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Review

MicroRNA-92a: The Administrator of Certain Diseases

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Abstract: MicroRNA-92a (miR-92a) is an evolutionarily conserved noncoding small RNA that can regulate gene expression after transcription. Previous studies have found that miR-92a is overexpressed in many tumors and can regulate numerous tumor suppressor genes negatively, with relevant effects on the development of different tumors, by regulating the DUSP10/c-Jun N-terminal kinase (JNK), phosphatase and tensin homologs (PTEN)/AKT, Wnt and EP4/Notch1 signaling axes. MiR-92a also promotes the proliferation and migration of vascular smooth muscle cells (VSMCs) through the Rho-associated coiled-coil-forming kinase/myosin light chain kinase signaling pathway and inhibits VSMC apoptosis through the MKK4/JNK signaling pathway. Moreover, miR-92a affects endothelial functions; mediates endothelial dysfunction in chronic kidney diseases; mediates THBS1 inhibition; promotes the migration, proliferation and angiogenesis of neighboring endothelial cells (ECs); mediates the Nrf2/KEAP1/ARE signaling pathway to regulate vascular endothelial aging; and is involved in immune responses to activate ECs. This review summarizes the potential role and pathogenic mechanism of the miR-92a gene in certain diseases to provide possible new treatment options.

Keywords: microRNA-92a, Cancer, Signaling Pathway, Endothelial Damage, Vascular Smooth Muscle Cell

Introduction

MicroRNAs (miRNAs) are small (19-24 nt) single-stranded noncoding RNAs that regulate messenger RNA (mRNA) translation and stability by binding to the 3'-Untranslated Region (UTR) of target genes (Sun and Lai, 2013; Ameres and Zamore, 2013). Numerous studies have demonstrated that miRNAs play critical roles in various biological processes, such as cell proliferation and apoptosis, glucose and lipid metabolism and infection and immune responses (Szabo and Bala, 2013; Pritchard *et al*., 2012; Rottiers and Naar, 2012). In addition, the function of miRNAs in human tumorigenesis has been well established, which can add new insights into diagnosis and prognosis procedures (Ling *et al*., 2013). The miR-17-92 cluster encodes six miRNAs, namely, miR-17, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a, which are located in the coding region of the open reading frame of the *C13* or *f25* gene. The human miR-17-92 cluster gene is mapped to chromosome 13q31 (Rao *et al*., 1998; Ota *et al*., 2004; Tagawa and Seto, 2005). MicroRNA-92a (miR-92a) is a member of the miR-17-92 cluster and an evolutionarily conserved noncoding small RNA that can regulate gene expression at the post-transcriptional level. In other words, one miRNA generally targets the 3'-UTR of various mRNAs involved in different steps of one precise metabolic/signaling pathway. Moreover, microRNA-92a is an oncogenic (Tsuchida *et al*., 2011; Wang *et al*., 2016) as well as a tumor suppressor gene (Shin *et al*., 2018; Smith *et al*., 2015). A change in the level of a key miR-92a affects the individual steps of a pathway; thus is promoted or suppressed (Wang *et al*., 2019) depending on the cancer model. Although the functions of most identified miRNAs have yet to be determined, they are considered as potential biomarkers for several human diseases and cancers (Calin *et al*., 2004; Volinia *et al*., 2006).

Relationship Between miR-92a and Tumors

Expression and Targeting of miR-92a in Different Tumors

The ability of miR-92a expression regulation to influence cell proliferation may prove to be a new mechanism for preventing and treating tumors. In addition, miR-92a has the advantage of being stable, noninvasive, convenient and highly sensitive as a biomarker for the early diagnosis of cancer (Yang *et al*., 2014a). MiR-92a is overexpressed in many tumors and can negatively regulate numerous tumor suppressor genes (Tsuchida *et al*., 2011), including the downregulated target genes of the von Hippel-Lindau tumor suppressor, farnesoid X receptor and cadherin1 (Scapoli *et al*., 2010; Yu *et al*., 2013; Si *et al*., 2013). Previous studies have shown that miR-92a is upregulated in the development of several tumors, including in cervical, colon, gastric, oral, breast and lung cancer (Tsuchida *et al*., 2011; Scapoli *et al*., 2010; Yu *et al*., 2013; Si *et al*., 2013; Valera *et al*., 2011; Al-Nakhle *et al*., 2010; Hayashita *et al*., 2005). Furthermore, miR-92a promotes cancer cell proliferation and survival through several mechanisms, such as downregulation of Estrogen Receptor beta (ER β), Phosphatase and Tensin Homologs (PTEN) and BH3-protein (Tsuchida *et al*., 2011; Yu *et al*., 2013; Al-Nakhle *et al*., 2010). The decreased expression of miR-92a in cancer stem cells leads to the high expression levels of target molecules, that is, integrin αV and α5 subunits, which in turn enhances TGF-β activation, as proven by increased phosphorylation of SMAD2 (Shidal *et al*., 2019).

MiR-92a and Signaling Pathways that Regulate Tumorigenesis and Development

MiR-92a Promotes Pancreatic Cancer Cell Proliferation Via DUSP10/c-Jun N-terminal Kinase (JNK) Signaling Axis

Pancreatic cancer is one of the most common causes of tumor-related deaths in the world (He *et al*., 2014). Rapid proliferation is the most important characteristic of cancer cells. JNK signaling is a well-known signaling pathway that regulates the formation and development of cancers and is related to oncogenic transformation (Takahashi *et al*., 2013; Nateri *et al*., 2005; Yunoki *et al*., 2013). MiR-92a enhances the activation of the JNK signaling pathway by directly targeting the JNK signaling inhibitor DUSP10. DUSP10 is responsible for miR-92a-induced JNK signaling and cell proliferation. Overall, the miR-92a/DUSP10/JNK signaling pathway plays an important role in regulating the proliferation of pancreatic cancer cells (He *et al*., 2014) (Fig. 1).

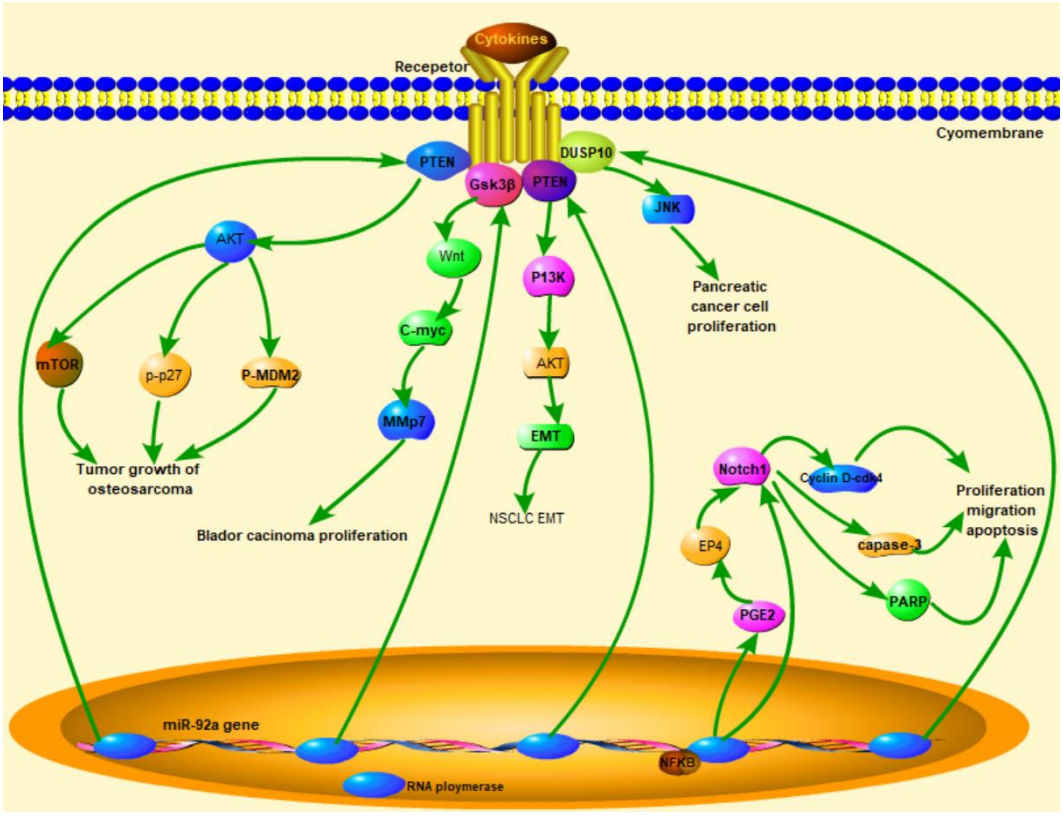

Fig. 1: Effect of miR-92a on cancer cell signaling axis

Role of miR-92a and PTEN-Related Signaling Pathways in Tumorigenesis and Development

PTEN, which is a well-known tumor suppressor, is the direct downstream target of miR-92a in osteosarcoma, nasopharyngeal carcinoma and Non-Small Cell Lung Carcinoma (NSCLC) (Xiao *et al*., 2017; Zhang *et al*., 2016; Lu *et al*., 2017). Moreover, PTEN, which is a versatile protein, can inversely regulate PI3K/AKT/Epithelial Mesenchymal Transition (EMT) signaling in NSCLC (Scapoli *et al*., 2010) (Fig. 1). The overexpression of miR-92a enhances EMT-related protein levels, promotes EMT in NSCLC metastasis, facilitates the migration and invasion of NSCLC cells in vitro and increases tumor growth *in vivo* (Lu *et al*., 2017). Furthermore, the PTEN/AKT pathway mediates the phosphorylation of p27 (Thr157), AKT (Ser473) and MDM2 (Ser166) (Xie *et al*., 2016) (Fig. 1). PTEN promotes OS proliferation, inhibits apoptosis and facilitates transfer in NPC by regulating the expression and phosphorylation of the aforementioned proteins (Xiao *et al*., 2017; Lu *et al*., 2017). Furthermore, miR-92a plays an oncogenic role in OS, NPC and NSCLC by targeting the PTEN signaling pathway.

MiR-92a Promotes Invasion and Chemoresistance by Targeting GSK3β and Activating Wnt Signaling in Bladder Cancer Cells

Prognosis for bladder cancer lies in its histological subtype, tumor size, lymph node metastasis and distant metastasis (Reddy *et al*., 2015; Szarvas *et al*., 2012; Yang *et al*., 2012; Wang *et al*., 2016). Luciferase reporter assays reveal that miR-92a can directly bind to the 3′-UTR of GSK3β, thereby demonstrating that GSK3β is a direct target of miR-92a (Wang *et al*., 2016). Additionally, depleted GSK3β replace the role of miR-92a in its downstream protein cyclin D1 and MMP7. Given that cyclin D1, c-myc and MMP7 are Wnt target proteins, miR-92a binds directly to the 3'-UTR region of GSK3β to promote proliferation, invasion and Wnt/c-myc/MMP7 signaling in bladder cancer cells (Wang *et al*., 2016) (Fig. 1).

MiR-92a Suppresses Proliferation and Induces Apoptosis by Targeting EP4/Notch1 Axis in Gastric Cancer

Notch signaling activation has been proven in gastric cancer growths and has a high expression level in human gastric cancer tissues (Yeh *et al*., 2009). The expression of mir-92a in primary tumors in patients with gastric cancer can be verified via real-time PCR. NF-κB expression is negatively regulated with miR-92 levels in gastric tissues, whereas transfection with NF-κB siRNA (p50 and p65) increases miR-92 expression in gastric cancer (Shin *et al*., 2018). Notch signaling has been implicated in various carcinogenesis, including gastric cancer. The phosphorylation of STAT3 and Twist-promoted gastric cancer progression is regulated by the Notch1 receptor intracellular domain (Hsu *et al*., 2012). Moreover, Prostaglandin E2 (PGE2) plays a crucial role in cancer initiation and progression through its receptors (EP receptor). PGE receptors comprise four G-protein-coupled cell surface receptors, namely EP1, EP2, EP3 and EP4, for signal transduction. Strong evidence shows that PGE2 and its receptors are implicated in the carcinogenesis of different types of tumors, including gastric cancer. Thus, miR-92a has been suggested to regulate cell proliferation and cell invasion through the EP4/Notch1 signaling pathway (Shin *et al*., 2018) (Fig. 1).

MiR-92a and Signaling Pathways Regulate Vascular Smooth Muscle Cells (VSMCs)

MiR-92a Promotes VSMC Proliferation and Migration through Rho-Associated Coiled-Coil-Forming Kinase (ROCK)/Myosin Light Chains (MLCK) Signaling Pathway

Endothelial Cells (ECs) and VSMCs are the main cell types within the vasculature and are closely related in terms of structure and function. ECs that cover the interior surface of blood play an important role in the regulation of vascular tone by releasing vasoactive agents that control VSMC proliferation or migration (Zhao *et al*., 2012). PDGF-BB, which is found in atherosclerotic lesions, is a well-known potent mitogen and chemoattractant for VSMCs. Moreover, PDGF-BB can activate ROCK and MLCK (Xiong *et al*., 2017), which regulate the phosphorylation of MLCs (Zhou *et al*., 2011). The phosphorylation of MLCs promotes cell contraction and cell motility, thereby generating changes in the actin cytoskeleton (Shimokawa and Rashid, 2007). In vitro results indicate that MLCK and miR-92a share the same signaling pathway. The transfection of miR-92a mimics can partially restore the effect of the deficiency of MLCK and antagonize the effect of Y27632 (an inhibitor of ROCK) on the downregulation of VSMC activities (Wang *et al*., 2019). ML-7 increases the expression of Kruppel-like factor 4 (KLF4, which is an miR-92a target) (Loyer *et al*., 2014) and siRNA-KLF4 increases the activity levels of VSMCs. The inhibition of either MLCK or ROCK enhances KLF4 expression consistently. Moreover, ROCK/MLCK upregulates miR-92a expression in VSMCs through Signal Transducer and Activator of Transcription 3 (STAT3) activation. In summary, the activation of ROCK/STAT3 and/or MLCK/STAT3 may upregulate miR-92a expression, which subsequently inhibits KLF4 expression and promotes the PDGF-BB-mediated proliferation and migration of VSMCs (Wang *et al*., 2019) (Fig. 2).

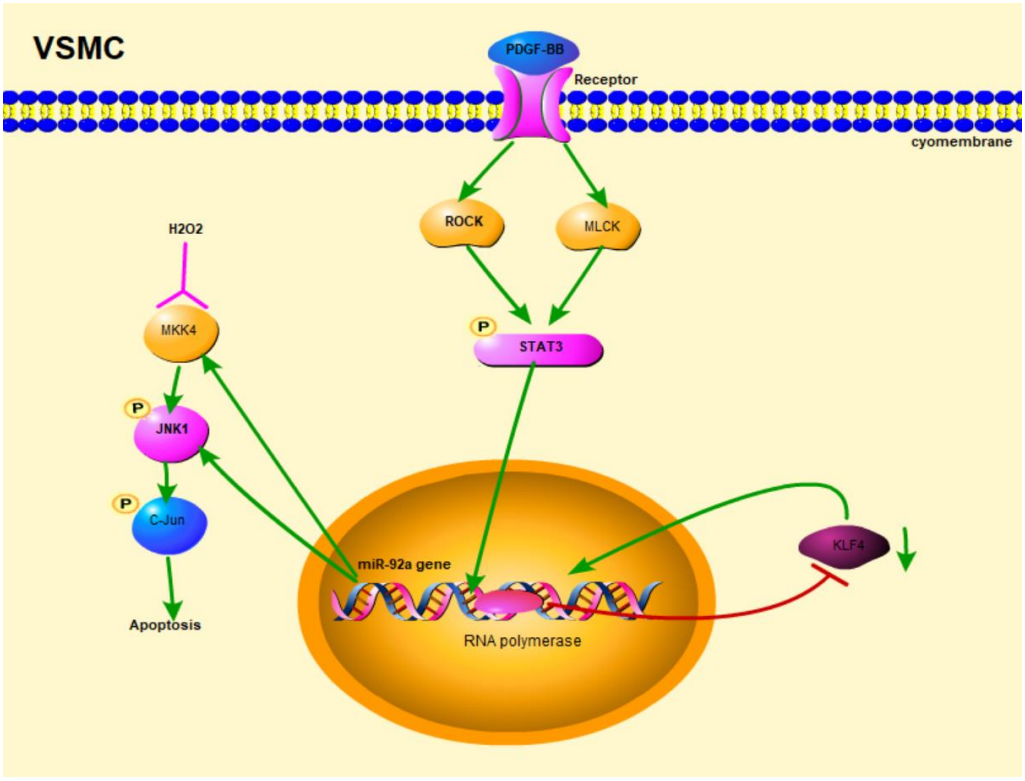

Fig. 2: Effect of miR-92a on VSMC signaling axis

MiR-92a Inhibits Apoptosis of VSMCs Through MKK4/JNK Signaling Pathway

The apoptosis of VSMCs is believed to be triggered by oxidative stress that is present in diseased vascular milieu (Loyer *et al*., 2014). The JNK pathway plays a crucial role in VSMC apoptosis in atherosclerotic plaque instability and rupture induced by oxidative stress (Loyer *et al*., 2014). Given that the JNK1 pathway is involved in VSMC apoptosis induced by oxidative stress (Tchivilev *et al*., 2008) and MKK4 and JNK1 are identified as target genes for miR-92a, the present study uses a luciferase reporter assay to show that miR-92a regulates the expression of MKK4 by targeting its 3'-UTR (Lai *et al*., 2013). The overexpression of miR-92a reduces the level of the MKK4 protein by 30% and that of the p54 JNK1 protein by 20% (Zhang *et al*., 2014). Moreover, MKK4 and JNK1 are downregulated by miR-92a, thereby inhibiting oxidative stress-induced VSMC apoptosis (Zhang *et al*., 2014) (Fig. 2).

MiR-92a and Signaling Pathways Regulate Endothelial Damage

MiR-92a Mediates Endothelial Dysfunction in Chronic Kidney Disease (CKD)

CKD is an independent risk factor for cardiovascular disease (CVD) (Jourde-Chiche *et al*., 2006). MiR-92a is induced by oxidative stress in ECs (Chen *et al*., 2015) and involved in angiogenesis and atherosclerosis (Loyer *et al*., 2014). Mechanistically, miR-92a targets the 39 UTRs of mRNA-encoding sirtuin 1 (SIRT1), KLF2 and KLF4, all of which positively regulate eNOS-derived NO (Fang and Davies, 2012). In ECs, miR-92a targets SIRT1, KLF2 and KLF4, which are essential for endothelial homeostasis and functions (Chen *et al*., 2015). CKD-induced miR-92a potentiates endothelial dysfunction and contributes to CVD. Uremic toxins (e.g., IS) in CKD increase the oxidative stress burden in vascular endothelium. In turn, oxidative stress-induced miR-92a can lead to endothelial dysfunction and is released by MPs into the circulation, which can impair endothelial homeostasis further and increase CVD risk (Shang *et al*., 2017) (Fig. 3).

Regulation of miR-92a in Vascular Endothelial Aging by Mediating Nrf2-KEAP1-ARE Signal Pathway

When a body is under oxidative stress, the overproduction of free oxygen species may exceed the clearance potency of the body, thereby leading to an imbalance in the oxidation/antioxidation system and causing further tissue inflammation and injury (Zhang *et al*., 2015). SOD is an important antioxidase in the body for clearing ROS and plays a critical role in oxidation/antioxidation homeostasis (Liu *et al*., 2015).

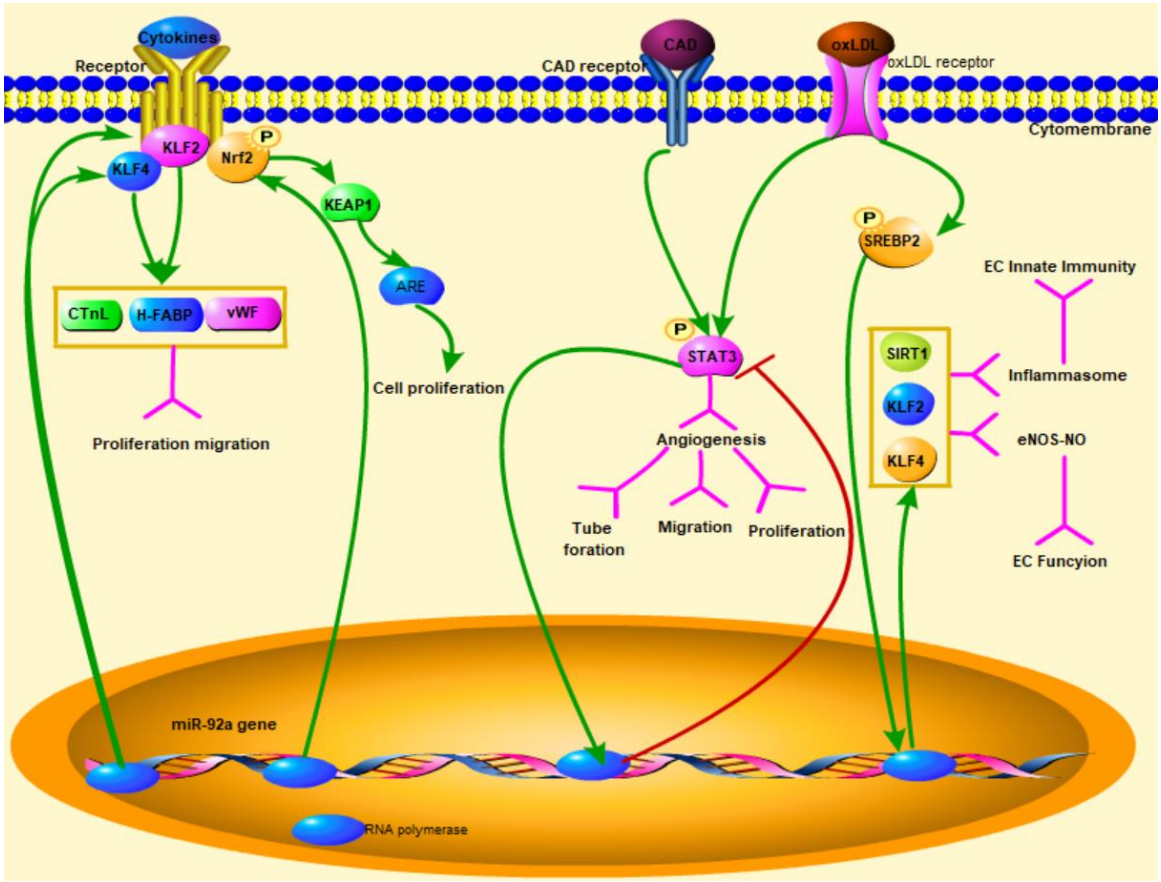

Fig. 3: Effect of miR-92a on EC signaling axis

MPO cannot penetrate a membrane alone but can be released abundantly under cell injury or death (Yang *et al*., 2014b). Moreover, the downregulation of miR-92a facilitates SOD expression in aging vascular ECs and decreases ROS and MPO, thereby further illustrating that miR-92a downregulation can mediate oxidation/antioxidation balance, thereby decreasing caspase-3 activity and facilitating proliferation and aging cells. Nrf2 is a transcription factor with cell-protecting effects (Jiang *et al*., 2016). The Nrf2-KEAP1-ARE signal pathway is a critical endogenous antioxidation signal pathway in the body and can resist internal/external oxidation and chemical substances by mediating redox balance, inhibiting oxidative stress further and exerting defense effects (Chatterjee *et al*., 2016; Menegon *et al*., 2016) (Fig. 3). Moreover, the downregulation of miR-92a can inhibit KEAP1 expression substantially and facilitate Nrf2 and ARE expression, thereby indicating that the Nrf2-KEAP1-ARE signal pathway plays a critical role in aging oxidative stress response. The downregulation of miR-92a can affect the aging process of vascular ECs by mediating the Nrf2-KEAP1-ARE signal pathway (Liu *et al*., 2017).

MiR-92 Promotes the Migration, Proliferation and Angiogenesis of Neighboring ECs by Mediating THBS1 Inhibition

As an independent risk factor of atherosclerosis, Low-Density Lipoprotein (LDL), specifically its oxidized form (i.e., oxLDL), plays a key role in endothelial dysfunction and atherogenesis (Pirillo *et al*., 2013). OxLDL induces the expression of miR-92 and promotes the packing of miR-92 from ECs into the EMV. Under atherosclerotic conditions, the expression of miR-92 in ECs and the EMV is upregulated in a STAT3-dependent manner. The EMV released from maternal ECs contains miR-92, which is transferred to neighboring ECs, thereby promoting the migration, proliferation and angiogenesis of adjacent ECs through the inhibition of miR-92-mediated THBS1 (Liu *et al*., 2019) (Fig. 3).

MiR-92a Activates EC Immunity

Given the positive effect of SIRT1, KLF2 and KLF4 on NO bioavailability, the finding that SREBP2-miR-92a suppresses the expression of SIRT1, KLF2 and KLF4 reveals a post-transcriptional mechanism through

which oxidative stress diminishes NO bioavailability, thereby resulting in endothelial dysfunction (Chen *et al*., 2015). Oxidative stress induces SREBP2 and miR-92a in ECs as well as SREBP2-activated miR-92a. Oxidative stress-induced miR-92a-targeting SIRT1, KLF2 and KLF4 increase endothelial innate immunity but decrease NO bioavailability. Moreover, miR-92a levels are negatively correlated with patient EC functions (Fang and Davies, 2012; Wu *et al*., 2011; Chen *et al*., 2010) (Fig. 3). SREBP2-induced miR-92a targets key molecules in endothelial homeostasis, including SREBP1, KLF2 and KLF4, thereby leading to NOD-like receptor family, pyrin domain containing 3 inflammasome activation and eNOS inhibition. In EC-specific SREBP2 transgenic mice, locked nucleic acid (LNA)-modified antisense miR-92a (LNA-92a) attenuates inflammasome, improves vasodilation and ameliorates Ang II-induced and aging-related atherogenesis (Chen *et al*., 2015).

Conclusion and Perspectives

MiR-92a binds different target genes to regulate numerous signaling pathways that can alter cancer cells and plays an important role in tumorigenesis, development and metastasis. Given that miRNAs are stable in tumor tissues and plasma, miR-92a is expected to make a breakthrough in early tumor diagnosis and tumor gene therapy research. MiR-92a promotes the proliferation and migration of VSMCs and inhibits the apoptosis of VSMCs effectively by regulating their related signaling pathways. Moreover, miR-92a mediates endothelial dysfunction in CKD, regulates vascular endothelial aging and promotes migration, proliferation and angiogenesis in adjacent ECs. These processes can in turn lead to endothelial damage in the human body, thereby reducing inflammation and improving vasodilation and atherosclerosis by regulating the expression level of miR-92a. Furthermore, miR-92a can be used as a biomarker and potential therapeutic target for the diagnosis of diseases. Overall, the miR-92a can participate in the regulation of multiple signaling pathways and play a potential role in certain diseases. Abnormal changes in different signaling pathways cause different diseases and also induce miR-92a abnormal expression (up- or down-). Different pathways correspond to different disease states or/and physiological environments. Under this specific state and environment, it is only possible to activate a related signaling pathway and other signaling pathways may not be activated. With further research, the differential expression of the miR-92a gene in cells, stem cells, or drug-resistant cells as well as its mechanism may provide a new direction for disease studies. Further research should be conducted in the future to discover the target of miR-92a and its role in different disease signaling pathways and to understand the pathogenic mechanism behind its activity.

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Author's Contributions

Zhiyuan Sun: Article conception and writing.
Qing Xu: Collection and analysis of literature data.
Xiaoyi Tian and Yingjie Yang: Data collection.
Qinglu Wang: Design and supervise the completion of the project.
Xuewen Tian: Participate in article writing, design and supervise project completion.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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