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Invited Review

miR-210: The Master Hypoxamir

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ABSTRACT

MicroRNAs are small non-coding RNAs implicated mainly in post-transcriptional gene silencing by interacting with the untranslated region of the transcript. miR-210 represents major hypoxia-inducible miRs, also known as hypoxamirs, which is ubiquitously expressed in a wide range of cells, serving versatile functions. This review article summarizes the current progress on biogenesis of miR-210 and its physiological roles including arrest of cell proliferation, repression of mitochondrial respiration, arrest of DNA repair, vascular biology, and angiogenesis. Given the fact that miR-210 is aberrantly expressed in a number of diseases such as tumor progression, myocardial infarction and cutaneous ischemic wounds, miR-210 could serve as an excellent candidate for prognostic purposes and therapeutic intervention. With the advancement of computational prediction, high-throughput target validation methodology, sequencing, proteomic analysis, and microarray, it is anticipated that more down-stream targets of miR-210 and its associated biological consequences under hypoxia will be unveiled establishing miR-210 as a major hub in the biology of hypoxia-response.

Key words: miR-210, hypoxamiRs, microRNAs, tissue repair

Abbreviation used: ACVR1B, activin receptor type 1 B; CASP8AP2, caspase-8-associated protein 2; COX10, cytochrome *c* oxidase assembly protein; DGCR8, DiGeorge critical region 8; EFNA3, ephrin-A3; FGFRL1, fibroblast growth factor receptor like 1; FLASH, FLICE-associated protein homolog; HIF, hypoxia inducible factor; HOXA1, homeobox A1; HRE, hypoxia responsive element; IP, ischemia preconditioning; I/R, ischemia/reperfusion; ISCU, iron–sulfur cluster assembly homologue; LNA, lock-nucleic acid; MNT, max-binding protein; MSCs, mesenchymal stem cells; miR, microRNAs; 3′ UTR, 3′ untranslated region; NFκB, nuclear factor κB; PTP1B, phosphatase 1B; RISC, RNA-induced silencing complex; SDHD, succinate dehydrogenase subunit D; Tcf7l2, transcription factor 7-like 2; VEGF, vascular endothelial growth factor.

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INTRODUCTION

MicroRNAs are small RNAs consisting of around 22 nucleotides. Unlike protein-coding genes, miRs exhibit extraordinary gene regulatory functions, silencing gene expression via interaction with the 3′ UTR of the transcript [3,8,12,44,74,81,82,85,87,88,90,91]. The biogenesis of miRs is a highly-orchestrated process, which essentially requires the co-ordination of ribonucleases, RNA-binding proteins and the miR gene itself [93]. Transcription and appropriate truncation of the nucleic acid, which is known as miR maturation, are vital for the synthesis of correct miR strand. Certain key proteins such as Drosha, DGCR8, exportin-5, Dicer and Ago2 are critical for this process. Any disruption or inactivation of these molecules results in pathological outcomes or developmental defects [56,101]. The details of miR maturation have been reviewed elsewhere and will not be discussed in this article [91,93].

Over decades, induction of protein coding genes by low-oxygen has dominated the focal point of hypoxia research. One of the most sensitive physiological sensors of hypoxia is HIF. HIFs control the cellular response to hypoxia by regulating genes that are involved in metabolism, angiogenesis, erythropoiesis, cell proliferation, differentiation, and apoptosis. Although three isoforms of HIF have been identified, HIF1α and HIF2α are the most dominant sensors of hypoxia [48]. When oxygen tension falls below the normoxic setpoint for any given tissue [50], HIF1α is stabilized and binds to its more constitutive partner HIF1β, and this complex regulates the expression of downstream genes [48]. HIF transactivates a wide variety of genes involved in the hypoxia response, some of the most noted ones being erythropoietin, VEGF, and glucose transporter 1 [72]. More recently, however, the study of gene regulation promoted by a low-oxygen microenvironment has received increased attention. The regulation is under the control of specific hypoxia-inducible miRs also termed as "hypoxamiRs." Some of the reported hypoxamirs are summarized in Table 1.

Table 1. Summary of hypoxamirs

	Name of microRNAs	Reference
Hypoxia up-regulated miRs	miR-21, -23a, -23b, -24, -26a, -26b, -27a, -30b, -93, -103, -103, -106a, -107, -125b, -181a, -181b, -181c, -192, -195, -210, -213, -429, -498, -572, -563, -637 and -628	[25,41,45,83]
Hypoxia down-regulated miRs	miR- 15b, -16, -19a, -20a, -20b, -29b, -30b, -30e-5p, -101, -122a, -141, -186, -195, -197, -200b, -224, -320, -374, -422b, -424, and -565	[12,41,78]

MIR-210: GENETIC LOCUS AND PROMOTER

miR-210 is a master hypoxamir, which is induced under hypoxia in wide range of primary and transformed cells [20]. The stem–loop of miR-210 is located in an intron of a non-coding RNA, which is transcribed from AK123483 on chromosome 11p15.5 [41]. miR-210 is regulated by both HIF1α [9,40,41] and HIF2α [104]. HIF1α directly binds to a HRE on the proximal miR-210 promoter, located 400 bp upstream of the structure [41]. The HRE of miR-210 promoter is highly conserved across species, suggesting that HIF is phylogenetically conserved in regulation of miR-210 *de novo* synthesis under hypoxia. Apart from HIF, NFκB, a hypoxia-sensitive transcription factor [18], is also responsible for miR-210 induction in responsive to hypoxia. Mapping of 200-bp core promoter region immediately upstream of miR-210 stem–loop structure indicated a conserved κB binding site [103]. Chromatin immunoprecipitation, promoter luciferase assay, gene knockdown studies revealed that NFκB p50 can physically interact with and transactivate miR-210 promoter under hypoxia [103]. Recent study also reported that Akt activation facilitates the hypoxia-associated accumulation of miR-210 in a HIF-independent manner [69], indicating that multiple circuits of signaling can switch on miR-210 in responsive to low-oxygen condition.

MIR-210 AND CELL GROWTH ARREST

miR-210 inhibits cell proliferation by targeting proteins that are crucial for cell cycle progression. A number of studies reported that hypoxia-driven miR-210 directly targets E2F3 in a wide variety of cells such as keratinocytes [8], ovarian cancer cells [31], and human embryonic kidney (HEK) cells [70]. E2F3 belongs to the E2F family transcription factor involved in regulation of cell proliferation, differentiation, and apoptotic response [35,58]. It is well documented that E2F3 promotes cell proliferation by allowing the cell cycle progression from G1 to S phase and the initiation of DNA replication [22,57,96]. Recently, miR-210 has been shown to target two other proteins, namely FGFRL1 [40,95] and HOXA1 [40] to modulate cell proliferation. FGFRL1 is the fifth FGFR family [100], which contains similar structure of extracellular-transmembrane domain to other FGFR family members, but lacks the intracellular protein tyrosine domain [92]. FGFRL1 promotes proliferation in esophageal squamous cell carcinoma cells by facilitating cell cycle progression [95]. More importantly, over-expression of FGFRL1 significantly rescued the growth inhibitory effect of miR-210 *in vitro* [95] and *in vivo* tumor xenograft [40], suggesting that miR-210 inhibits cell proliferation via a FGFRL1-dependent mechanism. HOXA1 is one of the members of the homeobox protein cluster A, which is essential in patterning the early hindbrain along the anterior–posterior axis during development [29]. It is highly expressed in a wide variety of cells including mammary epithelial cells, esophageal squamous cells, and cervical cancer cells. E-cadherin signaling induces HOXA1 expression, which subsequently promotes anchorage-dependent growth [102]. Forced over-expression of HOXA1 induced activation of p44/42 MAP kinase, supporting cell proliferation [66]. Over-expression of HOXA1 reversed growth inhibitory effect of miR-210 [40], indicating that miR-210-dependent growth inhibitory effect is, at least partially, due to direct silencing of HOXA1.

Expression profile of miR-210 targets is different in healthy *versus* cancer cells. Expression of some targets is restricted to transformed cells. Besides, some of the miR-210 target proteins serve different functions in different cell type. In cancer cells, miR-210 may support cell proliferation. miR-210 targets MNT, a Myc-antagonist, *promoting* cell cycle progression in transformed cells such as colon cancer cells and cervical cancer cells [104]. MNT competes with Myc for its binding partner myc-associated factor X and the Enhancer Box sequences to inhibit transactivation of genes that control cell cycle progression [42].

MIR-210 SUPPORTS STEM-CELL SURVIVAL

miR-210 supports stem-cell survival under hypoxic condition [51]. Episodes of IP enhanced MSCs survival under anoxic condition, with the concomitant elevation of miR-210. Interestingly, the cytoprotective effect of IP could be reversed by anti-miR-210. Studies dissecting mechanistic insight revealed that miR-210 promotes stem-cell survival

via targeting CASP8AP2 [51], or its human homologue FLASH, a protein that facilitates Fas-induced apoptosis [43].

MIR-210 REPRESSES MITOCHONDRIAL METABOLISM

When oxygen is available on a limited basis, metabolic shift from mitochondria respiration to glycolysis takes place, generating 2 mole of ATP (instead of 38 moles in normoxia) per 1 mole of glucose [41]. Accumulating evidence reveal that miR-210 inhibits mitochondrial metabolism by targeting a number of proteins that are crucial for normal TCA cycle. miR-210 delivery alone under normal oxygen condition was potent enough to inhibit mitochondrial energy production [11], impair the oxygen consumption [11], induce lactate accumulation [15,27], alter mitochondrial membrane potential [77], and disrupt mitochondrial structure [77]. The ISCU 1/2 is one of the direct targets of miR-210. ISCU1/2 expression is negatively correlated with miR-210 level in wide variety of cells, such as human pulmonary endothelial cells [11], breast cancer cells [27], colon cancer cells [27], and trophoblasts [55]. ISCU1/2 catalyzes the assembly of [4Fe-4S] and [2Fe-2S] iron-sulfur clusters. Fe-S clusters serve as prosthetic groups of the flavoproteins in electron transport chain, enabling the oxidation–reduction reactions in mitochondrial respiration and energy production [80]. Fe-S cluster is critical for the enzymatic activity of aconitase, a stereo-specific isomerization of citrate to isocitrate, which fuels the TCA-cycle [4,80]. Constitutive expression of miR-210-resistant form of ISCU1/2 (devoid of 3′ UTR region) partially reversed miR-210-dependent inhibition of mitochondrial respiration activity [15], indicating that miR-210 targets ISCU1/2 to suppress mitochondrial functions during hypoxia. MiR-210 not only targets ISCU1/2 but also regulates COX10 [15] and SDHD [77], repressing mitochondrial respiration. COX10 encodes the enzyme protoheme: heme O farnesyl transferase that facilitates the biosynthesis of heme-α, a vital component for the terminal enzyme of the respiratory chain cytochrome *c* oxidase [75]. Loss of COX10 inhibits the activity of mitochondrial complex I and complex IV [21]. SDHD is one of the subunits of the inner mitochondrial enzyme succinate dehydrogenase or succinate-coenzyme Q reductase (SQR), which catalyzes the oxidation of succinate (coupled to reduction of ubiquinone) during mitochondrial respiration [76]. In this regard, hypoxia-dependent elevation of miR-210 serves as a potent inhibitor of mitochondrial metabolism by targeting TCA cycle and electron transport chain activity. miR-210-dependent acute transient down-regulation of mitochondrial respiration is, on the one hand, important to enable the cells to "hang in there," as the cells are less sensitive to oxygen for energy production under hypoxic environment. On the other hand, it is in conflict with energy demanding processes such as tissue repair. If the inhibition of mitochondrial respiration is prolonged, cell death may ensue because of energy starvation. Interestingly, hypoxia-inducible miR-210 remains elevated even after return to normoxic environment for a day [25], suggesting that miR-210 induces a long-lasting inhibitory effect on mitochondrial metabolism even in the presence of sufficient oxygen. Strategies to antagonize the persistent miR-210 up-regulation during re-oxygenation phase would help re-establish normal mitochondrial respiration and direct the cells toward an effective energy metabolism status.

MIR-210 STALLS DNA REPAIR

DNA damage is induced under normal metabolic conditions and some environmental factors including UV and radiation. It is expected that over a million DNA lesions per cell take place in a day [68], leading to severe detrimental consequences including cell senescence and tumor transformation. DNA repair is particularly important to ensure that the genetic material remains intact throughout the life. Recently, it was reported that miR-210 can silence the DNA repair system via targeting the enzyme RAD52 [17]. RAD52 is a protein that fixes DNA double-strand break repair, repairs single-stranded DNA gaps and facilitates RAD51-mediated strand invasion during homologous recombination [67,99]. miR-210 directly binds to the 3′ UTR of RAD52 to induce translational repression [17]. Hypoxia-dependent down-regulation of RAD52 can be rescued by treatment with anti-miR-210 [17], suggesting that RAD52 is down-regulated via a miR-210-dependent mechanism under low-oxygen environment. Shutdown of the DNA repair under low-oxygen condition might be critical for ATP conservation for cell preservation ("hang in there" response) during acute hypoxic condition [17]. However, such shutdown is in direct conflict with tissue repair. Chronic hypoxia (thus subsequently leading to sustained miR-210 level) substantially arrests DNA repair mechanism and induces genetic instability, resulting in either cell senescence or conferring a mutation phenotype during tumor transformation.

MIR-210 INDUCES ANGIOGENESIS

Cells respond to hypoxic challenge by up-regulation of genes that are essential for endothelial cells laying new blood vessel, which would help correct hypoxia and ensure survival. While the majority of studies focus on the regulation of VEGF, which is a potent pro-angiogenic factor to support sprouting of endothelial cells, current progress in

miR biology has shed some light on the involvement of miR-210 in regulating angiogenesis under low-oxygen environment. Fasanaro *et al.* first reported that hypoxia-driven miR-210 supports angiogenic response in endothelial cells [25]. These effects were, at least partially due to the down-regulation of EFNA3, an ephrin family member involving vascular development [25,39]. Over-expression of EFNA3 significantly blocked the pro-angiogenic effect of miR-210 or hypoxia pre-conditioning [25]. Apart from EFNA3, miR-210 directly targets protein-tyrosine PTP1B [26,39], which negatively regulates VEGF signaling by de-phosphorylation of VEGFR2 in endothelial cells [71]. Elevation of miR-210 leads to repression of PTP1B, allowing successful VEGF signaling to proceed under hypoxia. The pro-angiogenic effect of miR-210 was evaluated in myocardial infarction, as evidenced by improved endothelial cell survival after delivery of miR-210 in the heart [39]. The involvement of miR-210 in regulation of pathophysiological angiogenesis has also been demonstrated in ischemic renal ischemia/reperfusion (I/R) injury, indicating that miR-210 induction is necessary to drive the expression of VEGF and VEGFR2 in endothelial cells [61]. In this regard, elevation of miR-210 supports angiogenic response and facilitates microcirculation under both physiological and pathophysiological conditions.

MIR-210 SUPPORTS CELL DIFFERENTIATION

Oxygen tension represents an important microenvironmental cue that directs the cell differentiation program toward lineage commitment [36,60,79]. In general, stem cells tend to retain their pluripotency and undifferentiated state under hypoxia, while certain progenitor cells exhibit either accelerated or arrested differentiation program depending on the cell type. A number of investigations revealed that miR-210 supports cell differentiation. Bianchi *et al.* reported that mithramycin, a DNA-binding drug, which promotes erythroid differentiation, induced the expression of miR-210 in erythroid progenitor cells [7], with the concomitant expression of erythroid marker γ-globin. On the other hand, miR-210 promotes bone morphogenic protein (BMP)-induced osteoblastic differentiation via targeting ACVR1B [65]. ACVR1B transmits signal from activin via Smad 2/3. Inhibition of Smad 2/3 leads to activation of Smad 1/5/8, resulting in promotion of differentiation of osteoblast to osteoclast [65]. In this regard, hypoxia-inducible miR-210 down-regulates ACVR1B, shutting down Smad 2/3 signaling, and promoting Smad 1/5/8-dependent osteoblastic differentiation [65]. In addition, miR-210 is strongly induced during adipogenesis [78]. Delivery of miR-210 markedly promoted lipogenesis, while anti-miR-210 treatment significantly impaired the expression of lithium-induced adipogenic markers [78]. The pro-adipogenic response may be attributed by direct targeting of Wnt signaling mediator Tcf7l2. Given the fact that hypoxia promotes adipogenic differentiation [45], it is anticipated that a low-oxygen environment fosters the accumulation of miR-210, which in turn down-regulates Tcf7l2 and subsequently induces adipogenesis. Figure 1 summarizes the major biological significance of miR-210 elevation and its corresponding targets under hypoxic condition.

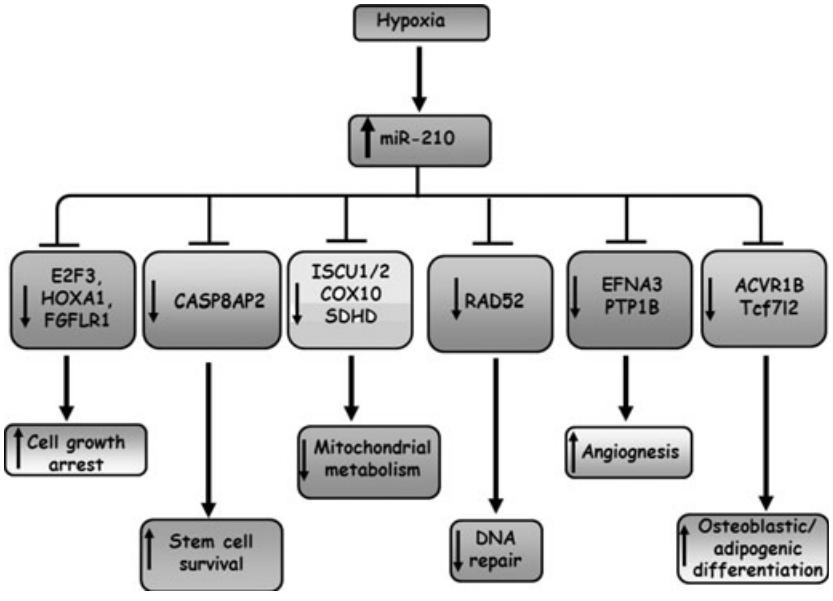

Figure 1. Summary of miR-210 targets and their biological consequences under hypoxia.

MIR-210 AS A PROGNOSTIC BIOMARKER

The average half-life of miRs is around five days, 10 times more than that of regular mRNA [28]. These small RNAs are extremely stable and are resistant to degradation by RNase A [14], high temperature, extreme pH, and freeze-and-thaw cycle [59]. The extraordinary stability of miR makes it suitable to serve as a biomarker of certain diseases for prognostic purpose. The expression of miR-210 is elevated in human solid tumors, including glioma [64], head and neck carcinoma [40], lung adenocarcinoma [16], late stage small cell lung cancer [77], malignant melanoma [83], and pancreatic ductal adenocarcinomas [32]. Aberrant miR-210 expression is not only present in the solid tumor or injured organs but also being secreted into circulation, which can be detected in the plasma of patients. Elevated circulating level of miR-210 can serve as a marker of diffuse large B-cell lymphoma [54], pancreatic ductal carcinoma [37,97], malignant solitary pulmonary nodules [89], and acute renal injury [62]. Recently, Lorenzen *et al.*, reported that miR-210 can also be detected in the urine from normal individual and renal allograft recipients [63], suggesting a wide variety of miR-210 source for prognosis. To date, a number of studies have worked on the prognostic power of miR-210 expression in different diseases. High levels of miR-210 were associated with disease recurrence and short overall survival in head and neck squamous cell carcinoma [30]. High miR-210 expression was also associated with a lower relative risk (RR) of tumor-related death compared with the intermediate expression of miR-210 expression in soft-tissue sarcoma patients [33].

MIR-210 DELIVERY OR ANTI-MIR-210: POTENTIAL THERAPY OF ISCHEMIC DISORDERS?

Given the fact that miR-210 exerts versatile effects on cellular functions and its deregulation under pathological conditions, strategies targeting correction of aberrantly expressed miR-210 might open up a new therapeutic avenue to a wide range of diseases such as ischemic disorders and tumor progression. The employment of miR-210 mimic delivery or anti-miR-210 therapy depends on whether miR-210 is insufficient or over-produced, respectively, under the corresponding disease state. Recently, it has been reported that intramyocardial injection of non-viral vector minicircle DNA carrying miR-210 precursor can stably transduce miR-210 expression for at least eight weeks in the heart [39]. More importantly, this strategy improved cardiac function, reduced the infarct size and rectified angiogenesis after myocardial infarction [39], indicating that miR-210 delivery might serve as a therapeutic approach in ischemic heart disease. On the other hand, aberrantly up-regulated miR-210 level can be suppressed by delivery of anti-miR-210 strategy using antagomir (with 2′O-methylation and phosphothioates) or LNA (with extra bridge connecting 2′ oxygen and 4′ carbon on ribose moiety). Stoffel and colleagues first reported that murine endogenous miRs could be silenced by bolus intravenous injection of antagomir in wide range of tissues [53]. The anti-miR *in vivo* study was further extended to non-human primates. Acute administration of unconjugated LNA-modified oligonucleotide against miR-122, a miR that regulates cholesterol biosynthesis, effectively down-regulated hepatic miR-122 in African green monkeys, which was accompanied by a decrease in plasma cholesterol in a dose-dependent manner [24].

Our group reported that ischemic cutaneous wounds exhibit elevated miR-210 expression, which was associated with the down-regulation of E2F3 and impairment in keratinocyte proliferation and wound re-epithelialization [8]. Besides arrest of keratinocyte proliferation, elevated miR-210 may complicate wound closure by repressing mitochondrial respiration and silencing DNA repair. Wound healing is an energy-demanding process [86]. Energy supply, as ATP, is required to fuel the growth of new tissue. Indeed, extracellular ATP supports wound-healing response by a number of mechanisms including epidermal growth factor (EGF) receptor transactivation, and NADPH oxidase activation [86]. Limited ATP generation is therefore in direct conflict with wound healing. Disruption of DNA repair system by elevated miR-210 in ischemic wounds is yet another roadblock as excessive DNA damage leads to cell senescence, which blunts the healing response. Angiogenesis is important in most cases but not singularly sufficient to drive wound healing [46]. Clinical experience shows that successful re-vascularization failed to heal ischemic lower extremity wounds [1,2,5,6,10,13,19,23,47,49,73,84,94]. Thus, elevation of miR-210 in ischemic wounds hurts wound closure by inhibiting keratinocyte

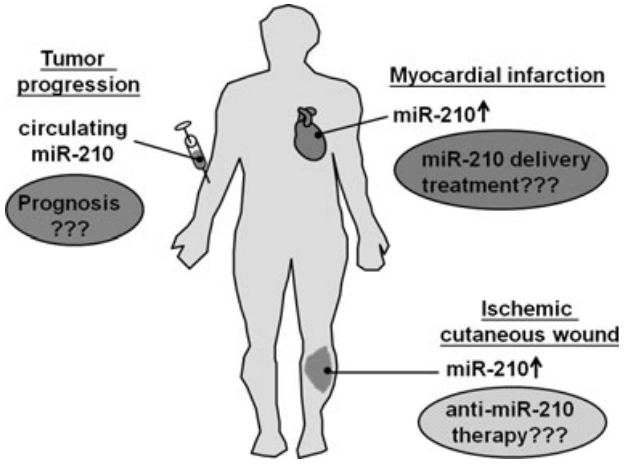

Figure 2. miR-210 serves as prognostic and therapeutic targets.

proliferation, disrupting mitochondrial metabolism, and compromising DNA repair despite pro-angiogenic effects. Delivery of anti-miR-210 should be tested for its efficacy to improve cutaneous wound outcomes.

PERSPECTIVE AND CONCLUDING REMARKS

miR-210 is steadily establishing itself as a major hypoxia-response factor that regulates several key aspects of health and disease. *In silico* prediction algorithms including Targetscan [38], MiRanda [38], Pictar [52], miRBase Target Database [34], and miRDB [98] represent powerful tools in the search for novel direct targets of miR-210. One of the limitations of these approaches is the possibility of raising false positive prediction because of the short seed sequence (7–8 nt). Experimental validation of specific miR-binding to 3′ UTR is necessary to confirm the induction of translational repression. Recently, the employment of RISC immunoprecipitation, a robust high-throughput approach to biologically validate the enrichment of transcript in RISC complex in responsive to miR-210 over-expression, has unveiled a number of novel miR-210 targets that are of significance in ischemic diseases [26,39,40]. Strategies adopting combined approaches including *in silico* prediction, RISC immunoprecipitation, proteomic analysis, microarray analysis, would help dissect the biological consequences of miR-210 and its associated target under diseases state. As it relates to regulating biological functions, miR-210 serves as a potent maestro in fine-tuning hypoxia response. Apart from prognostic value, miR-210 may serve as a target for therapeutic purpose in treating ischemic disorders such as myocardial infarction and cutaneous ischemic wounds (Figure 2).

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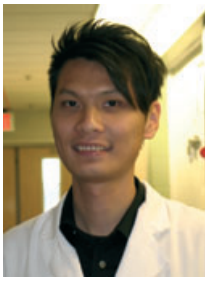

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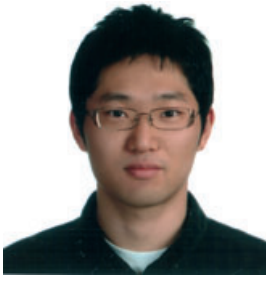

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