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Review

MicroRNA-210 and its theranostic potential

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Abstract

Introduction: MicroRNAs (miRNAs) are a set of small single-stranded noncoding RNAs with diverse biological functions. As a prototypical hypoxamir, human microRNA-210 (hsa-miR-210) is one of the most widely studied miRNAs thus far. In addition to its involvement in sophisticated regulation of numerous biological processes, miR-210 has also been shown to be associated with the development of different human diseases including various types of cancers, cardiovascular and cerebrovascular diseases, and immunological diseases. Given its multi-faceted functions, miR-210 may serve as a novel and promising theranostic target for prevention and treatment of diseases.

Areas covered: This review aims to provide a comprehensive overview of miR-210, the regulation of its expression, biological functions and molecular mechanisms, with particular emphasis on its diagnostic and therapeutic potential.

Expert opinion: Although the exact roles of miR-210 in various diseases have not been fully clarified, targeting miR-210 may be a promising therapeutic strategy. Further investigations are also needed to facilitate therapeutic-clinical applications of miR-210 in human diseases.

Keywords: microRNA-210, Hypoxia, Biomarker, Theranostic Target

Article highlights

- miRNAs perform diverse biological functions primarily by post-transcriptionally silencing target genes.
- The capacity to regulate a wealth of target mRNAs enables miR-210 to control a signaling network involved in multiple biological processes.
- There seems to be a general consensus that dysregulation of miR-210 expression plays a pivotal and causal role in numerous human diseases.
- miR-210, especially circulating miR-210, may represent a viable diagnostic biomarker for early detection or differential diagnosis of various diseases while this miRNA also shows promise as a prognostic factor. However its specific role may vary depending on the physio-pathological context.
- miR-210 has the potential to be a promising therapeutic target, despite its limitations.

1. Introduction

MicroRNAs (miRNAs) are tiny, evolutionarily conserved noncoding RNAs and have the essential function of gene regulation both in plants and animals [1]. As is described in the latest release of miRBase, there are 1881 precursors and 2588 mature miRNAs in human genome (miRBase Release 21, <http://www.mirbase.org>) [GRCh38]. Accumulating evidence suggests that extracellular miRNAs may originate from cell lysis in cell apoptosis or necrosis, chronic inflammation, and injury, or from the short half-life cells [2]. miRNAs can also be secreted into circulation via microvesicle such as exosomes [3]. Furthermore, a high-density lipoprotein pathway may be another distinct mechanism for exporting miRNAs [4]. As a result, miRNAs are readily detectable in serum and other body fluids, and exhibit striking stability compared with mRNAs and other long RNAs. Biogenesis of miRNA consists of multiple consecutive stages and mature single-stranded miRNA forms RNA-induced silencing complex (RISC) with proteins of Argonaut (Ago) family, especially Ago-2 [5]. RISC is mainly responsible for silencing the gene at the post-transcriptional level. The miRNA base-pairs with target mRNA achieve gene silencing by mRNA cleavage or translational repression. It is now widely acknowledged that the specificity of miRNA targeting depends on how complementary the 'seed' sequence (nucleotides 2-8 from 5' end of the miRNA) and the 'seed-match' sequence (usually in the 3' untranslated region (UTR) of the target mRNA) are [6]. However, miRNA has recently been demonstrated to bind to either the 5' UTRs of its target gene [7] or even the gene coding region [8]. Surprisingly, some miRNAs have also been found to activate rather

than inhibit gene expression, or enhance protein translation [9]. Usually, one miRNA has more than one target mRNA, and one mRNA is targeted by more than one miRNA [10]. This phenomenon results in formation of an intricate regulatory network that plays an important role in a myriad of biological processes, such as cellular proliferation, apoptosis, differentiation, and angiogenesis.

Hypoxia is a common causative hallmark of pathological conditions including tissue ischemia and solid tumours. Hypoxic adaptation is favorable to aerobic mammalian cells in the short term, whereas chronic hypoxia may cause adverse pathological consequences [11]. Mounting data demonstrate that under hypoxia, miRNAs are involved in regulating both upstream and downstream signaling of hypoxia-inducible transcription factor (HIF) pathways [12, 13]. Among them, human miR-210, also known as hypoxamir, is regarded as the most important one and appears to be a HIF target gene highly upregulated by both HIF-1 α and HIF-2 α in various cell types [12, 14]. In fact, miR-210 is involved in numerous biological processes, especially the pathogenesis of a variety of diseases. This review will focus on analyzing the biological functions and molecular mechanisms of miR-210, analyze its association with various diseases and evaluate its potential clinical applications in diagnosis and treatment of human diseases.

2. Biology of miR-210

The stem-loop form of miR-210 (pre-miRNA) is contained in the intron region of a noncoding RNA (pri-miRNA), which is transcribed from AK123483; AK123483 gene is

on chromosome 11, in the 11p15.5 region [14]. miR-210 genomic sequences, especially coding sequence and the hypoxia response element (HRE) site, are evolutionarily conserved across species, suggesting functional importance of these sequence [12]. There are overwhelming data demonstrating that miR-210 is ubiquitously expressed in hypoxic cell and tissue types including a variety of cancer cells, lymphocytes, myeloid cells, and hematopoietic stem cells [11, 15-19]. Aberrant miR-210 overexpression has been demonstrated during fibroblast senescence, causing reduction of cell proliferation and enhancement of DNA damage [20]. In addition, miR-210 may also be upregulated after treatment, such as photodynamic therapy [21]. Surprisingly, the elevated expression of miR-210 does not return to its normoxic level until 24 hours after hypoxic exposure [22], which can lead to an exceptionally long half-life. However, no evidence suggests the long-lasting miR-210 expression as a 'buffer' that gradually releases the suppression of its targets, thus easing the transition from hypoxia to normoxia for the cell. With respect to how circulating miR-210 coordinates hypoxic adaptation across anatomically distinct cells, Hale *et al.* [23] have recently reported a pivotal molecular switch, prolyl-hydroxylation of Ago-2 which can control miR-210' release and its activity upon uptake into recipient cells. miR-210 can also upregulate the mammalian target of rapamycin (mTOR) pathway, an essential driver of senescence^[24]. This, together with DNA damage and oxidative stress, may contribute to the process of senescence.

3. Regulation of miR-210 expression

Figure 1 summarizes regulation of miR-210 expression. As is the case with a number of classic HIF-1 α -regulated genes, HIF-1 α binds directly to a highly conserved HRE on the proximal miR-210 promoter [12]. miR-210 has also been documented to be induced by oxidative stress [25] under direct control of HIF-1 α [26]. While HIF-1 α pathway is regarded as a sufficient and predominant regulator of miR-210 expression and a positive feed-forward loop between them has been shown [12, 25, 27-29], HIF-2 α -dependent induction of miR-210 has also been recognized [30, 31]. Interestingly, miR-210 may contribute to activation and stabilization of HIF-1 by inhibiting succinate dehydrogenase complex subunit D (SDHD, a part of complex II) in respiratory chain [32].

Additionally, several emerging transcriptional factors have been confirmed to drive miR-210 expression in a tissue- or a cell type-specific manner, such as Oct2/4, E2F, and PPAR γ [33, 34]. Mutharasan *et al.* first suggested that miR-210 was upregulated in hypoxic cardiomyocytes through protein kinase B (Akt)- and p53-dependent pathways [35]. This phenomenon has been shown in both normal and transformed cells [36]. A novel transcriptional mechanism has also been revealed: NF κ B transcriptional factor p50 (NF κ B1) is an upstream regulator of miR-210 under hypoxia and can stimulate miR-210 expression in a fetal sex-dependent manner in placentas with maternal obesity [37]. Thus NF κ B1 and miR-210 form a positive feedback loop.

As such, increased miR-210 expression can be observed with the activation of PI3K, Akt, ERK, and NF κ B/ELK1 pathways by connective tissue growth factor (CTGF, namely CCN2, an inflammatory mediator) [38]. Furthermore, Chapoval *et al.* [39] have

first demonstrated that activation of Toll-like receptor (TLR) 3 can significantly upregulate miR-210 expression both in TLR3-induced mouse model of PE placentas and in human cytotrophoblasts. In addition, miR-210 overexpression occurs via an inhibitory-independent mechanism that is modulated by CD63 (cell surface receptor of TIMP-1) -TIMP-1 interaction [40].

Several studies show that miR-210 can stimulate the generation of reactive oxygen species (ROS) by targeting complexes I and II of the electron transport chain [19, 32]. Its overexpression thus induces accumulation of ROS [20]. Kim *et al.* [41] conversely demonstrated that ROS generation from various sources could induce miR-210 upregulation in adipose-derived stem cells. These findings suggest the interaction between miR-210 and ROS.

Furthermore, DNA damage can partially modulate the expression of miR-210 [20]. Xiong *et al.* [42] have provided evidence that DNA demethylation may mediate miR-210 expression independent of HIF-1 α pathway in neural progenitor cells (NPCs) under both normoxia and hypoxia conditions. Recently, a report reveals that leukocyte DNA methylation induced by exercise training can alter miR-210 gene, subsequently influencing expression of its mature miRNA [43]. Also, somatic von Hippel-Lindau (VHL) gene may contribute to the induction of miR-210 [44]. Succinate dehydrogenase (SDH) deficiency in pheochromocytomas (PCs), paragangliomas (PGLs) and gastrointestinal stromal tumours (GISTs) was reported to activate miR-210 expression, but the mechanism remains unclear [45].

4. Regulation of signaling network by miR-210

With the development of technology, such as whole transcriptome RNA sequencing (RNA-Seq), microarray and in silico, it is possible to identify numerous target genes of miR-210. However because miRNAs also regulate protein expression by repressing their protein translation without changing their mRNA expression, some bona fide targets of miRNA may be undetected by using the above strategies [46]. It has been demonstrated that miR-210 plays a critical role in the modulation of several signaling pathways including cell proliferation, apoptosis, angiogenesis, DNA damage repair, and immune responses as summarized in Figure 2.

4.1 Signaling pathways of proliferation regulated by miR-210

Emerging evidence suggests that miR-210 may attenuate cancer cell proliferation by suppressing fibroblast growth factor receptor-like 1 (FGFRL1) and inducing cell cycle arrest in G1/G0 phase (Figure 1) [47]. It has also been established that miR-210-mediated downregulation of some cell cycle regulators, especially E2F transcription factor 3 (E2F3, a crucial facilitator of cell proliferation), may alter centrosome replication in S phase to control cell cycle [26, 48]. Biswas *et al.* [27] used a murine ischemic wound model to further elucidate that miR-210 could limit keratinocyte proliferation by knockdown of E2F3 under hypoxia. Furthermore, a growing body of evidence suggests that miR-210 overexpression can not only govern the onset of mitosis by targeting Cdc25B and Plk1, but also control the mitotic progression by mediating Plk1, Cyclin F, Bub1B and Fam83D, inducing G2/M arrest and finally cell death in diverse type cells [26, 49]. Similarly, miR-210 may act as an

inhibitor on tumour initiation by suppressing homeobox protein Hox-A1 (HOXA1) [12] that helps prompt cell survival in a Bcl-2-dependent manner in mammary carcinoma cells [50] (Figure 2). Of note, with the development of a tumour, dramatically upregulated miR-210 could produce an inhibitory effect [49]. Also, miR-210 dramatically reduces cellular proliferation rate in senescent human diploid fibroblasts by targeting mTOR pathway [20].

With regard to infection, miR-210 is generally associated with inhibition of viral/bacterial replication. For example, miR-210 may function as a suppressor in HBV replication via directly targeting the transcripts of *hepatitis B virus* gene pre-S1 region [51]. During chronic *Helicobacter pylori* infection, miR-210 appears to be downregulated, resulting in augmentation of gastric epithelial cell proliferation through activating stathmin 1 and dimethyladenosine transferase 1 [52].

Nonetheless, contradictory results exist regarding the role of miR-210 in promoting or inhibiting cell proliferation. Hypoxia can promote proliferation of various cells via HIF-1 α and HIF-2 α [53], and also upregulate miR-210. This suggests that miR-210 may participate in cell proliferation. Indeed, miR-210 has been shown to mediate cell proliferation by targeting specific proteins such as transferrin receptor 1 (a major Iron-uptake protein) under hypoxic microenvironment in tumour [54]. Similar results have been shown in the endometriotic cyst stromal cells (ECSCs) where miR-210 targets signal transducer and activator of transcription 3 (STAT3) [55]. Moreover, by downregulating protein tyrosine phosphatase, non-receptor type (PTPN) 1 and PTPN2 respectively, miR-210 exhibits an increased proliferation of epithelial ovarian

cancer cells and adipose-derived stem cells [41, 56]. As described in some studies, miR-210 can boost cell proliferation through activating c-Myc signaling pathway via repressing MNT (Max's next tango, a Max-interacting transcriptional repressor) [31]. Since both MYC and miR-210 target E2F3, miR-210 may positively or negatively regulate MYC pathway at several points, as a rheostat to fine tune the net output of this pathway [27, 29].

Thus, the relationship between miR-210 and cell proliferation seems to be rather complex and the underlying molecular mechanisms remain to be determined.

Signaling pathways of apoptosis regulated by miR-210

Apoptosis is the most common form of programmed cell death in multicellular organisms in which the caspase family of cysteine proteases are mainly involved in the molecular events in the execution phase [57]. Within the caspase family, the effector caspases (caspases-3, -6 and -7) fine-tune the demolition stage of apoptosis [58]. Cheng *et al.* [59] first showed that blockade of miR-210 with antisense inhibitor could enhance the apoptosis level through inducing caspase-3 activity in HeLa cells. Since then, a multitude of similar results were further demonstrated in diverse cell types, such as endothelial cells (ECs) [22]. miR-210 overexpression directly inhibits the SH2-containing inositol phosphatase 1 (SHIP-1, a lipid phosphatase) and this may promote myeloid leukemic growth in CD34⁺ myelodysplastic syndromes (MDS) cells [60] (Figure 2). As presented in a previous study, miR-210 mimics may reduce cell death by suppressing both the expression of Bcl-2 adenovirus E1B 19 kDa-interacting protein 3protein and the translocation of apoptosis inducing factor (AIF) into nucleus

in NPCs [61]. Similarly, Jiang *et al.* [16] identified that miR-210 was a potential regulator in the antioxidant stress and anti-apoptosis responses induced by vagus nerve stimulation in ischemic stroke rats. Additionally, miR-210 is found to inhibit apoptosis by potentially targeting receptor tyrosine kinase ligand EphrinA3 and PTP1 β in a murine model of myocardial infarction (MI) [29]. Consistent results have been demonstrated in human pulmonary vascular smooth muscle cells with repression of E2F3 [62], and in ECSCs with activation of signal transducer and activator of transcription (STAT) 3 [55]. Yang *et al.* [63] suggested that knockdown of miR-210 could increase apoptosis-inducing factor, mitochondrion-associated 3 (AIFM3, an apoptotic promoter) expression, robustly inducing cell arrest in the G0/G1 phase in human hepatoma cells under hypoxia. Finally, the production of ROS stimulated by miR-210 [32] could decrease apoptosis. Thus miR-210 mainly suppresses apoptosis via its action on many key regulators of apoptosis.

On the other hand, miR-210 is also considered as a pro-apoptotic factor. Multiple dehydrogenases components, such as SDHD, have been validated as bona fide miR-210 targets that participate in mitochondrial dysfunctions in a variety of cell lines [32], consequently inducing cellular apoptosis. It has been established that enlarged mitochondria with a modified organization of cristae in miR-210-expressing cells is associated with an induction of apoptosis. Reportedly, miR-210 may partially participate in degradation of Bcl-2 mRNA (an anti-apoptotic factor and a target of miR-210), leading to hypoxia-induced apoptosis in insulted neurons [64]. Moreover, miR-210 controls mitochondrial function by repressing multiple related mitochondrial

targets in various cell lines, such as iron-sulfur cluster scaffold homolog1/2 (ISCU1/2) [65] and cytochrome-c oxidase assembly protein [19]. As a crucial physiological role of MNT is to inhibit apoptosis [66], miR-210 may promote apoptosis via its action on MNT. Hence, miR-210 seems to be either cytotoxic or cytoprotective in terms of cell apoptosis.

4.3 Signaling pathways of angiogenesis modulated by miR-210

Generally, angiogenesis refers to the process of vessel growth, while in the strictest sense, it denotes vessel sprouting from pre-existing ones [67]. It is essential for embryo development as well as the vascular homeostasis in adults. Angiogenesis is normally begun with preliminary destabilization of pre-existing vessels, and this is followed by EC proliferation and migration, canalization and eventually stabilization of the vessel wall, leading to tube formation [68]. . Since the stimulation of angiogenesis is a main biological effect of hypoxia, the unique hypoxamir miR-210 is likely to play a role in angiogenesis. Various modes of action for miR-210 in regulating angiogenesis are summarized in Figure 1.

In ECs, vascular endothelial growth factor (VEGF, a powerful angiogenic factor) can activate postnatal angiogenesis via upregulating miR-210 [69]. Indeed, miR-210 was most predominantly coupled to 'VEGF, hypoxia and angiogenesis' in breast cancer, which was identified by global testing [70]. By using miR-210 transfection in normal endometrial stromal cells, Okamoto *et al.* further demonstrated that STAT3 could be stimulated by miR-210, leading to induction of VEGF production [55]. Similarly, evidence was presented that miR-210 up-regulation under normoxic conditions in

ECs significantly triggered the formation of capillary-like structures and VEGF-driven cell migration, whereas miR-210 blockade under hypoxia markedly inhibited these events [22] that are key to the angiogenic process. Moreover, Kosaka *et al.* [71] first suggested that exosomal miR-210 could be horizontally transported from cancer cells to ECs via exosomes, which would trigger the angiogenic activity in vitro. More recently, in vitro and in vivo experiments in lung adenocarcinoma have substantiated that the TIMP-1-induced PI3K/AKT/HIF-1/miR-210/Ephrin A3 pathway promotes angiogenesis probably indirectly through an action on the exosomes that have proangiogenic properties. On the other hand, overexpression of miR-210 in exosomes can increase vessel formation of ECs by repression of anti-angiogenic Ephrin A3 [40]. Targeting PTP1 β , GPD1L and PHD2, miR-210 can also generate similar effects [29, 38]. Consistent with these data, miR-210 has been identified as a vital regulator for CD34⁺ cell-induced angiogenesis [72]. Furthermore, WSS25, a sulfated derivative of a type of glucan isolated from the well-known Chinese herb *Gastrodia elata* Bl has been reported to be closely correlated to downregulation of miR-210 and upregulation of miR-210 target Ephrin A3 in human microvascular endothelial cells, thus blocking angiogenesis [73]. Given these proangiogenic roles, studying the function of miR-210 may help to understand the process of many human diseases.

4.4 miR-210 and DNA damage repair

Under hypoxia, DNA repair capacity may be affected by increased genetic instability via numerous DNA repair-related genes including MLH1, MSH2 and RAD51 [74], where miR-210 is likely to play a functional role (Figure 2). Previous work elucidated

that forced miR-210 expression reduced endogenous levels of RAD52 (a recombination repair regulator) that assists in loading RAD51 onto DNA to form nucleoprotein filaments, resulting in decrease of homology-dependent DNA repair activity in response to hypoxic stress [75]. In addition, miR-210 is also implicated in double-strand DNA breaks and appearance of a DNA-damage response marker (rH2AX foci) in human cells which undergo replicative senescence, subsequently aggravating DNA damage [20]. All these findings help to understand the biological basis for prompting DNA damage under hypoxia. However, complete function of this miRNA has yet to be investigated.

4.5 miR-210 and immune responses

miR-210 can also modulate immune responses as shown in Figure 3. Previous studies have suggested that cytotoxic T lymphocytes (CTLs) are essential effector cells in tumour rejection and important players in host defense against malignancies [76]. A recent study revealed that miR-210 could dramatically downregulate tumour cell susceptibility to CTL-mediated cell lysis by targeting downstream PTPN1, HOXA1, and TP5311, therefore producing immunosuppressive effects under hypoxia [18]. More recently, miR-210 was reported to be involved in activation and differentiation of T cells, especially the T_H17 subset of helper T cells (T_H17 cells), consequently limiting the associated immunopathology [77].

Regulatory T cells (Tregs, a subset of T cells with immunosuppressive characteristics) are especially crucial for preventing autoimmune diseases and controlling chronic inflammatory illnesses [78]. One study has provided compelling

evidence that marked downregulation of miR-210 is one of the miRNA signatures of circulating CD4(+) Tregs from healthy adult subjects, and the transcription factor forkhead box P3 (FOXP3, mandatory for Treg cell function) is negatively modulated by miR-210 [79]. However, significant upregulation of miR-210 has been observed in CD4(+) T cells from patients with psoriasis vulgaris, and this led to damage of immunosuppressive function of Treg cells by directly targeting FOXP3 [80].

In addition to T cells, role of miR-210 in B cells has also been proposed. Overexpression of Oct-2-induced miR-210 after B cell activation can significantly inhibit production of age-associated autoantibodies, and also lead to abnormal B cell subsets and function, especially cell autonomous expansion of B1 lineage and damaged fitness of B2 cells [34]. Another study demonstrates that miR-210 driven by lipopolysaccharide (LPS), a new feedback negative player in LPS/Toll-Like Receptor 4 (TLR4) pathway, can decrease LPS-induced production of pro-inflammatory cytokines in murine macrophages; this is mediated by repressing NF κ B1, attenuating inflammatory responses and regulating immune responses [81]. These data may imply that miR-210 acts as a negative regulator in the prevention of age-associated autoimmunity.

As noted above, extensive studies have provided substantial evidence for miR-210 as a multifaceted mediator in cellular biology by regulating numerous signaling pathways, but its effects may depend on the specific physio-pathological context. Despite all this progress, the molecular mechanisms underpinning miR-210 regulation and function remain to be elucidated.

5. Roles for miR-210 in human diseases

5.1 Roles for miR-210 in cardiovascular and cerebrovascular diseases (CCVDs)

Table 1 outlines the role of miR-210 in CCVDs. Emerging technologies have promoted the study of miRNAs and their association with diseases [82]. To date, miR-210 stands out as the specific hypoxamir reported in almost cells studied, thus its induction may directly reflect the hypoxic state that is involved in a wide range of human diseases.

Over the last decade, miR-210 has attracted tremendous interest as a crucial epigenetic regulator of physiological and pathological events in cardiovascular system. Theoretically, release of miR-210 from endothelium in clinically healthy subjects with low maximal oxygen uptake ($VO_{2\max}$) may function as a novel early marker of cardiovascular disease (CVD) because this miRNA is related to subclinical atherosclerosis, hypoxia or inflammation [43]. Given miR-210 augmentation in low $VO_{2\max}$ set and significant correlation between them, miR-210 may be a promising biomarker of aerobic fitness level [43]. As a master hypoxamir, miR-210 is a well-characterized hypoxia-induced miRNA in ischemic cardiovascular diseases, such as MI [83], heart failure (HF) [84] and arteriosclerosis obliterans (ASO) [85]. Moreover, miR-210 is also identified as a potential stroke marker. miR-210 levels at different times was remarkably decreased in blood from stroke patients in contrast to healthy controls [86]. On the contrary, significantly upregulated miR-210 was shown in adult rat ischemic brain cortexes, which triggered the Notch pathway, leading to the

compensatory angiogenesis after cerebral ischemia [87].

Furthermore, White *et al.* [88] have observed miR-210 upregulation in lungs from multiple distinct pulmonary hypertension (PH) models including a genetic model, a chronic hypoxia-induced PH model, hypoxia/Sugen model, and inflammatory PH models. The authors also validated that chronic activation of miR-210-ISCU1/2 regulatory axis could cause a reduction in Fe-S clusters in vivo and promote the evolution of PH. Since the level of miR-210 can differentiate between the low and high VO_{2max} groups, which cannot be separated by the traditional risk factors, miR-210 may represent an early marker of CCVD risk even beyond traditional risk factors [88]. However, the specificity of miR-210 in detecting CCVD may be limited as many hypoxic conditions can influence its expression.

5.2 Roles for miR-210 in tumour biology

Based on the crucial roles of miRNAs in cancer initiation, progression and dissemination, many studies have explored the specific role of miR-210 in pathogenesis of malignancies [89] (Table 2). Certain microRNAs, known as oncomiRNAs, play a causal role in the onset and maintenance of cancer when overexpressed [90]. Currently, overwhelming data have identified miR-210 as an oncogenic miRNA in a wide range of human malignancies including pancreatic cancer, breast cancer, lung cancer, B cell malignancies, and hepatocellular carcinoma (HCC) [13, 14, 32, 91, 92]. Similarly, elevated expression of miR-210 has been detected in SDHB and VHL-mutated tumours including clear cell renal cell cancer (CCRCC), PCs, PGLs, and GISTs [30, 45]. Additionally, aberrant overexpression of miR-210 may

change normal fibroblasts into cancer associated fibroblasts (CAFs), which boosts aggressiveness of prostate tumour cells through driving epithelial to mesenchymal transition, supporting angiogenesis [93]. Foekens *et al.* has connected miR-210 to metastatic capability in estrogen receptor-positive/lymph node-negative breast cancer [70]. Furthermore, a mouse model of left and median bile duct ligation has shown increased expression of miR-210 that contributes to progression of cholestasis-accelerated cholangiocarcinoma (CCA) by MNT downregulation [31].

In contrast to above solid tumours, miR-210 is frequently reported to downregulate in esophageal squamous cell carcinoma (ESCC) and ovarian cancer cell lines and to generate a tumour-suppressor effect [47, 48]. Consistent with this, inflammation-induced silencing of miR-210 may augment cell proliferation, contribute to induction of helicobacter pylori -associated gastric diseases including cancer [52]. Several studies implicate a critical role of miR-210 in reducing cancer cell proliferation by repressing targets, such as E2F3 [27, 47]. A mouse xenograft model in an elegant study performed by Huang X *et al.* robustly demonstrated that miR-210 could suppress tumour growth initiation of head and neck tumour [12]. Hence it is not surprising that miR-210 is also likely a tumour-suppressive microRNA unfavorable to tumour onset and growth in some tumour circumstances.

In addition to upregulated or downregulated miR-210 in multiple tumour types, there may be no change in miR-210 expression in some tumours, for example, head and neck squamous cell carcinoma (HNSCC) [94]. Many different tumours frequently present with different levels of miR-210 expression, probably because expression of

miR-210 serves as a marker for tumour hypoxia [12, 94] that is extremely diverse in a variety of cancers. Possibly, deleted miR-210 genomic region is another explanation [44].

Because of inherent stability and good accessibility of circulating miRNAs [95], miR-210 can be an attractive candidate biomarker for diagnosis. Additionally, dysregulated miRNA expression partly represents the early event in tumourigenesis and In circulating miRNAs present unique profiles for each tumour and histopathological subtype [96]. In line with these findings, altered serum or plasma miR-210 may serve as a promising diagnostic biomarker for patients with malignancies, such as diffuse large B-cell lymphoma, CCRCC and pancreatic cancer [91, 97, 98]. Furthermore, to diagnose a disease, a specific pattern consisting of more than one miRNA, such as miR-210 combined with other miRNAs, may improve the power for differential diagnosis . For example, this could help to discriminate between pancreatic adenocarcinoma patients and controls [99], acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) [100], lung tumours and benign solitary pulmonary nodules (SPNs) [101], early stage diffuse-type gastric cancers (DGCs) and normal ones [102], and among grade IV, grade II and III astrocytomas [103]. For the first time, Eissa *et al.* [104] proposed a strategy for bladder cancer (BC) diagnosis which combines miR-210 with other two miRNAs in urine, superior to the urine cytology in sensitivity. Although these findings indicate the possibility of using circulating miR-210 as a biomarker for an early tumour diagnosis, specificity and sensitivity of diagnostics, standardization of blood sampling and analysis protocols to

make it's a routine clinical test, are still in infancy.

So far, the prognostic value of miR-210 expression in cancers has been widely investigated. Data from clinical cancer samples has elucidated that miR-210 upregulation is an independent prognostic factor of poor survival in multiple cancers including breast cancer, colorectal cancer (CRC), and pediatric osteosarcoma [14, 105, 106]. When combined with other miRNAs, miR-210 can be a more specific and accurate prognostic indicator for pancreatic ductal adenocarcinomas (PDAC) and glioblastoma patients [13, 107]. Similar results can be observed in head and neck cancer [94]. Since miR-210 is a significant element of chronic hypoxia irrespective of androgen dependency, it could be detected as a prognostic marker in high risk patients with prostate cancer [108]. Meanwhile, Tsang and colleagues [45] have substantiated miR-210 as a robust marker for pseudohypoxia (i.e. hypoxia gene expression despite normoxic conditions) in SDHB- and VHL-mutated PC/PGLs, which occurs even before tumour development.. Paradoxically, a recent study has revealed that patients with significantly lower expression of miR-210 tend to relapse and present with induction failure, even poorer treatment outcome in pediatric ALL [109]. McCormick *et al.* [30] have provided strong evidence that in CCRCC, increased miR-210 is associated with better prognosis. In non-small cell lung cancer (NSCLC) patients, highly expressed miR-210 in both cancer cells and stromal cells acts as a positive prognosticator with an improved disease-specific survival (DSS) [110]. miR-210 is also associated with poor prognosis in soft-tissue sarcoma (STS) [111]. On the other hand, ectopic expression of mir-210 represses tumour growth in human

head and neck or pancreatic tumours [12]. miR-210 could provide added value to other current diagnostic laboratory tests for cancers such as CCRCC where miR-210 level is significantly increased. With the use of next generation sequencing, miR-210 may be useful in monitoring the disease outcome over time.

Taken together, these data imply the dual roles of an oncomiRNA and a tumour-suppressive microRNA for miR-210, which may depend on tumour types or its different stages or tumour microenvironment. Further studies are required to clarify tissue- and cell type-specific profiles of miR-210. Although miR-210 has a potential value in prediction, prognosis, and treatment of cancer, it is still a long way to go before clinical applications.

5.3 Roles for miR-210 in other diseases

In addition to CCVD and tumour, the abundant data on miR-210 also shed light on further investigating the mechanisms of other human diseases as summarized in Table 3. A recent study suggests that upregulated miR-210 is likely to participate in the formation of gallstones by inhibiting *Homo sapiens* ATPase, class VI, type 11A (ATP11A, a novel ABC transporter homolog) [112]. Similar robust induction of miR-210 is proved to be involved in radiation-induced enteropathy. Interestingly, the miR-210 inhibitor showed an anti-fibrotic action by decreasing collagen I (Col 1a1) mRNA expression in fibrotic cells [113]. In addition, elevated plasma miR-210 levels in patients with acute kidney injury (AKI) may serve as an independent and powerful predictor of survival in critically ill patients with AKI [114]. In keeping with these findings, the attenuation of apoptosis via miR-210/SHIP-1/Akt pathway may contribute

to progression of MDS and hence miR-210 may serve as such a marker [60]. Lemaire and colleagues [115] have reported that the first 24h of *Leishmania* infection shows a rapid and significant alteration of miRNA profile of human primary macrophages, especially the progressive and robust increase of miR-210. While miR-210 has been identified as a significantly upregulated microRNA in periodontitis patients with obesity [116], downregulation of miR-210 by > 2-fold has been demonstrated in diseased gingiva compared to healthy gingival tissues [117]. However the biological significance of miR-210 aberration involved therein is poorly understood.

Additionally, accumulating evidence suggests that miR-210 is significantly involved in the erythroid phenotype. Kosaka *et al.* [118] reported that increased expression of miR-210 following erythroid differentiation in UT-7/erythropoietin (EPO) cells as well as in murine fetal liver erythroid cell differentiation in vitro, indicating that miR-210 is likely to be correlated to erythroid maturation. Similar results was found in the erythroid precursor cells from patients exhibiting hereditary persistence of fetal hemoglobin (HPFH), along with enhanced expression of the fetal γ -globin genes [119]. Sarakul *et al.* further confirmed that under hypoxia, miR-210 was elevated in both K562 and β -thalassemic erythroid progenitor cells, whereas miR-210 blockade inhibited these events [120]. However, downregulation of miR-210 can be surprisingly observed following erythroid induction of both K562 cells and CD34⁺ cells derived from human cord blood [121]. These data support a vital role of miR-210 in erythroid maturation, proliferation, and even γ -globin gene expression.

To date, overexpression of miR-210 in the syncytiotrophoblasts of preeclampsia

(PE) placentas has been increasingly reported by different groups, especially in severe PE [122]. The upregulated miR-210 may participate in occurrence of PE via reduction of trophoblast invasion by downregulating Ephrin-A3, Homeobox-A9, potassium channel modulatory factor 1 (KCMF1) [123, 124]. Currently, miR-210 has already been identified as a potential serum biomarker for PE, and miR-210 inhibition may promisingly ameliorate symptoms of PE. In addition to PE placenta, miR-210 expression is also significantly enhanced in placentas of maternal obesity in a fetal sex-dependent manner, thus resulting in repression of mitochondrial respiration and dysfunction of placenta [37]. Despite these recent advances, the mechanisms of miR-210 upregulation and downregulation, its target biomolecules as well as its pathophysiological roles in these diseases remain to be established.

6. A promising therapeutic target for miR-210

Given the fact that silencing aberrantly miRNAs in vivo has been achieved using antisense with a diversity of nucleic acid analogues such as 29-O-methyl oligonucleotides (for example, antagomiRs), locked nucleic acids (LNAs), and peptide nucleic acids (PNAs) or nanoencapsulated [125-127], miR-210 has garnered interest as a possible therapeutic target for human diseases in the last decade. Indeed, strategies for adjusting the aberrantly expressed miR-210 may provide a new therapeutic avenue for various diseases. Probably, one of the most exciting opportunities is potential use of miR-210 mimics or antagonists as therapeutics. For example, miR-210 has been knockdown by using a lentiviral-mediated antisense

miR-210 gene transfer technique, which may eliminate glioma stem cells (GSCs) located in hypoxic niches [128]. Since in vivo efficacy of current antagomiR techniques is impeded by physiological and cellular barriers to deliver into targeted cells, Cheng et al.^[90] have created a novel antagomiR delivery platform that targets the acidic tumour microenvironment, evades systemic clearance by livers, and facilitates cell entry via a non-endocytic pathway. Additionally, plant extract may be another choice for inhibiting miR-210. For example, *Difluorinated-Curcumin* (CDF), a novel synthetic analog of *curcumin* derived from the perennial herb *Curcuma longa*, with greater bio-availability in multiple tissues, , may function as a robust antitumour agent against prostate cancer in vitro and in vivo, at least partly by negatively regulating miR-210 [129].

On the other hand, miR-210 mimic treatment can ameliorate cardiac dysfunction of ischemic heart disease [29]. Based on the importance of miR-210 in Akt/HIF1 α -regulated cell survival, vector-based and ex-vivo stem-cell-based delivery of miR-210 has been performed for myocardial repair with encouraging results [130]. By using real-time PCR and histological analysis techniques, a study in a rat model has shown the effect of intra-articular injection of miR-210 on ligament healing [131]. The same technique has also produced a desired effect in accelerating avascular meniscal healing in rat medial meniscal injured model [132]. Since oligonucleotides or virus based constructs can systemically reintroduce a tumour-suppressor miRNA into cancer cells so as to repress tumour growth [133], miR-210 may be a favorable future treatment approach for ESCC patients. Forced overexpression of miR-210 may lead

to downregulation of Prolyl 4-hydroxylase, beta polypeptide (P4HB) and a reduction in temozolomide (TMZ)-resistance in cultured glioblastoma multiforme (GBM) cells and a reciprocal relationship between miR-210 and P4HB expression was also confirmed in clinical glioma specimens [134]. Moreover, miR-210 may have therapeutic applications in terms of cancer immunotherapy in view of its influence on tumour cell susceptibility to CTL-mediated lysis [18]. Meanwhile, targeting HIF-1 α by administering miR-210 mimics in vivo may be useful for T_H17 cell-dependent autoimmune diseases because miR-210 is a potent regulator of HIF-1 α in T cells [77]. Additionally, (-)-epigallocatechin-3-gallate (EGCG, green tea polyphenol) treatment can contribute to induction of miR-210, and then negatively regulate cell growth of human and mouse lung cancer [28]. Furthermore, WSS25 (a heparan sulfate mimetic) may be a promising drug applicable in angiogenesis in terms of targeting miR-210 [73]. In targeted delivery of miRNA-210 for cancer treatment, the types of cancer must be taken into consideration as the expression level and function of miR-210 vary among different types of cancer. Although manipulating miR-210 expression or function may have an effect on experimental models of diseases (especially carcinomas, autoimmune diseases, and injury disorders), and miR-210 has a potential role in human disease therapy, successful implementation of miR-210 therapeutics still requires more in vitro and in vivo experiments are required to research the safety and feasibility of agomiR-210 and antagomiR-210 in clinical application.

Despite these promises, the limitations of using miR-210 as a therapeutic target

must be recognized and there are also obstacles on the way for the successful delivery of miRNA. One issue is the systemic effect of miR-210, as the molecule has a diverse effect on multiple systems. Another challenge is targeted delivery to a specific organ or tissue. The antisense strategies for in vivo delivery with nucleic acid analogues have the problem of non-specific organ bio-distribution and clearance by reticuloendothelial system and the liver. Cheng's new anti-miR delivery approach targeting the acidic environment can only apply to the drug cargo with limited charge such as PNA¹¹⁸. There is still distribution to other acidic tissue environment, for example the kidney. Many of the miRNA approaches remain to be tested using in vivo models and over a long term with a view of assessing unknown side effects. The safety and efficacy in humans remain to be evaluated.

7. Conclusion

miR-210 has already been shown to be involved in sophisticated regulation of numerous biological processes almost throughout the human body. This multi-functional hypoxamir is proved to be correlated with the pathophysiology of different diseases, including tumours, CCVDs, immunological diseases, and PE. Among these diseases, miR-210 expression is frequently upregulated, and functions as an oncogene. Contradictory phenomenon for miR-210 is exhibited in other diseases, which mostly suggests miR-210 a protector against diseases. Importantly, circulating miR-210 seems to have great theranostic potential for future clinical practice. It can not only serve as a potent biomarker for diagnosis, disease

progression and patient prognosis, but also serve as a good theranostic target for treatment. However, it is worth noting that miR-210 therapeutics is a double-edged sword, further work remains required to improve its efficacy. In summary, the characteristics of miR-210 make it an attractive therapeutic candidate, and its real value will most likely be determined in the very near future.

8. Expert opinion

8.1 Identification of roles of miR-210 in disease diagnosis

Nowadays, the gold standard for cancer detection is the histological evaluation of biopsy because of its high sensitivity and specificity. But its usage is still restricted to clinical settings because of the suffering of patients resulting from the invasive nature [135]. Since deregulated miRNA expression is an early event in tumourigenesis, measuring circulating miR-210 levels has already shown promise as a noninvasive biomarker for early cancer detection without the unpleasant procedure [97, 98]. However, the application of miR-210 as an effective clinical biomarker still has a long way to go.

Firstly, although many studies investigated the important diagnostic value of miR-210 in various cancers, these studies often reached conflicting results due to the limited sample size, different study design, and lack of unified standard [135]. In addition, except cancers, studies related to miR-210 as an effective screening strategy in other human diseases are relatively sparse. More studies with better design and larger sample sizes are urgently needed for this task. Secondly, recent

studies suggested that hypoxic condition, a hallmark of virtually all solid cancers, may induce the expression of miR-210 by HIF-1a [27, 28, 135]. Although such connection of miR-210 and cancer opens the door for using miR-210 as a hypoxia marker for tumours, the exact mechanism in tumour development needs further investigation. Thirdly, there seems to be a general agreement that single miR-210 can cover a broad spectrum of neoplasms and the combination of miR-210 and other miRNAs may contribute to significant improvement in specificity [101, 102], but the combination approach, as well as the unique indicator for specific cancer, pose significant challenges.

8.2 Emerging roles of miR-210 in disease prognosis

A multitude of studies have firmly established the relationship between miR-210 and cancers, for instance, pancreatic tumour, breast cancer, glioblastoma, and CRC [13, 14, 70, 105]. Overexpression of miR-210 has been consistently linked to adverse prognosis in multiple solid tumour types, including CRC and pediatric osteosarcoma patients [105, 106], while expression of miR-210 in clear cell renal cell cancer (CCRCC) associated with a favorable prognosis [30]. Therefore, the impact of miR-210 on cancer prognosis still needs detailed studies and the results of existing researches may not be applicable for other carcinomas. Furthermore, the role of miR-210 in routine clinical management of cancer remains unevaluated. More clinical investigations with long follow-up period should be carried out before the practical application of miR-210 in prognosis of diseases [136].

8.3 Therapeutic potential of miR-210 in diseases

For the vast majority of tumours, chemotherapy or radiation therapy is still the cornerstone of treatment. Monoclonal antibodies only have little benefits in a limited proportion of patients. However drugs frequently face well-known clinical issues related to variable responses, toxicity and drug resistance. These issues highlight the urgent demand for the development of novel anti-cancer drugs. As an important class of gene regulators, miRNAs, in particular miR-210, possess high potential for anti-cancer therapeutic development. Nevertheless, from basic researches to clinical application, there is still a huge gap so far due to a number of limitations and challenges. Therefore, it is suggested that more research should be conducted along the following approaches to pave the way for miR-210 clinical application.

Currently, miR-210 has been identified as a member of a pan-cancer oncogenic microRNA 'superfamily' which shares a central GUGC core motif resulting in cotargeting critical tumour suppressors [137]. Hence therapeutically suppressing miR-210 may encounter compensation from other superfamily members yielding poor results and how to evaluate and handle this compensation is also a great challenge. To date, it is not fully understood whether miR-210 likely constitutes other oncomiRNA networks and plays greater roles. Additionally, determining accurate genomewide miR-210-target interactions is another difficult question to address. On the other hand, multidrug resistance (MDR) should be taken into account because it is a major clinical obstacle to the successful treatment of malignant diseases, but the underlying mechanisms remain unclear. A better understanding of the mechanisms may achieve

optimized therapy. Recently, emerging evidence suggests the contribution of hypoxia to drug resistance in a wide spectrum of neoplastic cells, in which HIF-1 has been widely studied, plays an important role [138]. As a hypoxamir, miR-210 is likely to play an important role in the process of MDR via regulation of its numerous targets, which remains to be prospectively validated. Reportedly, miR-210 may be a marker of radiotherapy resistance and offer the possibility of developing more efficient therapeutic strategies [94]. Trastuzumab resistance has been proved to be a major issue in antihuman epidermal growth factor receptor 2 therapy for breast cancer [139]. The levels of circulating miR-210 have been reported to correlate with trastuzumab sensitivity and tumour presence in patients with breast cancer [140], suggesting that plasma miR-210 may help identify subsets of patients who can benefit from such agents, and even serve as a potential novel patient selection criteria for clinical trials in the future. It is conceivable that miR-210 in combination with other anti-cancer therapies could contribute greatly to the success of cancer treatment, but further work will be required. The possibility that inactivation of miRNAs involved in hypoxic adaptation may be a viable strategy, poses significant therapeutic challenges. Therefore, a complete understanding of miR-210 regulatory architecture and net production will help develop more efficient therapeutic strategies for human diseases. A series of in vitro and in vivo experiments and bioinformatics analysis are needed, and with improvements in drug delivery technology, will enable miR-210-mediated therapy to open a new era.

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Conflict of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Reference annotations

* Of interest

** Of considerable interest

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Table 1 Roles of miR-210 in CCVDs

CCVD	Expression	Function of miR-210	Reference
CVD	Up	Overexpressed miR-210 can be used as a novel biomarker of fitness level and future CVD.	[43]
MI	Up	miR-210 is highly upregulated during in MI.	[83]
HF	Up	miR-210 is one of the upregulated miRNAs in HF.	[84]
ASO	Up	miR-210 significantly increases in both sclerotic and serum samples.	[85]
Stroke	Down	As blood miR-210 levels at different times are remarkably decreased, miR-210 may be as a potential stroke marker.	[86, 87]
	Up	Conversely, significantly upregulated miR-210 can trigger the Notch pathway, contributing to angiogenesis after cerebral ischemia.	
PH	Up	Chronic activation of miR-210-ISCU1/2 regulatory axis can promote the evolution of PH.	[88]

Table 2 Roles of miR-210 in tumours

Tumour	Expression	Function of miR-210	Reference
Head and neck tumour	Up or no difference	<p>Ectopic expression of miR-210 can inhibit the tumour growth initiation of head and neck tumour.</p> <p>In HNSCC, no difference of miR-210 expression is observed between HNSCC tissues and control ones, whereas tumour miR-210 expression is an adverse prognostic factor.</p> <p>miR-210 is capable to differentiate grade IV from grade II and III astrocytomas.</p>	[12, 94, 103]
ESCC	Down	<p>Downregulation of miR-210 in human ESCC, especially in poorly differentiated carcinomas can function as a tumour-suppressive microRNA with effects on cancer cell proliferation through FGFR1.</p>	[47]
Lung cancer	Up	<p>miR-210 overexpressed in late stages of lung cancer mediates mitochondrial alterations, which correlates with modulation of HIF-1 activity.</p>	[32, 110]

Tumour	Expression	Function of miR-210	Reference
Breast cancer	Up	In NSCLC, high expression of miR-210 is a positive prognostic factor for DSS.	
		Overexpression of miR-210 indicates worse prognosis, especially in triple- negative primary breast cancers.	
		miR-210 combined with other three miRNAs (miR-7, miR-128a, and miR-516-3p) links to ER(+)/LNN breast cancer aggressiveness.	[14, 70, 140]
		Plasma miR-210 may possibly predict and monitor response to trastuzumab for breast cancer patients.	
GC	Up	Circulating miR-210 can accurately detect DGC at an early stage.	[102]
HCC	Up	Hypoxia/miR-210/VMP1 pathway regulates hypoxia-induced HCC cell metastasis.	[92]
CCA	Up	Activation of HIF-2 α -miR-210-MNT pathway leads to cyclin D1 upregulation, thus regulating the chronic cholestasis accelerated progression of CCA.	[31]

Tumour	Expression	Function of miR-210	Reference
Pancreatic cancer	Up	Elevated miR-210 plays an oncogenic role in the development of pancreatic cancer and is associated with poorer survival. Circulating miR-210 might serve as a novel biomarker of this disease.	[13, 98, 99]
PC, PGL, and GIST	Up	miR-210 is upregulated in SDH- or VHL-mutated tumours.	[45]
CRC	Up	Hypoxia-inducible miR-210 is a useful biomarker and an independent prognostic factor that contributes to cancer metastasis.	[105]
CCCRC	Up	Elevated serum miR-210 is associated with better clinico-pathological prognostic factors and may be a promising biomarker for detecting CCRCC.	[30, 97]
BC	Up	miR-210 in urine is one of the potential miRNA signatures for BC.	[104]
Prostate cancer	Up	miR-210 expression may augment when prostate cancer cells were exposed to hypoxia, therefore it may be useful for high risk prostate cancer patients, irrespective of the androgen	[93, 108, 129]

Tumour	Expression	Function of miR-210	Reference
		dependency.	
		miR-210 overexpression can increase senescence-associated features for young fibroblasts and convert them into CAF-like cells, thus promoting cancer progression.	
		Prostate cancer may be treated at least partly due to by CDF negatively regulating miR-210.	
Ovarian cancer	Down	High frequency of miR-210 gene copy deletions contributes to causing low expression of miR-210.	[48]
B cell malignancies	Up	Levels of serum miR-210 are higher in diffuse large B-cell lymphoma (DLBCL) patients than healthy controls, acting as diagnostic biomarkers.	[91]

Tumour	Expression	Function of miR-210	Reference
Pediatric ALL	Down	Lower expression of miR-210 suggests worse prognosis and poorer treatment outcome.	[109]

Table 3 Roles of miR-210 in other diseases

Disease	Expression	Function of miR-210	Reference
Gallstone	Up	miR-210 likely participates in the formation of gallstones by inhibiting ATP11A.	[112]
Radiation enteropathy	Up	miR-210 is likely involved in radiation-induced enteropathy.	[113]
AKI	Up	Increased plasma levels of miR-210 may be as an independent and powerful predictor of survival in critically ill patients with AKI.	[114]
Obese periodontitis	Up	miR-210 is one of the significantly upregulated microRNAs.	[116]
Diseased gingiva	Down	Downregulation of miR-210 has been demonstrated in diseased compare to healthy gingiva.	[117]
MDS	Up	miR-210/SHIP-1/Akt pathway attenuating apoptosis may be involved in progression of MDS.	[60]
<i>Leishmania</i> infection	Up	miR-210 abundance is progressively and robustly increased throughout the time course of infection.	[115]
PE	Up	As a potential serum biomarker, overexpression of miR-210 may participate in occurrence of	[37,

PE by downregulating ephrin-A3, HOXA9, and KCMF1.

122-124]

It is especially correlated with severe PE.

Figure 1 Regulation of miR-210 expression. The figure summarizes how miR-210 expression may be regulated or influenced. Sharp arrows indicate activation/upregulation and double arrows indicate interaction between them.

Figure 2 Regulation of signaling pathways by miR-210: miR-210 regulates several key biological processes including proliferation, apoptosis, DNA repair, angiogenesis and immune responses via the action of a vast variety of transcription factors and inflammatory mediators. Sharp arrows suggest stimulatory effects whereas blunt arrows are inhibitory.

Figure 3 miR-210 and immune response miR-210 regulates both acquired and innate immune responses, via its action on hypoxia-mediated pathway, transcription factors, and cytokines.