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Review

MicroRNAs regulate cell proliferation and angiogenesis in wound healing

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ABSTRACT

MicroRNAs (miRNAs) are a family of small non-coding RNA molecules of 18-25 nucleotides in length. MiRNA expression patterns are highly conserved and can regulate many cellular processes which are essential in tissue development and functional maintenance. They are also crucial in the inflammation, repair, and remodelling response of tissue during wound healing. Wound healing is an intricate process to repair the skin or other organs after injury. Cell proliferation and angiogenesis play crucial roles in this process. MiRNAs have emerged as critical factors in cell proliferation, angiogenesis, and wound healing. In this review, we examine the effects of different microRNAs in cell proliferation and angiogenesis associated with wound healing.

KEYWORDS: microRNA, 3'UTR, non-coding RNA, angiogenesis

ABBREVIATIONS

miRNA, microRNA; mRNA, messenger RNA; ncRNA, non-coding RNAs; lncRNA, long non-coding RNA; 3'UTR, 3'-untraslated region

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1. INTRODUCTION

MicroRNAs (miRNAs) are small non-coding RNAs that are 18-25 nucleotides in length [1-3]. Similar to protein coding genes, miRNA genes code for individual miRNAs. In some cases, miRNAs are transcribed as a single polycistronic transcript, which contain more than one miRNA precursor [4]. MiRNAs expressed in the same cluster may not share sequence similarities for gene targeting, but they can function together to control multiple target genes [4]. Many genes encoding for miRNAs overlap with protein coding genes or are located in the introns of protein-coding genes [5]. In humans, over 247 miRNAs occur in clusters with an inter-miRNA spacer [6]. Some miRNAs in the clusters can have a high degree of homology, such as miR-17 and miR-20a in the miR-17~92 cluster, and miR-106a, miR-20b, miR-106b, and miR-93 in the paralogs [7, 8]. Similar functions have been reported for miR-17 and miR-93 [8-10].

In mammals, most miRNAs bind through base pairing and target the 3'-untranslated region (3'UTR) of mRNAs with imperfect complementarity. This binding can induce mRNA degradation or translational repression. Binding specificity and targeting efficiency are determined by the seed sequence of miRNAs, which are located near the 5' region, typically in nucleotides 2-8 of the miRNAs [11, 12]. This binding between the seed sequence and the mRNA also determines whether the target mRNA is degraded or translational repression occurs [13, 14]. While studies have shown that miRNAs can regulate mRNA stability

and translation, recent studies have also shown that the 3'UTRs and other non-coding RNAs can regulate miRNA stability and functions [15-17]. Transgenic mice expressing versican 3'UTR displayed increased organ adhesion and cell adhesion [15]. Exogenous expression of the versican 3'UTR could bind and modulate functions of many miRNAs and regulate their stability and functions [15, 18, 19]. Similarly, the 3'UTR of CD44 was shown to regulate miR-216a, miR-330 and miR-608 functions. This regulation increased CD44 and CDC42 expression and increased cell apoptosis and endothelial cell activities, but decreased cell proliferation and survival [16, 20]. Pseudogenes and long non-coding RNAs have also been implicated in the regulation of miRNA functions [21, 22].

By regulating gene expression, microRNAs have been shown to exert diverse biological functions in regulating cell activities such as cell proliferation [23-26], cell differentiation [10, 27, 28], autophagy [29], apoptosis [30, 31], morphogenesis [32], invasion [33-35], tissue growth [7], tumor formation [36-38], angiogenesis [39-41], and metastasis [10, 42, 43]. On the other hand, miRNA function can also be regulated by other components, including 3'UTRs of versican [15, 44, 45], CD44 [16], nephronectin [17, 46], pseudogene PTENP1 [21, 22], long non-coding RNAs [47], circular RNAs [48], and miRNA-binding sponges [49, 50]. Experimentally, a number of strategies have been taken to regulate miRNA activities including the use of decoys, sponges, locked nucleic acids, miR-Pirate, and antagomirs [19, 49, 51-53]. Regulation of miRNA has been shown to modulate cell proliferation, adhesion, differentiation, migration, invasion, and angiogenesis.

2. MicroRNAs regulate wound healing

Chronic wounds constitute a substantial health and economic burden to our society. In addition to the 1.3–3 million individuals in the United States having pressure ulcers, 10–15% of the population with diabetes are at risk of developing diabetic ulcers [54, 55]. The treatment of these chronic wounds is estimated to cost $5–10 billion each year [56]. The healing process is regulated by a great number of factors. Emerging evidence has indicated that miRNAs play a key role in regulating wound inflammation, cell proliferation, migration, angiogenesis, and tissue remodelling. Proper angiogenesis and tissue remodelling are the crucial processes that determine success in ischemic wound repair. Understanding the mechanisms of miRNA functions in wound inflammation, angiogenesis, and remodelling may lead to the development of therapeutic strategies for management of chronic non-healing wounds.

As the largest organ of the body which protects against environmental hazards, most wounds occur in the skin [57]. The physiological functions of skin are strictly controlled by the gene regulatory networks that involve numerous factors including regulation of gene expression by miRNAs. MicroRNAs play integral roles in the maintenance of skin physiology. In normal skin, miRNA-200 and miRNA-205 are highly expressed, both of which target Zinc finger E-box-binding homeobox 1 (ZEB1) and survival of motor neuron protein-interacting protein 1 (SIP1) [58, 59]. Since SIP1, also known as ZEB2, is a transcriptional repressor of E-cadherin, repression of SIP1 by these two miRNAs is expected to regulate E-cadherin positively for maintaining epithelial stability.

During the cutaneous wound healing process, expression of certain miRNAs is aberrantly regulated. miR-210 regulates keratinocyte proliferation and wound repair [60]. Under the hypoxic conditions of chronic wound repair, this miRNA is up-regulated [61-63]. One of the targets for miR-210 is the transcription factor E2F3, which attenuates keratinocyte proliferation and wound closure [60]. In mammalian skin wound healing, a scarring phenotype is always seen, and only fetal mammalian skin can heal without scar formation. When comparing these types of skin, some miRNAs are found to be differentially expressed, including miRNA-29b, miRNA-29c, and miRNA-192 [64]. It is known that TGF-β, Smads, and β-catenin are implicated in scar formation. Repression of these proteins by miRNA-29b and miRNA-29c may influence the formation of scars [65, 66].

Psoriasis of the skin is an immune-mediated chronic inflammatory disease. Several miRNAs have been found to be up-regulated in psoriasis including miRNA-203, miRNA-146a, and miRNA-21, while

miRNA-125b has been found to be down-regulated [67, 68]. These two types of miRNAs may play roles in regulating the pathogenesis of psoriasis. Systemic sclerosis is a chronic disorder characterized by scarring in the skin and other organs, whereby normal extracellular molecules are progressively replaced by collagen. MiRNA-29a can repress expression of type I and type III collagens and is implicated in the formation of the sclerosis [69]. Since cell self-renewal, proliferation, differentiation, survival, migration, invasion, and morphogenesis are key to proper healing, understanding the miRNA regulatory networks of these processes will be key for further understanding wound healing. Recently, we showed that the functions of a number of miRNAs can be regulated through its binding to the 3'UTR of versican in the process of wound repair [45], because versican is an essential extracellular molecule playing roles in mediating cell activities [70-74].

3. MiRNAs regulate angiogenesis

Angiogenesis is the process by which new vessels develop from pre-existing blood vasculature. Under normal conditions, the vascular endothelium is quiescent in adults, but stimuli, such as stroke, injury and cancer, can initiate an angiogenic response. New vasculature is usually formed in regions of tissue where blood circulation is required. The formation of new blood vessels is regulated by many factors and recent studies have indicated that microRNAs play an important role in angiogenesis. A number of miRNAs have been identified to be abundantly expressed in angiogenesis-associated endothelial cells. Using an *in silico* approach, some of these miRNAs have been predicted to target angiogenic factors. For example, miR-221 and miR-222 target *c-kit*, a receptor tyrosine kinase that binds stem cell factors and mediates VEGF expression [75]. Transfection of *miR-221/222* represses *c-kit* protein expression without affecting mRNA level.

Endothelial cell activities play important roles in angiogenesis. miR-126 is an endothelial cell-specific miRNA[76] and it is enriched in highly vascularized tissues [77]. Since all miRNAs are processed by Dicer, silencing Dicer impairs the development of capillary-like structures and exerts an antiproliferative effect on endothelial cells [78]. In human microvascular endothelial cells (HMECs), silencing Dicer resulted in diminished tube formation and cell migration [79]. These studies confirmed that miRNAs are essential in endothelial cell activities associated with angiogenesis. To this point, the roles of miRNAs in angiogenesis have been well studied. Vascular Endothelial Growth Factor (VEGF) treatment increases expression of many miRNAs including miR-17, miR-18a, and miR-20a, whose activities are implicated in angiogenesis [78]. VEGF can also promote proliferation of cortical neurons precursors by regulating E2F expression, which is involved in cell proliferation and apoptosis [80, 81]. The oncogene *c-myc* can activate expression of the *miR-17~92* cluster [82], also involved in angiogenesis. Ectopic expression of miR-17 enhances formation of blood vessels by targeting the tumor suppressor phosphatase and tensin homolog (PTEN), Vimentin, and GalNT7 [8]. Endothelial cells transfected with miR-17 showed increased rates of proliferation, survival, and migration [8]. Other miRNAs expressed in endothelial cells include let-7f and miR-27b. These two miRNAs have pro-angiogenic effects [83]. Silencing Dicer and Drosha reduced lef-7f and mir-27b expression and sprout formation. Inhibitors against let-7f and mir-27b also reduced sprout formation [83]. These results indicated that let-7f and mir-27b promote angiogenesis by targeting anti-angiogenic genes. In breast cancer cells, hyaluronan synthase 2 (HAS2) was identified as a target of let-7 [50]. Nevertheless, the let-7 family is widely accepted as a tumor suppressive miRNAs. How tumor suppressive miRNAs promoted angiogenesis await further investigation. There may be common mechanism underlying these effects. It is also possible that these miRNAs play different roles in different cell types and different functional environments. A member of the let-7 family, miR-98, has been shown to play roles in angiogenesis [84]. Expression of miR-98 inhibited breast cancer cell proliferation, survival, invasion, and angiogenesis. Inhibition of endogenous miR-98 with miR-98 inhibitors or by transfection with an anti-miR-98 construct promoted cell proliferation, survival, invasion, and angiogenesis. Activin receptor-like kinase-4 and matrix metalloproteinase-11 were

identified as the targets of miR-98. Specific siRNAs silencing these molecules inhibited cell proliferation, cell survival, and angiogenesis [84]. By identifying miRNA signatures for angiogenesis, investigators maybe able to identify previously unknown targets through novel miRNA recognition elements. This may lead to the identification of new approaches for innovative therapies in angiogenesis-related diseases.

4. MiRNAs promote cell proliferation

Cellproliferation is a crucial event in tissue patterning during animal development and in tissue remodelling during wound repair. Cell apoptosis is another critical event coordinated with cell proliferation during tissue development, wound healing, and tumor growth. Many proteins that play roles in cell proliferation and apoptosis have been identified. Recently, it has become clear that miRNAs regulate expression of many proteins associated with cell proliferation and apoptosis. Interestingly, individual microRNAs have been found to simultaneously stimulate cell proliferation and prevent apoptosis, depending on the biological context [85]. It appears that this regulation may occur through the Hippo signaling pathway which controls tissue growth [86]. In general, overall reduction in miRNA expression may favor cellular proliferation, since impaired miRNA processing results in global repression of miRNA maturation, promoting cellular growth [87]. Nevertheless, an increasing number of studies have shown that individual miRNAs have diverse activities in both promoting and inhibiting cell proliferation. Thus, the functions of individual miRNAs remain to be dissected in different functional environments and in different signaling pathways associated with cell proliferation, cell cycle progression, and cell apoptosis.

One of the earliest miRNA studies showed that depletion of miR-125b had a profound effect on the proliferation of adult differentiated cancer cells [88]. It was later found that expression of miR-125b could be induced by CD154 and this contributed to regulating proliferation by targeting BCL2 [89]. Another target identified for miR-125b was found to be E2F2. Repression of E2F2 inhibits proliferation of CD133 positive glioma stem cells and reduced the expression of stem marker CD133 [90]. miR-125 has also been shown to repress the expression of matrix metallopeptidase 13 (MMP13) and inhibit cell proliferation, thus, playing a role as a tumor suppressor [91].

Although miR-221 has been characterized as an oncogenic miRNA, it has also been shown to play a role in injury-induced phenotypic modulation of Schwann cells. Increased expression of miR-221 has been shown to promote Schwann cell proliferation *in vitro*, while inhibiting its expression decreases cell proliferation [25]. The longevity assurance homologue 2 (LASS2) was a direct target of this miRNA. Over-expression of miR-221 repressed both mRNA and protein levels of LASS2. miR-222 is a paralog of miR-221 and it plays similar roles in regulating Schwann cell activities [25]. miR-222 has also been shown to be up-regulated in gastric mucosa and gastric cancer. miR-222 transfection promoted cell proliferation and colony formation *in vitro* by targeting RECK [92]. The cell cycle regulator p27 is also a target of the miR-221/222 cluster in chronic lymphocytic leukemia cells. Increased levels of miR-221/222 cluster in the chronic lymphocytic leukemia cell line MEC1 repressed p27 expression and conferred a proliferative advantage to the transduced cells and promoted faster progression of the cell cycle [93]. The regulation was also seen in glioblastomas and prostate cancer, where deregulated expression of miR-221/222 increased cancer growth by repressing p27 expression [94, 95]. Expression of the miR-221/222 cluster is also up-regulated in vascular smooth muscle cells (VSMCs) during vascular wall injury. In cultured VSMCs, treatment with growth stimulators increased expression of miR-221 and miR-222, while silencing miR-221 and miR-222 resulted in decreased cell proliferation [96].

5. MiRNAs inhibit cell proliferation

MiRNAs that can inhibit cell proliferation were initially reported using a loss-of-function allele in mice. The myeloid-specific miR-223 can negatively regulate progenitor proliferation and granulocyte differentiation [97]. It was identified that Mef2c, a transcription factor that promotes myeloid progenitor proliferation, is a target of the miRNA. Genetic ablation of Mef2c was shown to suppress progenitor expansion and reverses the neutrophilic phenotype

in the miR-223 mutant mice. Granulocytes lacking miR-223 were hypermature and hypersensitive to activating stimuli. As a consequence, the miR-223 null mice developed inflammatory pathology and tissue destruction when the mice were challenged with endotoxin [97]. In HeLa cells, miR-u223 significantly inhibited cell proliferation and colony formation [98]. Tumor formation in nude mice was suppressed in cells expressing miR-223. Insulin-like growth factor-1 receptor (IGF-1R) was identified as the functional target of miR-223 in the inhibition of cell proliferation. The downstream signalling pathway of IGF-1R, Akt/mTOR/p70S6K, was inhibited by miR-223 as well. Silencing IGF-1R expression produced similar inhibitory result as miR-223 did. Rescuing IGF-1R expression in the cells that over-expressed miR-223 reversed the inhibitory effect on cell proliferation caused by miR-223 [98]. Over-expression of miR-223 was also shown to down-regulate IGF-1R expression and activity in vascular smooth muscle cells (VSMCs) under stretch stress. As a consequence, over-expression of miR-223 inhibited stretch stress-enhanced VSMC proliferation and the activity of PI3K-AKT signalling [99]. Thus, miR-223 may be a viable therapeutic target for mechanical stretch-induced neointimal hyperplasia in vein grafts [99]. In a number of cancer cell lines including HCT116 colorectal cancer cells, HeLa cervical cancer cells and HuH-7 hepatoma cells, miR-223 is expressed at low levels [100]. Ectopic expression of miR-223 in these cells inhibited cell proliferation. Expression levels of forkhead box protein 01 (FOXO1) mRNA and protein levels became significantly lower in these cells than those of their controls. It appears that miR-223 inhibited proliferation by regulating FOXO1 expression [100].

As under-expression of miR-9 occurs in many cancer types, miR-9 may be classified as tumor suppressive miRNA. In human breast cancer cell lines MDA-MB-231 and MCF-7, miR-9 expression is down-regulated as compared with the normal breast cell line MCF-10-2A [101]. Increasing miR-9 expression in breast cancer cells inhibited cell proliferation and invasion. Methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) was identified as a miR-9 target gene. Silencing MTHFD2 expression mimicked the effects observed when miR-9 was over-expressed by decreasing cell viability and increasing apoptosis. In primary breast tumor specimens, miR-9 and MTHFD2 were shown to be inversely related [101]. miR-9 has also shown to be inversely correlated with the expression of cyclin D1 and the oncogene Ets1 in gastric cancer tissues and cancer cell lines [102]. Both mRNAs were shown to be targeted by miR-9. Expression of cyclin D1 and Ets1 were repressed by ectopic expression of miR-9 but promoted by miR-9 knockdown in gastric cancer cell lines SGC-7901 and AGS. Silencing cyclin D1 or Ets1 expression partially mimicked the effects of miR-9 over-expression on cell proliferation, migration and invasion of gastric cancer cells, while an anti-miR-9 inhibitor promoted these processes [102]. MiR-9 was also shown to inhibit proliferation of glioma cells by directly targeting cyclic AMP response element-binding protein (CREB) [103]. Since CREB controls miR-9 transcription, this regulation forms a negative feedback minicircuitry [103].

Many additional miRNAs have been reported to inhibit cell proliferation. MiR-29a can inhibit epididymal epithelial cell proliferation by targeting nuclear autoantigenic sperm protein (NASP) [104]. MiR-29a can also inhibit cell proliferation and induces cell cycle arrest in human gastric cancer by repressing p42.3 expression at both the mRNA and protein levels via directly binding to its 3'UTR [105]. MiR-149 was reported to inhibit proliferation and cell cycle progression through targeting the transcription factor ZBTB2 in human gastric cancer [106]. miR-210 can disturb mitotic progression by regulating a group of mitosis-related genes [26]. Both miR-127 and miR-26a can suppress hepatocyte proliferation [107, 108], while miR-219-5p and miR-1 can inhibit hepatocellular carcinoma cell proliferation [109, 110]. MiR-182 can inhibit Schwann cell proliferation and migration by targeting Fibroblast Growth Factor 9 (FGF9) and Neurotrimin (NTM) [111], while miR-195 and miR-483-5p are able to inhibit human glioma cell proliferation by targeting Cyclin D1 and Extracellular signal-regulated kinase 1 (ERK1), respectively [112, 113].

6. The roles of miR-21 in cell proliferation

Although an individual miRNA may play different roles in different cell types, some miRNAs have

consistent functions in cell proliferation in different cell types. A very well studied example is miR-21. This miRNA has been identified as a unique miRNA over-expressed in a wide variety of cancer cells. Initially, it was found that inhibition of miR-21 expression in HeLa cells suppressed cell proliferation [114]. miR-21 was found to be involved in adventitial fibroblast (AFs) and myofibroblast (MFs) proliferation, while also playing important roles in vascular remodelling [115]. Both AF and MF cells over-express miR-21. Over-expression of miR-21 by transfection with pre-miR-21 increased proliferation and decreased apoptosis of both AF and MF cells, while inhibition of miR-21 decreased proliferation and increased apoptosis of AF and MF cells. In these cells, programmed cell death 4 (PDCD4) was validated as a direct target of miR-21 by a dual-luciferase reporter assay and gain and loss of function experiments. This conclusion was supported by the observation that repressing PDCD4 expression by miR-21 increased JNK/c-Jun activity, while enhancing PDCD4 levels by miR-21 inhibition decreased JNK/c-Jun activity [115]. miR-21 may play a critical role in regulating proliferation and apoptosis of AF and MF cells associated with vascular remodelling. Human aortic smooth muscle cells (HASMCs) represent another cell type in the vascular system. Expression of miR-21 is modulated by mechanical stretch of cultured HASMCs. Stretch up-regulates miR-21 expression and cell proliferation, which may regulate expression of p27 and phosphorylated retinoblastoma protein (p-Rb). Endothelial cells are a large population of cells in the vascular system. Treatment of endothelial cells with rapamycin can suppress endothelial cell proliferation, which leads to delayed re-endothelialization. It was found that rapamycin treatment increased expression of miR-21 in human umbilical vein endothelial cells (HUVECs). Down-regulation of miR-21 function by miR-21 inhibitor abolished the negative effects of rapamycin on endothelial cell growth. RhoB appears to be a direct target of miR-21 in mediating endothelial cell proliferation [116]. In high-fat diet (HFD)-induced obesity mice, miR-21 regulates mesenchymal stem cell proliferation. Over-expression of miR-21 inhibited cell proliferation, whereas miR-21 inhibitor increased proliferation. Both protein and mRNA levels of STAT3 were repressed by over-expression of miR-21 [117].

A large body of literature indicates that miR-21 plays roles in the development of a number of cancers. Expression of miR-21 was found to be significantly higher in 15 esophageal cancer cell lines [118]. Cells transfected with pre-miR-21 showed increased rates of proliferation, while cells transfected with anti-miR-21 had decreased rates of proliferation [118]. In HEK293 and several colorectal cancer cells, the levels of miR-21 were found inversely correlated with ras homolog gene family member B (RhoB) expression. Exogenous expression of miR-21 was able to mimic the effect of RhoB knockdown, which promoted cell proliferation and inhibited cell apoptosis. Expression of miR-21 significantly suppressed luciferase activity when the construct contained RhoB 3' UTR, but the inhibitory effect was abolished when the miR-21 target sites were mutated, confirming a direct repression of the tumor suppressor RhoB by miR-21 [119]. miR-21 was found over-expressed in endometrioid endometrial cancer (EEC) and was inversely correlated with protein levels of PTEN, a well-studied tumour suppressor [120]. Direct targeting of PTEN by miR-21 was confirmed using a dual-luciferase reporter assay. In renal carcinoma cells, miR-21 also decreases PTEN expression and augments Akt phosphorylation [121]. Over-expression of a miR-21 sponge was employed as an approach to quench endogenous miR-21 levels, which inhibited renal cancer cell proliferation. Down-regulation of PTEN prevented miR-21 sponge-induced inhibition of renal cancer cell proliferation [121]. The PTEN, PI3K and, Akt signalling pathways are also regulated by miR-21 during early Diabetic nephropathy. Repression of PTEN increased PI3K and p-Akt levels in miR-21-treated mesangial cells and db/db mice [122]. P12 (CDK2AP1) is another tumor suppressor protein that has been predicted computationally to be targeted by miR-21. An inverse correlation of miR-21 and CDK2AP1 was observed experimentally [123]. Direct repression of P12(CDK2AP1) by miR-21 was confirmed by luciferase assay. In addition, anti-miR-21-transfected Tca8113 cells showed an increased CDK2AP1 levels and decreased cell proliferation, while increased expression of miR-21 promoted cell proliferation in cultured cells [123].

7. Cell proliferation regulated by miR-17~92 cluster and its paralogs

A well-studied miRNA cluster is the miR-17~92 cluster and its paralogs miR-106a~363 and miR-106b~25. Initially, it was found that expression of the miR-17~92 cluster enhanced cell proliferation and development of human lung cancer [124]. It was soon observed that expression of miR-17-5p, a miRNA within the cluster, decreased breast cancer cell proliferation by repressing AIB1 [125]. It has been suggested that miR-17 may play different roles in different cell types [126, 127]. Indeed, in transgenic mice expressing miR-17, fibronectin levels were repressed, reducing cell proliferation and inhibiting tissue growth [7]. Additionally, these miR-17 transgenic mice developed liver cancer at old age [8]. Human liver cancer cell lines transfected with miR-17 formed larger tumors in nude mice as compared with the controls [8]. In colorectal carcinoma, miR-17 can also promote cell proliferation, tumour growth and cell cycle progression, and the target mediating these effects appears to be the tumor suppressor Rho GTPase 3 (RND3) [128]. Expression of miR-17 is negatively correlated with RND3 levels in colorectal carcinoma tissues and colorectal carcinoma cells. Inhibition of miR-17 suppressed tumour growth and up-regulated RND3 expression in a nude mouse xenograft model [128]. miR-17 and miR-19a are expressed by the miR-17~92 cluster. Expression of these two miRNAs can be induced by phosphatase of regenerating liver-3 (PRL-3), leading to promotion of proliferation and metastasis of colon cancer as a result of STAT3 activation [129].

miR-93 belongs to the cluster of miR-106b~25 that is a paralog of the miR-17~92 cluster [9]. In human breast carcinoma, expression of miR-93 is up-regulated. Tumors formed by miR-93-transfected cells were more highly vascularized as compared to the controls [10]. *In vitro* and *in vivo* experiments demonstrated that miR-93 enhanced tumor growth and angiogenesis by targeting the large tumor suppressor, homology 2 (LATS2) [10].

CONCLUSION

Since the discovery of miRNAs, the interest and research within this field has dramatically increased. New knowledge and results have also opened up the potential for innovative therapeutic opportunities. Given that a wide cascade of biological processes are involved in the recovery and repair of wounds, current drugs targeting single molecules have shown to be less effective. Since individual miRNAs can target multiple genes, miRNA gene therapy may represent a new avenue towards developing new approaches for treating chronic wounds. Nevertheless, since the same miRNAs have often been found to have differential functions based on tissue-specific and spatiotemporal expression patterns, they should be investigated cautiously in any translational work. Understanding the network of genetic regulatory elements in wound repair and biological processes such as cell proliferation and angiogenesis will be critical in translating miRNA research into the clinic.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest for the work reported.

REFERENCES

1. Bartel, D. P. 2009, Cell, 136, 215.
2. Yang, W., Lee, D. Y. and Ben-David, Y. 2011, Int. J. Physiol. Pathophysiol. Pharmacol., 3, 140.
3. Rutnam, Z. J., Wight, T. N. and Yang, B. B. 2013, Matrix Biol., 32, 74.
4. Baskerville, S. and Bartel, D. P. 2005, RNA, 11, 241.
5. Rodriguez, A., Griffiths-Jones, S., Ashurst, J. L. and Bradley, A. 2004, Genome Res., 14, 1902.
6. Griffiths-Jones, S., Saini, H. K., van Dongen, S. and Enright, A. J. 2008, Nucleic Acids Res., 36, D154.
7. Shan, S. W., Lee, D. Y., Deng, Z., Shatseva, T., Jeyapalan, Z., Du, W. W., Zhang, Y., Xuan, J. W., Yee, S. P., Siragam, V. and Yang, B. B. 2009, Nat. Cell Biol., 11, 1031.
8. Du, W. W., Fang, L., Li, M., Yang, X., Liang, Y., Peng, C., Qian, W., O'Malley, Y. Q., Askeland, R. W., Sugg, S., Qian, J., Lin, J., Jiang, Z., Yee, A. J., Sefton, M., Deng, Z., Shan, S. W., Wang, C. H. and Yang, B. B. 2013, J. Cell Sci., 126(Pt 6), 1440-53.

9. Fang, L., Deng, Z., Shatseva, T., Yang, J., Peng, C., Du, W. W., Yee, A. J., Ang, L. C., He, C., Shan, S. W. and Yang, B. B. 2011, Oncogene, 30, 806.
10. Fang, L., Du, W. W., Yang, W., Rutnam, Z. J., Peng, C., Li, H., O'Malley, Y. Q., Askeland, R. W., Sugg, S., Liu, M., Mehta, T., Deng, Z. and Yang, B. B. 2012, Cell Cycle, 11, 4352.
11. Latronico, M. V., Catalucci, D. and Condorelli, G. 2007, Circ. Res., 101, 1225.
12. Lewis, B. P., Burge, C. B. and Bartel, D. P. 2005, Cell, 120, 15.
13. Berezikov, E., Guryev, V., van de Belt, J., Wienholds, E., Plasterk, R. H. and Cuppen, E. 2005, Cell, 120, 21.
14. Lim, L. P., Lau, N. C., Garrett-Engele, P., Grimson, A., Schelter, J. M., Castle, J., Bartel, D. P., Linsley, P. S. and Johnson, J. M. 2005, Nature, 433, 769.
15. Lee, D. Y., Shatseva, T., Jeyapalan, Z., Du, W. W., Deng, Z. and Yang, B. B. 2009, PLoS One, 4, e4527.
16. Jeyapalan, Z., Deng, Z., Shatseva, T., Fang, L., He, C. and Yang, B. B. 2011, Nucleic Acids Res., 39, 3026.
17. Lee, S. C., Fang, L., Wang, C. H., Kahai, S., Deng, Z. and Yang, B. B. 2011, FEBS Lett., 585, 2610.
18. Lee, D. Y., Jeyapalan, Z., Fang, L., Yang, J., Zhang, Y., Yee, A. Y., Li, M., Du, W. W., Shatseva, T. and Yang, B. B. 2010, PLoS One, 5, e13599.
19. Deng, Z., Yang, X., Fang, L., Rutnam, Z. J. and Yang, B. B. 2013, Biochem. J., 450, 375.
20. Rutnam, Z. J. and Yang, B. B. 2012, J. Cell Sci., 125, 2075.
21. Poliseno, L., Salmena, L., Zhang, J., Carver, B., Haveman, W. J. and Pandolfi, P. P. 2010, Nature, 465, 1033.
22. Rutnam, Z. J., Du, W. W., Yang, W., Yang, X. and Yang, B. B. 2014, Nat. Commun., 5, 2914.
23. Viticchie, G., Lena, A. M., Latina, A., Formosa, A., Gregersen, L. H., Lund, A. H., Bernardini, S., Mauriello, A., Miano, R., Spagnoli, L. G., Knight, R. A., Candi, E. and Melino, G. 2011, Cell Cycle, 10, 1121.
24. Shatseva, T., Lee, D. Y., Deng, Z. and Yang, B. B. 2011, J. Cell Sci., 124, 2826.
25. Yu, B., Zhou, S., Wang, Y., Qian, T., Ding, G., Ding, F. and Gu, X. 2012, J. Cell Sci., 125, 2675.
26. He, J., Wu, J., Xu, N., Xie, W., Li, M., Li, J., Jiang, Y., Yang, B. B. and Zhang, Y. 2013, Nucleic Acids Res., 41, 498.
27. Goljanek-Whysall, K., Pais, H., Rathjen, T., Sweetman, D., Dalmay, T. and Munsterberg, A. 2012, J. Cell Sci., 125, 3590.
28. Deng, Z., Du, W. W., Fang, L., Shan, S. W., Qian, J., Lin, J., Qian, W., Ma, J., Rutnam, Z. J. and Yang, B. B. 2013, J. Biol. Chem., 288, 319.
29. Wan, G., Xie, W., Liu, Z., Xu, W., Lao, Y., Huang, N., Cui, K., Liao, M., He, J., Jiang, Y., Yang, B. B., Xu, H., Xu, N. and Zhang, Y. 2014, Autophagy, 10, 70.
30. Ye, G., Fu, G., Cui, S., Zhao, S., Bernaudo, S., Bai, Y., Ding, Y., Zhang, Y., Yang, B. B. and Peng, C. 2011, J. Cell Sci., 124, 359.
31. Rutnam, Z. J. and Yang, B. B. 2012, Histol. Histopathol., 27, 1263.
32. Wang, C. H., Lee, D. Y., Deng, Z., Jeyapalan, Z., Lee, S. C., Kahai, S., Lu, W. Y., Zhang, Y. and Yang, B. B. 2008, PLoS One, 3, e2420.
33. Luo, L., Ye, G., Nadeem, L., Fu, G., Yang, B. B., Honarparvar, E., Dunk, C., Lye, S. and Peng, C. 2012, J. Cell Sci., 125, 3124.
34. Deng, M., Tang, H., Zhou, Y., Zhou, M., Xiong, W., Zheng, Y., Ye, Q., Zeng, X., Liao, Q., Guo, X., Li, X., Ma, J. and Li, G. 2011, J. Cell Sci., 124, 2997.
35. Yang, X., Du, W. W., Li, H., Liu, F., Khorshidi, A., Rutnam, Z. J. and Yang, B. B. 2013, Nucleic Acids Res., 41, 9688.
36. Volinia, S., Calin, G. A., Liu, C. G., Ambs, S., Cimmino, A., Petrocca, F., Visone, R., Iorio, M., Roldo, C., Ferracin, M., Prueitt, R. L., Yanaihara, N., Lanza, G., Scarpa, A., Vecchione, A., Negrini, M., Harris, C. C. and Croce, C. M. 2006, Proc. Natl. Acad. Sci. USA, 103, 2257.
37. Nohata, N., Hanazawa, T., Enokida, H. and Seki, N. 2012, Oncotarget, 3, 9.
38. Liu, F., Lv, Q., Du, W. W., Li, H., Yang, X., Liu, D., Deng, Z., Ling, W., Zhang, Y. and Yang, B. B. 2013, Biochim. Biophys. Acta, 1833, 3272.

39. Zou, C., Xu, Q., Mao, F., Li, D., Bian, C., Liu, L. Z., Jiang, Y., Chen, X., Qi, Y., Zhang, X., Wang, X., Sun, Q., Kung, H. F., Lin, M. C., Dress, A., Wardle, F., Jiang, B. H. and Lai, L. 2012, Cell Cycle, 11, 2137.
40. Smits, M., Nilsson, J., Mir, S. E., van der Stoop, P. M., Hulleman, E., Niers, J. M., de Witt Hamer, P. C., Marquez, V. E., Cloos, J., Krichevsky, A. M., Noske, D. P., Tannous, B. A. and Wurdinger, T. 2010, Oncotarget, 1, 710.
41. Shan, S. W., Fang, L., Shatseva, T., Rutnam, Z. J., Yang, X., Du, W., Lu, W. Y., Xuan, J. W., Deng, Z. and Yang, B. B. 2013, J. Cell Sci., 126, 1517.
42. Ma, L., Teruya-Feldstein, J. and Weinberg, R. A. 2007, Nature, 449, 682.
43. Huang, Q., Gumireddy, K., Schrier, M., le Sage, C., Nagel, R., Nair, S., Egan, D. A., Li, A., Huang, G., Klein-Szanto, A. J., Gimotty, P. A., Katsaros, D., Coukos, G., Zhang, L., Pure, E. and Agami, R. 2008, Nat. Cell Biol., 10, 202.
44. Fang, L., Du, W. W., Yang, X., Chen, K., Ghanekar, A., Levy, G., Yang, W., Yee, A. J., Lu, W. Y., Xuan, J. W., Gao, Z., Xie, F., He, C., Deng, Z. and Yang, B. B. 2013, FASEB J., 27, 907.
45. Yang, W. and Yee, A. J. 2014, Biochim. Biophys. Acta, 2014, pii:S0167-4889(14) 00071-8. doi:10.1016/j.bbamcr.2014.02.015. (Epub ahead of print).
46. Kahai, S., Lee, S. C., Lee, D. Y., Yang, J., Li, M., Wang, C. H., Jiang, Z., Zhang, Y., Peng, C. and Yang, B. B. 2009, PLoS One, 4, e7535.
47. Cesana, M., Cacchiarelli, D., Legnini, I., Santini, T., Sthandier, O., Chinappi, M., Tramontano, A. and Bozzoni, I. 2011, Cell, 147, 358.
48. Hansen, T. B., Jensen, T. I., Clausen, B. H., Bramsen, J. B., Finsen, B., Damgaard, C. K. and Kjems, J. 2013, Nature, 495, 384.
49. Ebert, M. S., Neilson, J. R. and Sharp, P. A. 2007, Nat. Methods, 4, 721.
50. Yang, X., Rutnam, Z. J., Jiao, C., Wei, D., Xie, Y., Du, J., Zhong, L. and Yang, B. B. 2012, Cell Cycle, 11, 3097.
51. Haraguchi, T., Ozaki, Y. and Iba, H. 2009, Nucleic Acids Res., 37, e43.
52. Orom, U. A., Kauppinen, S. and Lund, A. H. 2006, Gene, 372, 137.
53. Krutzfeldt, J., Rajewsky, N., Braich, R., Rajeev, K. G., Tuschl, T., Manoharan, M. and Stoffel, M. 2005, Nature, 438, 685.
54. Sen, C. K. and Roy, S. 2008, Biochim. Biophys. Acta, 1780, 1348.
55. Shilo, S., Roy, S., Khanna, S. and Sen, C. K. 2007, DNA Cell Biol., 26, 227.
56. Kuehn, B. M. 2007, JAMA, 297, 938.
57. Kanitakis, J. 2002, Eur. J. Dermatol., 12, 390.
58. Gregory, P. A., Bert, A. G., Paterson, E. L., Barry, S. C., Tsykin, A., Farshid, G., Vadas, M. A., Khew-Goodall, Y. and Goodall, G. J. 2008, Nat. Cell Biol., 10, 593.
59. Korpal, M., Lee, E. S., Hu, G. and Kang, Y. 2008, J. Biol. Chem., 283, 14910.
60. Biswas, S., Roy, S., Banerjee, J., Hussain, S. R., Khanna, S., Meenakshisundaram, G., Kuppusamy, P., Friedman, A. and Sen, C. K. 2010, Proc. Natl. Acad. Sci. USA, 107, 6976.
61. Fasanaro, P., D'Alessandra, Y., Di Stefano, V., Melchionna, R., Romani, S., Pompilio, G., Capogrossi, M. C. and Martelli, F. 2008, J. Biol. Chem., 283, 15878.
62. Hua, Z., Lv, Q., Ye, W., Wong, C. K., Cai, G., Gu, D., Ji, Y., Zhao, C., Wang, J., Yang, B. B. and Zhang, Y. 2006, PLoS One, 1, e116.
63. Pulkkinen, K., Malm, T., Turunen, M., Koistinaho, J. and Yla-Herttuala, S. 2008, FEBS Lett., 582, 2397.
64. Cheng, J., Yu, H., Deng, S. and Shen, G. 2010, Tohoku J. Exp. Med., 221, 203.
65. Li, Z., Hassan, M. Q., Jafferji, M., Aqeilan, R. I., Garzon, R., Croce, C. M., van Wijnen, A. J., Stein, J. L., Stein, G. S. and Lian, J. B. 2009, J. Biol. Chem., 284, 15676.
66. van Rooij, E., Sutherland, L. B., Thatcher, J. E., DiMaio, J. M., Naseem, R. H., Marshall, W. S., Hill, J. A. and Olson, E. N. 2008, Proc. Natl. Acad. Sci. USA, 105, 13027.
67. Bostjancic, E. and Glavac, D. 2008, Acta Dermatovenerol. Alp. Panonica. Adriat., 17, 95.
68. Chen, C. Z., Li, L., Lodish, H. F. and Bartel, D. P. 2004, Science, 303, 83.
69. Maurer, B., Stanczyk, J., Jungel, A., Akhmetshina, A., Trenkmann, M., Brock, M., Kowal-Bielecka, O., Gay, R. E., Michel, B. A., Distler, J. H., Gay, S. and Distler, O. 2010, Arthritis Rheum., 62, 1733.

70. Yee, A. J., Akens, M., Yang, B. L., Finkelstein, J., Zheng, P. S., Deng, Z. and Yang, B. 2007, Breast Cancer Res., 9, R47.
71. Zheng, P. S., Vais, D., Lapierre, D., Liang, Y. Y., Lee, V., Yang, B. L. and Yang, B. B. 2004, J. Cell Sci., 117, 5887.
72. Wu, Y., Chen, L., Cao, L., Sheng, W. and Yang, B. B. 2004, J. Cell Sci., 117, 2227.
73. Yang, B. L., Cao, L., Kiani, C., Lee, V., Zhang, Y., Adams, M. E. and Yang, B. B. 2000, J. Biol. Chem., 275, 21255.
74. LaPierre, D. P., Lee, D. Y., Li, S. Z., Xie, Y. Z., Zhong, L., Sheng, W., Deng, Z. and Yang, B. B. 2007, Cancer Res., 67, 4742.
75. Poliseno, L., Tuccoli, A., Mariani, L., Evangelista, M., Citti, L., Woods, K., Mercatanti, A., Hammond, S. and Rainaldi, G. 2006, Blood, 108, 3068.
76. Fish, J. E., Santoro, M. M., Morton, S. U., Yu, S., Yeh, R. F., Wythe, J. D., Ivey, K. N., Bruneau, B. G., Stainier, D. Y. and Srivastava, D. 2008, Dev. Cell, 15, 272.
77. Wienholds, E., Kloosterman, W. P., Miska, E., Alvarez-Saavedra, E., Berezikov, E., de Bruijn, E., Horvitz, H. R., Kauppinen, S. and Plasterk, R. H. 2005, Science, 309, 310.
78. Suarez, Y., Fernandez-Hernando, C., Yu, J., Gerber, S. A., Harrison, K. D., Pober, J. S., Iruela-Arispe, M. L., Merkenschlager, M. and Sessa, W. C. 2008, Proc. Natl. Acad. Sci. USA, 105, 14082.
79. Shilo, S., Roy, S., Khanna, S. and Sen, C. K. 2008, Arterioscler Thromb. Vasc. Biol., 28, 471.
80. Zhu, Y., Jin, K., Mao, X. O. and Greenberg, D. A. 2003, FASEB J., 17, 186.
81. Wu, L., Timmers, C., Maiti, B., Saavedra, H. I., Sang, L., Chong, G. T., Nuckolls, F., Giangrande, P., Wright, F. A., Field, S. J., Greenberg, M. E., Orkin, S., Nevins, J. R., Robinson, M. L. and Leone, G. 2001, Nature, 414, 457.
82. O'Donnell, K. A., Wentzel, E. A., Zeller, K. I., Dang, C. V. and Mendell, J. T. 2005, Nature, 435, 839.
83. Kuehbacher, A., Urbich, C., Zeiher, A. M. and Dimmeler, S. 2007, Circ. Res., 101, 59.
84. Siragam, V., Rutnam, Z. J., Yang, W., Fang, L., Luo, L., Yang, X., Li, M., Deng, Z., Qian, J., Peng, C. and Yang, B. B. 2012, Oncotarget, 3, 1370.
85. Brennecke, J., Hipfner, D. R., Stark, A., Russell, R. B. and Cohen, S. M. 2003, Cell, 113, 25.
86. Thompson, B. J. and Cohen, S. M. 2006, Cell, 126, 767.
87. Kumar, M. S., Lu, J., Mercer, K. L., Golub, T. R. and Jacks, T. 2007, Nat. Genet, 39, 673.
88. Lee, Y. S., Kim, H. K., Chung, S., Kim, K. S. and Dutta, A. 2005, J. Biol. Chem., 280, 16635.
89. Willimott, S. and Wagner, S. D. 2012, J. Biol. Chem., 287, 2608.
90. Wu, N., Xiao, L., Zhao, X., Zhao, J., Wang, J., Wang, F., Cao, S. and Lin, X. 2012, FEBS Lett., 586, 3831.
91. Xu, N., Zhang, L., Meisgen, F., Harada, M., Heilborn, J., Homey, B., Grander, D., Stahle, M., Sonkoly, E. and Pivarcsi, A. 2012, J. Biol. Chem., 287, 29899.
92. Li, N., Tang, B., Zhu, E. D., Li, B. S., Zhuang, Y., Yu, S., Lu, D. S., Zou, Q. M., Xiao, B. and Mao, X. H. 2012, FEBS Lett., 586, 722.
93. Frenquelli, M., Muzio, M., Scielzo, C., Fazi, C., Scarfo, L., Rossi, C., Ferrari, G., Ghia, P. and Caligaris-Cappio, F. 2010, Blood, 115, 3949.
94. le Sage, C., Nagel, R., Egan, D.A., Schrier, M., Mesman, E., Mangiola, A., Anile, C., Maira, G., Mercatelli, N., Ciafre, S. A., Farace, M. G. and Agami, R. 2007, EMBO J., 26, 3699.
95. Galardi, S., Mercatelli, N., Giorda, E., Massalini, S., Frajese, G. V., Ciafre, S. A. and Farace, M. G. 2007, J. Biol. Chem., 282, 23716.
96. Liu, X., Cheng, Y., Zhang, S., Lin, Y., Yang, J. and Zhang, C. 2009, Circ. Res., 104, 476.
97. Johnnidis, J. B., Harris, M. H., Wheeler, R. T., Stehling-Sun, S., Lam, M. H., Kirak, O., Brummelkamp, T. R., Fleming, M. D. and Camargo, F. D. 2008, Nature, 451, 1125.
98. Jia, C. Y., Li, H. H., Zhu, X. C., Dong, Y. W., Fu, D., Zhao, Q. L., Wu, W. and Wu, X. Z. 2011, PLoS One, 6, e27008.
99. Song, L., Duan, P., Guo, P., Li, D., Li, S., Xu, Y. and Zhou, Q. 2012, Arch. Biochem. Biophys., 528, 204.

100. Wu, L., Li, H., Jia, C. Y., Cheng, W., Yu, M., Peng, M., Zhu, Y., Zhao, Q., Dong, Y. W., Shao, K., Wu, A. and Wu, X. Z. 2012, FEBS Lett., 586, 1038.
101. Selcuklu, S. D., Donoghue, M. T., Rehmet, K., de Souza Gomes, M., Fort, A., Kovvuru, P., Muniyappa, M. K., Kerin, M. J., Enright, A. J. and Spillane, C. 2012, J. Biol. Chem., 287, 29516.
102. Zheng, L., Qi, T., Yang, D., Qi, M., Li, D., Xiang, X., Huang, K. and Tong, Q. 2013, PLoS One, 8, e55719.
103. Tan, X., Wang, S., Yang, B., Zhu, L., Yin, B., Chao, T., Zhao, J., Yuan, J., Qiang, B. and Peng, X. 2012, PLoS One, 7, e49570.
104. Ma, W., Xie, S., Ni, M., Huang, X., Hu, S., Liu, Q., Liu, A., Zhang, J. and Zhang, Y. 2012, J. Biol. Chem., 287, 10189.
105. Cui, Y., Su, W. Y., Xing, J., Wang, Y. C., Wang, P., Chen, X. Y., Shen, Z. Y., Cao, H., Lu, Y. Y. and Fang, J. Y. 2011, PLoS One, 6, e25872.
106. Wang, Y., Zheng, X., Zhang, Z., Zhou, J., Zhao, G., Yang, J., Xia, L., Wang, R., Cai, X., Hu, H., Zhu, C., Nie, Y., Wu, K., Zhang, D. and Fan, D. 2012, PLoS One, 7, e41693.
107. Wu, Q. P., Xie, Y. Z., Deng, Z., Li, X. M., Yang, W., Jiao, C. W., Fang, L., Li, S. Z., Pan, H. H., Yee, A. J., Lee, D. Y., Li, C., Zhang, Z., Guo, J. and Yang, B. B. 2012, PLoS One, 7, e44579.
108. Zhou, J., Ju, W., Wang, D., Wu, L., Zhu, X., Guo, Z. and He, X. 2012, PLoS One, 7, e33577.
109. Huang, N., Lin, J., Ruan, J., Su, N., Qing, R., Liu, F., He, B., Lv, C., Zheng, D. and Luo, R. 2012, FEBS Lett., 586, 884.
110. Li, D., Yang, P., Li, H., Cheng, P., Zhang, L., Wei, D., Su, X., Peng, J., Gao, H., Tan, Y., Zhao, Z., Li, Y., Qi, Z., Rui, Y. and Zhang, T. 2012, Life Sci., 91, 440.
111. Yu, B., Qian, T., Wang, Y., Zhou, S., Ding, G., Ding, F. and Gu, X. 2012, Nucleic Acids Res., 40, 10356.
112. Hui, W., Yuntao, L., Lun, L., Wensheng, L., Chaofeng, L., Haiyong, H. and Yueyang, B. 2013, PLoS One, 8, e54932.
113. Wang, L., Shi, M., Hou, S., Ding, B., Liu, L., Ji, X., Zhang, J. and Deng, Y. 2012, FEBS Lett., 586, 1312.
114. Yao, Q., Xu, H., Zhang, Q. Q., Zhou, H. and Qu, L. H. 2009, Biochem. Biophys. Res. Commun., 388, 539.
115. Wang, F., Zhao, X. Q., Liu, J. N., Wang, Z. H., Wang, X. L., Hou, X. Y., Liu, R., Gao, F., Zhang, M. X., Zhang, Y. and Bu, P. L. 2012, J. Cell. Biochem., 113, 2989.
116. Jin, C., Zhao, Y., Yu, L., Xu, S. and Fu, G. 2013, FEBS Lett., 587, 378.
117. Kim, Y. J., Hwang, S. H., Cho, H. H., Shin, K. K., Bae, Y. C. and Jung, J. S. 2012, J. Cell. Physiol., 227, 183.
118. Mori, Y., Ishiguro, H., Kuwabara, Y., Kimura, M., Mitsui, A., Ogawa, R., Katada, T., Harata, K., Tanaka, T., Shiozaki, M. and Fujii, Y. 2009, Mol. Med. Rep., 2, 235.
119. Liu, M., Tang, Q., Qiu, M., Lang, N., Li, M., Zheng, Y. and Bi, F. 2011, FEBS Lett., 585, 2998.
120. Qin, X., Yan, L., Zhao, X., Li, C. and Fu, Y. 2012, Oncol. Lett., 4, 1290.
121. Dey, N., Das, F., Ghosh-Choudhury, N., Mandal, C. C., Parekh, D. J., Block, K., Kasinath, B. S., Abboud, H. E. and Choudhury, G. G. 2012, PLoS One, 7, e37366.
122. Zhang, Z., Peng, H., Chen, J., Chen, X., Han, F., Xu, X., He, X. and Yan, N. 2009, FEBS Lett., 583, 2009.
123. Zheng, J., Xue, H., Wang, T., Jiang, Y., Liu, B., Li, J., Liu, Y., Wang, W., Zhang, B. and Sun, M. 2011, J. Cell. Biochem., 112, 872.
124. Hayashita, Y., Osada, H., Tatematsu, Y., Yamada, H., Yanagisawa, K., Tomida, S., Yatabe, Y., Kawahara, K., Sekido, Y. and Takahashi, T. 2005, Cancer Res., 65, 9628.
125. Hossain, A., Kuo, M. T. and Saunders, G. F. 2006, Mol. Cell. Biol., 26, 8191.
126. Li, S. H., Guo, J., Wu, J., Sun, Z., Han, M., Shan, S. W., Deng, Z., Yang, B. B., Weisel, R. D. and Li, R. K. 2013, FASEB J., 27, 4254.
127. Li, H. and Yang, B. B. 2012, Oncotarget, 3, 1653.
128. Luo, H., Zou, J., Dong, Z., Zeng, Q., Wu, D. and Liu, L. 2012, Biochem. J., 442, 311.
129. Zhang, J., Xiao, Z., Lai, D., Sun, J., He, C., Chu, Z., Ye, H., Chen, S. and Wang, J. 2012, Br. J. Cancer, 107, 352.