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OxymiRs in Cutaneous Development, Wound Repair and Regeneration

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Abstract

The state of tissue oxygenation is widely recognized as a major microenvironmental cue that is known to regulate the expression of coding genes. Recent works have extended that knowledge to demonstrate that the state of tissue oxygenation may potentially regulate the expression of microRNAs (miRs). Collectively, such miRs that are implicated in defining biological outcomes in response to a change in the state of tissue oxygenation may be referred to as oxymiRs. Broadly, oxymiRs may be categorized into three groups: (A) the existence (expression and/or turnover) of which is directly influenced by changes in the state of tissue oxygenation; (B) the existence of which is indirectly (*e.g.* oxygen-sensitive proteins, metabolites, pH etc) influenced by changes in the state of tissue oxygenation; and (C) those that modify biological outcomes to changes in the state of tissue oxygenation by targeting oxygen sensing pathways. This work represents the first review of how oxymiRs may regulate development, repair and regeneration. Currently known oxymiRs may affect the functioning of a large number of coding genes which have hitherto fore never been linked to oxygen sensing. Many of such target genes have been validated and that number is steadily growing. Taken together, our understanding of oxymiRs has vastly expanded the implications of changes in the state of tissue oxygenation. This emerging paradigm has major implications in untangling the complexities underlying diseases associated with ischemia and related hypoxic insult such as chronic wounds.

MicroRNAs (miRs) are a class of ~21-23 nucleotide long non-coding RNAs (ncRNAs). The human genome is estimated to encode over a 1000 miRs which in turn regulates the functionality of the majority of protein-coding human genes. miRs bind to their target mRNA transcripts by partial sequence complementarity. Such RNA-RNA interaction is usually implicated in post-transcriptional gene silencing by causing translational repression or degradation of the coding target mRNA. The state of tissue oxygenation is widely recognized as a major microenvironmental cue that regulates the expression of coding genes. Recent works have extended that knowledge to demonstrate that the state of tissue oxygenation may potentially regulate the expression of miRs [1-7]. Hypoxia-sensitive miRs are collectively referred to as hypoxamirs. The presence of hyperoxia-inducible miRs has now made it clear that the miR turnover machinery is sensitive to changes in the state of tissue oxygenation in both directions [7-9]. Furthermore, there are miRs that modify the

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biological responses to changes in the state of tissue oxygenation. Expression of these miRs may not be directly regulated by changes in tissue oxygenation but these miRs silence mediators of the oxygen-sensing pathways. Collectively, such miRs that are implicated in defining biological outcomes in response to a change in the state of tissue oxygenation may be referred to as *oxymiRs* (Figure 1). Advances in our understanding of the significance of oxymiRs add a new dimension of sophistication to how the state of tissue oxygenation may regulate coding genes. We now know that oxygen-sensitive coding genes are not simply limited to those with oxygen-sensitive transcriptional control. A much larger subset of the human genome may be regulated by the state of tissue oxygenation through post-transcriptional gene silencing executed by oxymiRs. On one hand, oxygen-sensitive transcription regulatory pathways may control the expression of both mRNAs as well as miRs. On the other hand, oxygen-sensitive miRs may cause post transcriptional silencing of a large number of target mRNAs most of which were hitherto not known to be oxygen-sensitive. Introduction of the concept of oxymiRs substantially adds to the overall biological significance of tissue oxygenation as it relates to regulating gene function and downstream biological outcomes. Change in tissue oxygenation is recognized as key drivers of embryonic development and tissue repair (Figure 2). In addition, stem cell biology is highly oxygen sensitive. In this work, we maintain focus on the skin as an organ and draw an outline of the expanded potential significance of changes in tissue oxygenation in light of the emergent knowledge on oxymiRs.

Molecular Aspects of Oxygen Sensing

Under conditions of oxygen limitation, the respiratory chain is limited by the unavailability of oxygen as the final electron acceptor. In order to support survival, cells switch from aerobic to anaerobic metabolism. This was first described as the *Pasteur Effect* which was based on the observation that oxygen-starved yeast markedly increased carbohydrate consumption. The switch from aerobic to anaerobic metabolism is enacted by metabolites acting on enzymes of the glycolytic pathway. Poor oxygen availability trigger austerity measures aimed at energy conservation [10-11]. Non-essential energy consuming functions are suspended to support cell survival. As part of ensuring cell survival hypoxia induces glycolytic enzymes and glucose transporters that are optimized to function better under hypoxia [12]. One such hypoxia-induced systemic survival response is represented by the induction of glycoprotein hormone erythropoietin (EPO). EPO stimulates red cell blood cell and hemoglobin production strengthening blood-borne oxygen delivery to tissues. The study of EPO reporter genes to explain the underlying hypoxia-dependent mechanisms of induction led to the discovery of hypoxia-inducible factor-1 (HIF-1). HIF-1 was recognized as a hypoxia-inducible transcription factor. Today, HIF-1 has emerged as a global regulator of hypoxic gene expression [13]. More recently, HIF has been directly implicated as a transcription factor that drives the expression of hypoxamirs [14-15]. Rapid and reversible regulation of gene expression by hypoxamirs tune metabolic networks with precision and control. In this way, hypoxamirs may function as molecular rheostats facilitating survival and adaptation to hypoxic conditions [16].

OxymiRs: miRs responsible for biological response to changes in tissue oxygenation

Broadly, oxymiRs may be categorized into three groups (Figure 3): **(A)** the existence (expression and/or turnover) of which is directly influenced by changes in the state of tissue oxygenation; **(B)** the existence of which is indirectly (*e.g.* oxygen-sensitive proteins, metabolites, pH etc) influenced by changes in the state of tissue oxygenation; and **(C)** those that modify biological outcomes to changes in the state of tissue oxygenation by targeting mediators of oxygen sensing pathways (Table 1). That changes in oxygenation state may influence the expression of miRs was initially observed when cancer and transformed cell

lines were exposed to hypoxia and differentially expressed miRs were cataloged [6, 45, 49, 103-104]. These hypoxamirs, which would fall under *group A* oxymiR, were noted to be highly abundant in human tumors. Profiling studies have led to the recognition of hypoxia inducible miRs including including miR-23, -24, -26, -27, -103, -107, -181, -210, and -213 [45]. Among the hypoxia-sensitive miRs only four, miR-210, miR-30b, miR-93 and miR-181b, were common across studies hypoxamirs are likely to be cell-type specific. SOLiD sequencing of small RNAs obtained from human endothelial cells exposed to hypoxia or normoxia identified two novel miRNAs which were down-regulated by hypoxia, while miR-210 was significantly induced [40]. Currently held as the master hypoxamir [1], miR-210 emerged as the first miR the expression of which is directly regulated by HIF1alpha as transcription factor [14]. Other miRs in this category include miR-373 [15]. Examples of *group B* oxymiRs would include miRs sensitive to anaerobic metabolites such as lactate or to oxidative stress caused by say hyperoxic insult. miRs are now recognized to be integral to the classical Warburg effect or aerobic glycolysis, a hallmark of cancer cells [105]. Oxidative stress responsive miRs regulates glycolysis in diverse biological system [106]. *Group C* oxymiRs are exemplified by say miRs which are now known to target and silence HIF-1. In this way, miRs may regulate hypoxia response as a whole. For example, in cancer cells miR-17-92 cluster silences HIF-1alpha *via* a c-myc dependent pathway [18]. In cardiac myocytes, miR-199a silences HIF-1alpha. Downregulation of miR-199a de-repressed HIF1alpha and enabled hypoxia preconditioning [64]. miRs may regulate HIF-1alpha function *via* hypoxia-independent mechanisms as well. For example, miR-519c can bind to the 3'UTR and functions as a hypoxia-independent silencer of HIF-1a [102]. In chronic lymphocytic leukemia B cells, miR-92-1 silences the von Hippel-Lindau protein (pVHL) enhancing HIF-response and VEGF expression [107]. In cancer cells, miR-20b silences HIF1alpha as well as its downstream product VEGF. miR-20b directly target the 3'UTR of *Hif1a* and *Vegfa*. Interestingly, forced overexpression of HIF-1alpha in normoxic tumor cells repressed miR-20b pointing towards a close bidirectional circuitry that enables amplification of hypoxia response in a setting where stabilized HIF-1alpha drives its own gene expression by downregulating miR-20b [23-24]. Other modifiers of HIF-1 response include miR-31. miR-31 targets the 3'UTR of factor-inhibiting hypoxia-inducible factor (FIH). FIH is known to inhibit the ability of HIF to act as a transcriptional regulator under normoxic conditions. Thus, as silencer of an inhibitor, miR-31 supports HIF function [108]. Repressed by hypoxia, miR-135a and miR-199a-5p are directly implicated in the induction of 5-lipoxygenase activating protein in response to lowered state of oxygenation. Thus, these miRs directly contribute to hypoxia-induced leukotriene formation [109].

Development

The changing oxygen tensions *in utero* help develop the mammalian conceptus. It is long known that changes in tissue oxygenation during the course of embryonic development are strategic and serve as a key driver of the overall development process [110-112]. Both cleavage and post-compaction stages of development are highly sensitive to the state of tissue oxygenation [113]. During the course of development, exposure of embryos to oxygen is minimized such that the state of oxygenation is just sufficient to sustain life. Thus, compared to the maternal tissue, embryos and fetuses are hypoxic (Figure 2). The trophoblast shell excludes entry of maternal blood protecting the developing embryo from oxygen toxicity as could be posed by normoxic maternal blood. Temporarily, embryos may have to rely on anaerobic energy. While such oxygen minimized state averts the risk of oxygen toxicity [114-116], any further worsening of the state of oxygenation poses serious threat to the health of the developing embryo [117-118]. The state of tissue oxygenation of the developing embryo, like for other scenarios, depend on the balance between oxygen supply and utilization. In humans, the heart is the first organ to become functionally active in the developing embryo. As early as in the 4th week of gestation, beating of the heart

starts. Within a few days of that, circulation of blood is enabled to provide blood borne factors such as oxygen to the rapidly growing embryo. Expressed per unit of body weight, oxygen uptake markedly increases starting on the third day after fertilization. The development sequel is designed to provide the lowest required state of oxygenation throughout prenatal stages. At birth, oxygen uptake increases marginally. Lactate serves as the primary metabolic fuel for the brain during the early neonatal period [119]. In the old adult, slowing down of oxygen uptake per unit weight resembles that of the newly fertilized zygote [120]. Fluxes of tissue oxygenation within the hypoxic range is a quintessence driver of fetal development [121]. The low state of fetal tissue oxygenation is known to activate hypoxia-inducible factor-1 (HIF-1), which in turn specifically induces expression of a variety of genes that help execute successful development. Fetal hypoxia is known to induce a number of biophysical, cardiovascular, endocrine, metabolic and cell signaling responses that are required to support fetal development in the intrauterine environment [122-123]. At the stage of pre-implantation embryo development, even transient disruption of the hypoxic *milieu* may adversely influence embryo development [124]. Fetal carbohydrate metabolism is highly sensitive to such disruption in tissue oxygenation [124]. Indeed, improved *in vitro* fertilization outcomes have been obtained by culturing human embryo under low oxygen tension (5% O₂) [125-127].

OxymiRs in Skin Development

Skin morphogenesis is governed by a discrete sets of differentially expressed miRs [128]. The severe pathological phenotype of mice deficient in key enzymes of the miR biogenesis pathway in the skin argues in favor of essential functions of miRs in skin development. Deep sequencing analysis of miR depletion in both Dicer- and DGCR8-null skin demonstrated that the most abundantly expressed skin miRs are dependent on both Dicer and DGCR8 pathways of miR biogenesis [129]. Skin development is tightly regulated by post-translational gene silencing executed by miR-mRNA regulatory networks [130]. On one hand, miRs regulate the expression of cell type-specific master transcription regulators implicated in skin development and homeostasis. On the other hand, miRs regulate the effects of these developmental pathways by targeting downstream signaling mediators. The embryonic epidermis originates as a single layer of multipotent epithelial cells which progresses in development through stratification and differentiation. While a causal relationship remains to be established, the master hypoxamir-210 is known to be responsive to human keratinocyte differentiation both *in vitro* and *in vivo* [131].

SMADs antagonize the transforming growth factor-beta (TGF-beta) superfamily including TGF-beta, Activin, and bone morphogenetic proteins (BMPs). These three signaling pathways play important roles in skin development [132]. OxymiR-210 is known to silence the Activin A receptor type 1B (AcvR1b) gene, a member of the TGF family of receptors [133]. Bone morphogenetic proteins regulate embryonic development and postnatal life. In developing and postnatal skin, BMPs play a key role in driving cell proliferation and differentiation in the epidermis and in the hair follicle. BMP signaling is essential in the control of cell differentiation and apoptosis in developing epidermis [134]. Elevated miR-21 may bolster HIF-signaling by increasing the expression of HIF-1alpha and VEGF [35]. OxymiR-21 represents an important downstream component of BMP signaling in epidermal keratinocytes. miR-21 is expressed in the epidermis and hair follicle epithelium in normal mouse skin. BMP4 inhibits miR-21 expression in keratinocytes. In transgenic mice overexpressing the BMP antagonist noggin under control of the K14 promoter, miR-21 expression was markedly higher. Transfection of keratinocytes with miR-21 mimic identified two groups of the BMP target genes, which were differentially regulated by miR-21. These include BMP-dependent tumor-suppressor genes (Pten, Pdcd4, Timp3 and

Tpm1) negatively regulated by miR-21, as well as miR-21-independent Id1, Id2, Id3 and Msx2 that predominantly mediate the effects of BMPs on cell differentiation [135].

OxymiRs in Skin Repair

The basal proliferating compartment of the skin hosting epidermal stem cells is the primary driver of skin renewal which is responsible for tissue homeostasis and repair. miRs play a central role in the formation of epidermis and skin appendages, in particular, at the interface between stemness and differentiation [136]. Cutaneous wound healing involves changes in the expression of specific miRNA at specific phases of wound healing [137] which in turn influences healing outcomes [138]. miR-200b is an oxymiR because in human microvascular endothelial cells it is repressible by hypoxia [68-69]. In dermal microvascular cells, miR200b silences Ets-1, VEGFR2 and GATA2 to silence angiogenesis in the mature skin. Upon injury, hypoxia-represses miR-200b to switch on wound angiogenesis. In mice with diabetes mellitus, excessive tumor necrosis factor-alpha disrupts wound-induced repression of miR-200b blunting wound angiogenesis [69].

p63 is a master transcription regulator that is abundant in the basal proliferative compartment of the epidermis and its expression is directly associated with the and regenerative capacity of keratinocytes [139]. p63 maintains keratinocyte cell cycle progression by directly repressing oxymiR-34a and miR-34c [140]. Thus, specific miR-34 family members have a significant role downstream of p63 in controlling epidermal cell proliferation. miR-34a is repressed by mild hypoxia and could promote epithelial-mesenchymal transition (EMT). During EMT epithelial cells lose their epithelial characteristics and acquire a mesenchymal-like phenotype. In early embryogenesis EMT is implicated in migration and transient dedifferentiation of embryonic epithelial cells, gastrulation and the migration of neural crest cells. During cutaneous wound re-epithelialization, cell migration and the reduced intercellular adhesion of keratinocytes recapitulate several aspects of EMT [141].

The two most studied oxymiRs are represented by miR-210 and miR-21 (Figure 1). In the following segment, we direct the spotlight on the functional significance of these two oxymiRs.

OxymiRs miR-210 and miR21

Development

Implantation of the blastocyst embryo to the wall of the uterus enables the fetus to receive oxygen and nutrients from the mother. Regulated by active blastocysts miR-21 is highly expressed in the subluminal stromal cells at the implantation site. Current evidence supports that miR-21 plays a central supporting role during embryo implantation [142]. Deep sequencing studies revealed that although the number of miR-21 reference sequence under activation was slightly lower than that under delayed implantation, the total level of miR-21 under activation was higher than that under delayed implantation [143]. Maternal cigarette smoking may down-regulate placental miR-21 expression possibly complicating fetal development [144]. Interestingly, miR-21 expression is markedly reduced in infants with the lowest birthweights [145]. During the onset of development, oogenesis, populations of both maternal RNA and protein are accumulated as the oocyte grows and matures. The entry of sperm into the ovulated oocyte triggers the embryogenesis phase of the developmental program. Thus, the earliest stages of embryogenesis are regulated oocytes charged with maternally inherited components. As development progresses maternally inherited components wither and early embryogenesis becomes dependent on the embryonic genome. miR-21 is known to be implicated in such maternal-to-embryonic transition. During the

development of 1-8 cell stage, the expression of mature miR-21 steadily increases suggesting potential involvement of this oxymiR during early development [146]. In vertebrates, neural crest cells are a transient, multipotent, migratory cell population that gives rise to a diverse cell lineage including melanocytes, craniofacial cartilage and bone, smooth muscle, peripheral and enteric neurons and glia. In neural crest cells, miR-21 silences Sprouty 2, an inhibitor of Erk1/2 signaling, and results in loss of function of the miR biogenesis enzyme Dicer. In this way, miR-21 may regulate neural crest cell survival, migration, and patterning in craniofacial and cardiovascular development [147]. Morphogenesis is a fundamental aspect of developmental biology that causes an organism to develop its shape. Branching morphogenesis is responsible for the creation of branched structures in the body. Branching morphogenesis in murine submandibular glands is regulated by many biological processes through interactions between the epithelium and the mesenchyme. In the mesenchyme, miR-21 has been implicated in branching morphogenesis through silencing of messenger RNAs for Reck and Pcd4 [148]. Evidence on the role of miR-210 in development is relatively scanty. Hypoxamir-210 is known to be implicated in the pathophysiology of gestational hypertension or preeclampsia [149-153]. miR-210 silences iron-sulfur cluster scaffold homologue in human trophoblast cell lines disrupting iron metabolism associated with defective placentation [88].

Stem Cell Biology

Committing human embryonic stem cells to defined cell lineages is a critical requirement for evaluating their potential in regenerative medicine. miR-210 [1] is a hallmark of commitment of human embryonic stem cells to vascular endothelial cells [154]. Recent studies indicate pro-angiogenic properties of endothelial miR-210 [155]. Differentiation and proliferation of hematopoietic stem cells to mature red blood cells represents erythropoiesis. During erythropoiesis, globin gene expression is regulated by a sophisticated network of factors. miR-210 has been directly implicated in increased expression of gamma-globin genes in differentiating erythroid cells [156-157]. Under conditions of hypoxia, miR-210 supports stem cell survival [158]. Survival of mesenchymal stem cells under conditions of anoxic stress was improved by episodes of ischemic pre-conditioning by a miR-210 dependent mechanism. Inhibition of miR-210 abrogated such cytoprotection pointing towards miR-210 as a stem cell survival factor in the heart. In this case, miR-210 promoted stem cell survival by targeting caspase-8-associated protein 2 (CASP8AP2) [79], or its human homologue FLICE-associated protein homolog (FLASH), a protein that facilitates Fas-induced apoptosis. More recent studies recognize the cardioprotective properties of miR-210 against anoxia-reoxygenation [159]. Direct transfer of miR-210 from mesenchymal stem cells to host cardiomyocytes seemed to improve functional recovery of the ischemic heart [160]. Mild hypoxia supports the survival and proliferation of neural progenitor cells. Consistent with findings in cardiac mesenchymal stem cells, miR-210 expression seems to support survival of neural progenitor cells. In these cells, under hypoxic conditions miR-210 expression was directly induced by a HIF1alpha-dependent pathway [161].

miR-21 regulates self-renewal of embryonic stem cells. Maintenance of pluripotency under continued proliferation is a key requirement for stem cell renewal. Proliferation of embryonic stem cells, previously thought to be constitutive, is now known to be regulated by several factors. In murine embryonic stem cells, the neuronal repressor REST maintains self-renewal and pluripotency by suppressing miR-21. Thus, miR-21 is a REST-regulated miR that specifically suppresses the self-renewal of mouse embryonic stem cells [162]. Residing within a niche microenvironment in the testes, spermatogonial stem cells represent the foundation of spermatogenesis regulating self-renewal, pluripotency, quiescence and ability to differentiate. Transient inhibition of miR-21 in germ cell cultures enriched from spermatogonial stem cells increased the number of germ cells undergoing apoptosis and

significantly reduced the number of donor-derived colonies of spermatogenesis. In these cells, miR-21 is regulated by the transcription factor ETV5, known to be critical for self-renewal of spermatogonial stem cells [163]. The adipose tissue is an abundant source for mesenchymal stem cell supply for regenerative medicine. Through its effect on TGF-beta signaling miR-21 plays a key role in adipogenic differentiation of human adipose tissue-derived mesenchymal stem cells [164]. miR-21 level tightly correlated with the adipocyte number in the white adipose tissue of obese mice providing novel testable hypothesis explaining the mechanisms of obesity [165]. The Notch signaling pathway is critically involved in stem-cell maintenance with various capacities to induce proliferation or differentiation. Interestingly, elevated Notch-1 levels lead to increased expression of miR-21 hinting at the possible significance of miR-21 in stem cell maintenance [166]. Comparable to miR-210, miR-21 also serves as a survival factor of mesenchymal stem cells [158]. In the liver, miR-21 enables rapid hepatocyte proliferation during organ regeneration by accelerating the translation of cyclin D1 [167].

Wound Healing

Despite having favorable effects of stem cell biology, angiogenesis and insults involving mild (compared to near-anoxic insult associated with infected ischemic skin wounds [168]) hypoxic insult, miR-210 stalls the healing of ischemic open wounds [1, 94]. The recognition that miRs may have cell and organ specific effects is on the rise [98, 169-173]. Compelling support of this notion is provided by the observation that individual miRs can be heterogeneous in length and/or sequence. These variants, isomiRs, can be expressed in a cell-specific manner. Some isomiRs may affect target selection, miRNA stability, or loading into the RNA-induced silencing complex thus affecting the overall post-transcriptional gene silencing process [174]. In keratinocytes, miR-210 arrests cell growth by silencing E2F3 [94]. Growth arrest by miR-210 has been consistently reported in other cell types as well including human embryonic kidney [90] and ovarian cancer cells [14]. Emerging evidence supports that miR-210 also inhibits cell proliferation by a FGFR1-dependent mechanism. FGFR1 signaling is known to support cell proliferation by facilitating cell cycle progression [175]. Over-expression of FGFR1 significantly rescued the growth inhibitory effect of miR-210 *in vitro* [175] and *in vivo* [78], establishing that miR-210 inhibits cell proliferation by a FGFR1-dependent mechanism. miR-210 also stalls cell proliferation by silencing homeobox genes. Over-expression of HOXA1 induces activation of p44/42 MAP kinase leading to increased cell proliferation [66]. Because over-expression of HOXA1 reverses the growth inhibitory effect of miR-210 [40] it is plausible that the miR-210-dependent growth inhibitory effect is, at least partially, due to direct silencing of HOXA1 [176]. The keratinocyte growth arrest property of miR-210 stalls wound re-epithelialization [94]. The wound tissue, especially one complicated by sustained inflammation and build-up of reactive oxygen species, is expected to suffer from DNA damage that needs to be repaired during the healing process. miR-210 opposes DNA repair by silencing repair enzymes such as RAD52 [96].

Wound healing is a energy demanding process that relies on mitochondrial oxidative metabolism [168]. Another property of miR-210 that is in conflict with wound healing is its repression of mitochondrial metabolism. miR-210 is known to silence several proteins required for the normal functioning of the tricarboxylic acid cycle. miR-210 delivery inhibited mitochondrial energy production [76], lowered oxygen consumption [76], elevated lactate levels [83-84], lowered mitochondrial membrane potential [91] and compromised mitochondrial structural integrity [91]. These findings are consistent with a more recent report demonstrating mitochondrial dysfunction following miR-210 overexpression [177]. Fe-S cluster is responsible for the catalytic function of aconitase, a stereo-specific isomerization of citrate to isocitrate which fuels the TCA-cycle. miR-210 silences the Fe-S

cluster assembly homologue (ISCU) 1/2 [76, 83]. In addition, miR-210 regulates cytochrome c oxidase assembly protein (COX10) [83] and succinate dehydrogenase subunit D (SDHD) [91], slowing down mitochondrial respiration. Oxygen conservation following severe hypoxic insult is a well known austerity measure aimed at affected cells living longer in a somewhat suspended animation mode. Such response does not favor active tissue regrowth as would be necessary for wound healing. The observation that miR-210 remains elevated even after when normoxia is restored or a day [73, 178] suggests that miR-210 induces a long-lasting inhibitory effect on mitochondrial metabolism even in the presence of sufficient oxygen. Inhibition of miR-210 in the ischemic wound may therefore prove to be an effective strategy to re-establish normal mitochondrial respiration and resume the healing process.

Like miR-210, miR-21 elevation has been observed to delay cutaneous wound healing [138]. The study of clinically presented venous ulcers, a type of chronic non-healing wound, identified miR-21 as suppressor of wound epithelialization. Here, miR-21 silenced early growth response factor 3 (EGR3) as well as the leptin receptor (LepR) [138]. In keratinocytes, miR-21 is TGF β -inducible and accounts for its growth arrest properties [179]. Although reports on the effect of miR-21 on wound epithelialization remain somewhat conflicting [180], the body of literature on the role of miR-21 in fibrosis is more decisive. miR-21 has emerged to be a major driver of fibroblast biology [181]. Elevated miR-21 causes fibroblast dysfunction leading to fibrosis outcome. First evidence on this was reported by our laboratory describing changes in miR expression in response to ischemia-reperfusion in the murine heart, demonstrating that miR-21 regulates matrix metalloproteinase-2 (MMP-2) expression in cardiac fibroblasts of the infarct zone via a phosphatase and tensin homologue (PTEN) pathway [182]. The observation that miR-21 silences PTEN has additional implications. Endothelial-to-mesenchymal transition (EndMT) is emerging as a significant contributor to transforming growth factor- β (TGF- β) dependent fibrosis. miR-21 contributes to, at least in part, TGF- β -mediated EndMT via silencing of PTEN [183]. In the skin, abundance of miR-21 correlated with fibrosis associated with systemic sclerosis [184].

Conclusion

Changes in the state of tissue oxygenation are commonly noted during development as well as during conditions such as wound healing where vascular supply to the tissue is disrupted (Figure 4). From a systemic to molecular level, the body is supported by a range of networked oxygen sensors that reads changes in the flux of tissue oxygenation as a cue and mounts biological responses. Our understanding of this process of oxygen sensing and related biological response has been substantially enhanced by the recognition that the expression of small non-coding genes such as miRs may be oxygen-sensitive. Both hypoxia as well as hyperoxia-responsive miRs has been reported giving rise to a broad class of miRs which may be broadly referred to as oxymiRs. This work categorizes oxymiRs into three defined groups. Which oxymiR gets induced in response to a given situation is not only decided by the state and flux of tissue oxygenation but also on co-cues elicited by the specific biological condition. The number of miRs represented by these three groups is rapidly growing. According to computational predictions currently known oxymiRs may affect the functioning of a large number of coding genes which have hitherto fore never been linked to oxygen sensing or responsiveness. Many of such target genes have been validated and that number is steadily growing. Taken together, the concept of oxymiRs has vastly expanded the implications of changes in the state of tissue oxygenation. This emerging paradigm has major implications in untangling the complexities underlying diseases associated with ischemia and related hypoxic insult such as chronic wounds.

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HIGHLIGHTS

- The state of tissue oxygenation may potently regulate the expression of microRNAs (miRs)
- Collectively, such miRs may be referred to as oxymiRs
- OxymiRs include both hypoxia as well as hyperoxia-responsive miRs
- OxymiRs have major implications in untangling the complexities underlying ischemic diseases
- The two most studied oxymiRs are represented by miR-210 and miR-21

Figure 1. Two major oxymiRs: human miR-210 and miR-21 stem loops

Art developed based on miRNAMap (<http://mirnamap.mbc.nctu.edu.tw>). The stem loops for each miR is highlighted.

Figure 2. Hypoxia: A major factor regulating embryonic development as well as wound healing
M, oxygen-rich maternal tissue; E, hypoxic embryonic tissue. Bar, tissue oxygenation scale with blue end representing hypoxia and red end representing oxygenated tissue.

Figure 3. OxymiRs: broadly categorized into three groups

Group A: the existence (expression and/or turnover) of which is directly influenced by changes in the state of tissue oxygenation; *Group B*: the existence of which is indirectly (e.g. oxygen-sensitive proteins, metabolites, pH etc) influenced by changes in the state of tissue oxygenation; and *Group C*: those that modify biological outcomes to changes in the state of tissue oxygenation by targeting oxygen sensing pathways. Groups A and C are depicted by the two faces of the pyramid. Group B representing oxymiRs responsive to biological derivatives of hypoxia and hyperoxia is depicted by the platform connected by spirals to the main pyramid. Graphic elements presented near the apex of the pyramid represent miR structural shape underscoring the fact that this illustration addresses classification of miRs.

Figure 4. Pockets of tissue oxygenation at the cutaneous wound site

Shade of red or pink represents oxygenated tissue (A-B). Shade of black (anoxia) or blue represents graded hypoxia (C-D). Tissue around each blood vessel is dark pink in shade representing regions that are well oxygenated (oxygen-rich pockets). Bacteria and bacterial infection are presented by shades of yellow and green (E, F) on the surface of the open wound.

Table 1

OxymiRs: A Steadily Growing List Recognizing the Global Impact of Tissue Oxygenation on Biological Regulatory Networks

<i>miR-16</i>	[17]
(miR-17-92)	[18]
miR-20a	[19-22]
(miR-20b)	[23-24]
miR-21	[25-42]
(miR-22)	[43]
miR-23b	[44]
miR-26	[45]
miR-27	[46]
(miR-31)+	[47]
<i>miR34a</i>	[48]
miR-93	[49]
miR-101	[50]
miR-107	[45]
(miR-107)	[51]
(miR128)	[52]
(miR-130)+	[53]
(miR-138)	[54]
miR-145	[55]
miR-155	[30, 56-63]
miR-199a	[21, 64-67]
<i>miR-200b</i>	[68-69]
(miR-200b)	
miR-205	[70]
miR-210	[1-2, 4, 14, 28, 71-94]
miR-328	[95]
miR-373	[15, 34, 92, 96]
miR-375	[97]
miR-424	[49, 98-99]
miR-484	[100]
miR-495	[101]
(miR-519c)	[102]
Hyperoxamirs	[7-9]

Hypoxamir component of oxymiRs are listed individually. miRs in parentheses target HIF signaling. miRs in parentheses marked with a plus sign target elements of the HIF signaling pathway such that they support HIF function. Italicized miRs are down-regulated by hypoxia. Non-italicized miRs are upregulated in response to hypoxia. Hyperoxamir studies are fewer and therefore lumped at the end.