9–11]. microRNAs need to function together with RNA-binding proteins. The role of RNA-binding proteins in regulation of gene expression at post-transcriptional level has been emerging.

3 RNA-binding proteins in vascular endothelial dysfunction

3.1 Tristetraprolin

Tristetraprolin (TTP), also known as Nup475, G0S24, and TIS11, is the best known member of a class of proteins containing tandem CCCH zinc fingers. It is an mRNA-destabilizing protein that binds to AU-rich elements in labile transcripts, such as the mRNA encoding TNF, and promotes their deadenylation and degradation [39–41]. TTP destabilizes mRNA transcripts encoding multiple inflammatory modulators, including granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, IL-6, C-FOS, iNOS, cyclooxygenase 2, CCL2, CCL3, CXC-chemokine ligand 1 (CXCL1), IFNγ and IL-10 [42–47]. As a consequence, TTP-deficient mice exhibit an early-onset, severe inflammatory phenotype, with cachexia, erosive arthritis, left-sided cardiac valvulitis, myeloid hyperplasia, and autoimmunity, which can be prevented by injection of anti-TNF antibody, or interbreeding with TNF receptor-deficient mice [48,49]. TTP promotes mRNA decay by binding directly to components of the mRNA decay machinery, including the mRNA-decapping enzymes DCP1A and DCP2, the deadenylaseCNOT6 (CCR4-NOT transcription complex subunit 6), the 5′–3′ exoribonuclease 1 (XRN1), exosome complex endonuclease PM-SCl75 (also known as RRP45) and argonaute 2 (AGO2), an argonaute protein component of the RNA-induced silencing complex [50–52]. TTP exerts its role in miRNA-dependent and independent ways [53].

It was observed that TTP-deficient mice also developed endothelial dysfunction [54]. $TTP^{-/-}$ mice showed a significant reduction of acetylcholine-induced nitric oxide-mediated vasorelaxation, which was associated with increased levels of reactive oxygen and nitrogen species. The altered reactive oxygen and nitrogen species generation correlates with increased expression of NADPH oxidase 2 resulting from enhanced NADPH oxidase 2 mRNA stability. Zhang et al. [55] recently observed that ZFP36 (TTP) is expressed in the vascular endothelium of mice with atherosclerosis but not in the vascular endothelium of normal mice.

Overexpression of TTP inhibited the expression of proinflammatory mRNA transcripts in vascular endothelial cells. The anti-inflammatory effects of TTP in endothelial cells occur via both transcriptional and post-transcriptional mechanisms. These studies suggest that enhancing vascular TTP expression might reduce vascular inflammation. Dai et al. [56] also found that TTP promoted decay of CD36 mRNA, by which it may inhibit macrophage foam-cell formation. Thus, TTP may function as an important inhibitor in the development of atherosclerosis through multiple mechanisms.

Endothelial cells are primary sensors of variations in blood oxygen concentrations. They use the hypoxia-sensitive stabilization of the hypoxia-inducible factor-1α (HIF-1α) transcription factor to engage specific transcriptional programs in response to oxygen changes. It was observed that silencing TTP in endothelial cells reverses hypoxia-induced down-regulation of HIF-1α mRNA. In addition, TTP mediated prolonged hypoxia-induced increase in the half-life of luciferase-HIF-1α-3′ UTR reporter transcript, suggesting that TTP plays a new role in the control of gene expression during the response of endothelial cell to hypoxia [57]. Besides the important role of chronic vascular inflammation, TTP is also important in regulation of acute vascular inflammation. Qiu et al. [58] recently observed that myeloid-specific TTP deficiency in mice results in extreme lipopolysaccharide sensitivity, with rapid development of typical endotoxemia signs and extensive organ damage, and elevation of serum TNF levels to 110-fold greater than that of the control. It is clear that TTP appears to regulate the different steps of mRNA processing and fate including transcription, splicing, polyadenylation, translation, and degradation. The role of TTP in vascular endothelial dysfunction is emerging. Understanding the intricacies of TTP-mediated cytokine mRNA degradation and having more detailed knowledge of the mRNAs which are regulated by TTP will identify potential targets for the development of anti-inflammatory drugs.

3.2 HuR

HuR is a member of the *Drosophila* Elav protein family that binds mRNA degradation sequences and prevents RNase-mediated degradation [59,60]. HuR also binds to ARE in inflammatory cytokine mRNAs. In contrast with TTP, HuR increases the stability of tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), cyclooxygenase 2 (COX-2) and toll-like receptor 4 (TLR4) mRNAs [61–63]. HuR and TTP are both RNA-binding proteins, which are characterized as binding to the AU-rich elements (AREs) in the 3′-untranslated region (3′-UTRs) of target mRNAs. Studies have shown that some ARE-containing mRNAs are stabilized by HuR, whereas are destabilized by TTP. For example, HuR can up-regulate TNF-induced IL-6 expression by stabilizing its mRNA in human pulmonary microvascular endothelial cells, whereas TTP promotes IL-6 mRNA degradation [64]. In addition, Tiedie et al. [65] demonstrated that translation of the TNF-precursor at the ER requires expression of the ARE-binding and -stabilizing factor HuR or the absence of the ARE-binding and -destabilizing factor TTP. Phosphorylation of TTP by MK2 deceases its affinity to the ARE, inhibits its ability to replace HuR, and permits HuR-mediated initiation of translation of TNF mRNA. Activation of inflammatory pathways in the endothelium contributes to vascular diseases, including sepsis and atherosclerosis. Cheng et al. [66] demonstrated that HuR promoted endothelial activation by suppressing expression of endothelial nitric oxide synthase. Moreover, HuR also promotes the stability of ICAM-1 and VCAM-1 and increases leukocyte-endothelial cell adhesion. Knockdown of HuR with small interfering RNA (siRNA) inhibited inflammatory responses in endothelial cells, including ICAM-1 and VCAM-1 up-regulation, NF-κB phosphorylation, and adhesion of monocytes. Interestingly, tissue staining of the mouse aorta revealed increased HuR expression in the arch that is exposed to disturbed flow. These results suggest that HuR plays a critical role in inducing inflammatory response of endothelial cells under mechanical and biochemical stresses. The microvascular angiogenic response to an inflammatory stimulus was markedly diminished in the macrophages from HuR knockout mice despite the equal levels of macrophage localization to those observed in littermate wild-type controls. Furthermore, blood flow recovery and ischemic muscle neovascularization after femoral artery ligation were impaired in the conditional macrophage-specific HuR knockout mice. These results demonstrate that dynamic effects on mRNA, mediated by the RNA-binding and RNA-stabilizing protein HuR, are required for macrophage production of angiogenic factors, which play critical roles in the neovascular responses to a variety of stimuli, including tissue ischemia [67]. In another *in vitro* study, stimulation of HASMCs with LPS significantly increased the cytosolic HuR level *in vitro*. Systemic inflammation induced by LPS caused intimal hyperplasia and increased TLR4 and HuR expression. Further studies demonstrated that HuR can increase TLR4 mRNA stability by binding to its 3′UTR, which is correlated with the increased vascular smooth muscle proliferation. These results suggest that HuR contributes to regulation of hVSMC growth and homeostasis in pathologies associated with vascular smooth muscle proliferation [68]. Taken together, HuR is emerging as an important regulator in vascular biology by targeting either vascular endothelial inflammation, or VSMC proliferation or macrophage activation. It may significantly contribute to the pathogenesis of vascular inflammatory diseases such as sepsis-induced organ injury and atherosclerosis-associated diseases.

3.3 MCPIP1

MCP-induced protein 1 (MCPIP1), also known as Regnase-1 orZc3h12a, was identified as a novel protein harboring a CCCH-type zinc-finger domain and a PIN-like RNase domain [69,70]. MCPIP1 mRNA expression is induced by Toll-like receptor (TLR) ligands, interleukin (IL)-1β and various stress stimuli [71−74]. MCPIP1 functions as an important negative regulator in both adaptive and innate immune response through destabilizing mRNAs encoding immune related proteins including IL-6, IL-2 and IL-12p40 via their 3′ untranslated regions [71,72,75]. As a consequence, Mcpip1-deficient mice developed severe systemic inflammation, characterized by growth retardation, splenomegaly, lymphadenopathy, severe anemia and premature death [71,76]. In addition, the serum levels of proinflammatory cytokine and production of autoantibodies are also dramatically increased in Mcpip1-deficient mice [77]. MCPIP1 was firstly identified as an endogenous inhibitor in macrophage-induced inflammation. Under normal condition, MCPIP1 protein is highly enriched in the mouse lung, spleen, thymus, colon and intestine. MCPIP1 expression was significantly induced in macrophages by bacterium and virus infection and by endogenous cytokines such as TNFα and IL-1β. Overexpression of MCPIP1 in macrophages significantly suppressed the proinflammatory cytokine production such as IL-6 and IL-12. In the Mcpip1-deficient macrophages, the expression of IL-6 was increased as its mRNA decay was impaired [71,72]. Besides macrophages, our previous studies also showed that MCPIP1 expression is up-regulated in the endothelial cells and VSMCs in the advanced atherosclerotic lesions. In culturing human umbilical vein endothelial cells (HUVECs), MCPIP1 expression was significantly induced by inflammatory cytokines TNFα and IL-1β and overexpression of MCPIP1 suppresses cytokine-induced expression of VCAM-1, as well as monocyte adhesion to human ECs [78]. These studies demonstrated MCPIP1 as a feedback control of cytokine-induced endothelial inflammation and suggest that MCPIP1 may be a critical regulator in vascular diseases such as sepsis and atherosclerosis. Indeed, Mcpip1-deficient mice are extremely sensitive to LPS-induced septic shock [79]. Especially, a minimum LPS challenge can cause severe inflammatory lung and liver injury and death in Mcpip1-deficient mice, suggesting that Mcpip1 may play an important role in maintaining the vascular homeostasis under severe bacterium and virus infection. Activator of MCPIP1 enzymatic action may have therapeutic benefits for the patients with sepsis, severe viral infection and atherosclerosis-associated diseases. Besides MCPIP1, the other member in MCPIP1 protein family Zc3h12c (also known as MCPIP3) also significantly inhibited the endothelial cell inflammatory response *in vitro*. Overexpression of Zc3h12c significantly attenuated TNFα-induced expression of chemokines and adhesive molecules, and thus reduced monocyte adherence to HUVECs. Conversely, siRNA-mediated knockdown of Zc3h12c increased the TNFα-induced expression of chemokines and adhesive molecules in HUVECs. Furthermore, forced expression of Zc3h12c decreased TNFα-induced IKKα/β (IκB (inhibitor of nuclear factor κB) kinase α/β), IκBα phosphorylation and p65 nuclear translocation, suggesting that Zc3h12c exerted its anti-inflammatory function probably by suppressing the NF-κB (nuclear factor κB) pathway. Thus Zc3h12c is also an endogenous inhibitor of TNFα-induced inflammatory signaling in HUVECs and might be a therapeutic target in vascular inflammatory diseases [80]. How does MCPIP1 selectively target some specific mRNAs? Structural and biochemical analysis demonstrated that MCPIP1 contains a PIN-like RNase domain and can directly degrade mRNA *in vitro* [81]. In the cells, MCPIP1 is predominantly localized in cytoplasm as small granule-like pattern. We have found that MCPIP1 is co-localized with GW-182 and Ago-2, which are major components of miRNA-mediated RNA silencing complex [82], suggesting that MCPIP1 may be involved in the miRNA-effector pathway. Further studies are needed to clarify this mechanism. Interestingly, Suzuki et al. [83] reported that MCPIP1 can specifically recognize the terminal loops of precursors miRNAs and suppress miRNA biosynthesis, suggesting that MCPIP1 may affect cell behavior by influencing the miRNA generation.

3.4 Drosha and DGCR8

microRNAs (miRNAs) represent a family of conserved short (≈22 nt) noncoding single-strand RNAs that have been identified in plants and animals. They are generated by the sequential processing of the RNA template by the enzyme Drosha and Dicer, and mature miRNAs can regulate the levels of gene expression at the posttranscriptional level. microRNAs participate in a diverse range of regulatory events via regulation of genes involved in the control of process such as development, differentiation, homeostasis, metabolism, growth, proliferation, and apoptosis [9−11]. microRNAs are highly expressed in endothelial cells and they regulate various aspects of vascular endothelial biology, which have been extensively reviewed elsewhere [12−15]. In this review, we focus on the miRNA biogenesis enzyme Drosha and Dicer as well as RNA-binding protein DGCR8. They not only function through generation of miRNAs but also function independently of miRNAs. Drosha cleaves double-stranded primary miRNA by interacting with double-stranded RNA binding protein DGCR8 and processes primary miRNA into precursor miRNA to participate in the miRNA biogenesis pathway. Fan et al. [84] found that disruption of Drosha in VSMCs resulted in embryonic lethality at E14.5 with severe liver hemorrhage in mutant embryos. The vascular structure was absent in the yolk sac of Drosha homozygotes at E14.5. Loss of Drosha reduced VSMC proliferation *in vitro* and *in vivo*. The VSMC differentiation marker genes, including αSMA, SM22, and CNN1, and

endothelial cell marker CD31 were significantly down-regulated in Drosha conditional knockout (CKO) mice compared to controls. ERK1/2 mitogen-activated protein kinase and the phosphatidylinositol 3-kinase/AKT were attenuated in VSMCs *in vitro* and *in vivo*. These data demonstrated that Drosha is required for VSMC survival by targeting multiple signaling pathways [84]. Consistently, Chen et al. [85] also found that loss of DGCR8 in VSMCs resulted in extensive liver hemorrhage and embryonic mortality between embryonic days (E) 12.5 and E13.5. DGCR8 CKO embryos displayed dilated blood vessels and disarrayed vascular architecture. Blood vessels were absent in the yolk sac ofDGCR8 KOs after E12.5. Disruption of DGCR8 in VSMCs reduced VSMC proliferation and promoted apoptosis *in vitro* and *in vivo*. In DGCR8 CKO embryos and knockout VSMCs, differentiation marker genes, including αSMA, SM22, and CNN1, were significantly down-regulated, and the survival pathways of ERK1/2 mitogen-activated protein kinase and the phosphatidylinositol 3-kinase/AKT were attenuated. The mechanisms that cause these phenotypes are not completely clear. Knockout of DGCR8 in VSMCs has led to down-regulation of the miR-17/92 and miR-143/145 clusters, suggesting that the misprocessing of miRNA maturation may contribute to the abnormal differentiation and proliferation of VSMCs [85]. Pan et al. [86] also reported that conditionally deleted the miRNA-processing enzyme Dicer in the proepicardium using Gata5-Cre mice leads to impaired epicardial epithelial-to-mesenchymal transition and reduction in epicardial cell proliferation and differentiation into coronary smooth muscle cells.

3.5 Argonaute 2

Argonaute 2 (Ago2) is a central component of RNA-induced silencing complex and plays a key role in RNA interference and miRNA effector pathway. Ago2 is expressed in vascular endothelial cells and may play an essential role in regulation of endothelial dysfunction in miRNA-dependent mechanisms. In addition, some reported that Ago2, as a RNA binding protein, may function in a miRNA-independent way. Asai et al. [87] reported that knocking down of Ago2 significantly suppressed VEGF- induced angiogenesis, which suggests that Ago2 is required for angiogenesis. Endothelial cell migration induced in response to VEGF is a crucial step of angiogenesis and it is dependent on the activation of the p38 MAP-kinase pathway downstream of VEGFR2. Pin et al. [88] found that overexpression of Ago2 impaired VEGF-induced p38 activation and endothelial cell migration. The role of Ago2 in endothelial dysfunction needs to be further explored.

3.6 Others

The RNA-binding protein Quaking (QKI) is a member of the "STAR" (signal transduction and activation of RNA) family. Proteins in this family are characterized by the presence of RNA-binding motif, KH domains, as well as SH2 and SH3 domains and potential phosphorylation sites, suggesting that they function in signal transduction pathways [89]. It is well known that QKI plays an important role in the postnatal central nervous system during myelination. Recent studies suggest that it also plays an essential role in blood vessel development [90]. In addition, van der Veer et al. [91] observed that QKI is highly expressed in neointimal VSMCs of human coronary restenoticlesions and neointima hyperplasia of mice. Abrogation of QKI attenuated fibroproliferative properties of VSMC and potently induced contractile apparatus protein expression. Further studies indicate that QKI localizes to the spliceosome and regulates myocardin splicing. Similarly, RA301/Trabeta, a sequence-specific RNA-binding protein, has also been found highly expressed in coronary artery with intimal thickening, and atherosclerotic aorta. RA301/Trabeta seems to also regulate VSMC proliferation [92]. The roles of these RNA-binding proteins in vascular endothelial dysfunction need to be further explored.

4 Conclusion and future direction

Normal EC function is critical for all aspects of vascular

Table 1 Overview of RNA-binding proteins and their function

RNA-binding proteins	Function	Refs
Tristetraprolin	Inhibition of vascular inflammation by promoting mRNA degradation of inflammatory cytokines	[39–41,42–47,55,56]
HuR	Promotion of endothelial activation by stabilizing the mRNAs of cytokines and adhesion molecules	[61–63,66]
MCPIP1	Inhibition of vascular inflammation by degradation the mRNA of inflammatory cytokines and suppressing NF-κB signaling	[69–74,78,79]
Zc3h12c	Inhibition of vascular inflammation by suppressing NF-κB signaling	[80]
Drosha	Required for VSMC survival	[84]
DGCR8	Required for VSMC differentiation and proliferation	[85]
Argonaute 2	Promotion of VEGF-induced angiogenesis	[87]
Quaking	Promotion of fibroproliferative properties of VSMC	[88]
RA301/Trabeta	Regulation of VSMC proliferation	[89]

homeostasis, such as control of blood vessel development, growth and differentiation; control of leukocyte trafficking; control of vascular tone; control of vascular barrier; control of platelet function, coagulation and fibrinolysis. Vascular endothelial dysfunction is associated with many important diseases such as atherosclerosis-associated heart attack and stroke, diabetes, sepsis and septic shock, severe virus infection-caused organ injury. Understanding of the pathogenesis and molecular regulatory mechanisms will provide insights into development of new therapeutic approaches to cure these diseases. microRNAs represent a novel layer that controls the gene expression at a post-transcriptional level and have emerged as important regulators in endothelial dysfunction. However, miRNAs do not function alone. microRNAs must get the jobs done by closely cooperating with RNA-binding proteins. Increasing evidences suggest that the RNA-binding proteins such as TTP, MCPIP1, HuR, Drosha, and DGCR8 act as important components in gene expression at post-transcriptional level in a miRNA-dependent and/or independent manner. Their roles in regulation of vascular endothelial dysfunction are also characterized in recent publications (Table 1). Further studies *in vivo* and translational to human diseased samples will be definitely needed.

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