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# The Balance Mediated by miRNAs and the Heme Oxygenase 1 Feedback Loop Contributes to Biological Effects

Ning Ma,[1,2] Ying Xiang,[1,3] Yanfen Zhang,[4] Xia Zhao,[5] Lingyun Zhou,[1,2] and Xu Gao[1,2,6*]

[1]*Department of Biochemistry and Molecular Biology, Harbin Medical University, Harbin, China*
[2]*Translational Medicine Center of Northern China, Harbin, China*
[3]*Department of Cell Biology, Medical School, Yangtze University, China*
[4]*Department of Laboratory Diagnosis, Affiliated Hospital of Harbin Medical University, Harbin, China*
[5]*Laboratory Medicine, Heilongjiang Nursing College, Harbin, China*
[6]*Key Laboratory of Cardiovascular Medicine Research, Ministry of Education, Harbin, China*

## ABSTRACT

Heme oxygenase-1 (HMOX1) is a ubiquitously expressed inducible enzyme that degrades heme to carbon monoxide, biliverdin, and free iron ions. Since 1950, many studies have revealed the role of HMOX1 in reducing the impact of oxidative stress in many types of diseases, such as Alzheimer's disease, heart disease, and the development of tumors. These effects arise as a result of the removal of heme, the biological activities of the products of HMOX1 and the activity of HMOX1 itself. However, HMOX1 has some contradictory effects. The discovery of microRNAs (miRNAs) and their relationship with HMOX1 has provided a new direction for research in this field. Here, we discuss the role of a potential regulatory feedback loop between HMOX1 and miRNAs in pathological processes based on recently published data. We hope to describe a new mechanism for HMOX1 function based on miRNAs to address the contradictory results reported in the literature. J. Cell. Biochem. 114: 2637–2642, 2013. 

**KEY WORDS:** HEME OXYGENASE-1; microRNA; FEEDBACK LOOP; TARGETS POOLS

Heme oxygenase-1 (HMOX1) is an inducible enzyme that is responsible for the degradation of heme to biliverdin, carbon monoxide (CO), and ferrous iron. HMOX1 expression is up-regulated in response to cellular stress and by pro-oxidative stimuli, such as heme, UV light, LPS (lipopolysaccharide), hydrogen peroxide, cobalt protoporphyrin, heat shock, heavy metals, pro-inflammatory cytokines, NO, ethanol, and prostaglandins [Jozkowicz et al., 2007]. HMOX1 serves a wide variety of functions in cells that frequently extend beyond substrate catabolism. Multiple studies have indicated that the products of HMOX1 and the protein itself are involved in nerve degenerative disease, heart disease, kidney disease, and tumor biology [Zhao et al., 2012]. A large body of evidence indicates that HMOX1 serves protective roles based on anti-oxidation, anti-apoptosis, and anti-inflammatory activities [Gong et al., 2012; Hamedi-Asl et al., 2012]. However, some contradictory effects have been reported, such as pro-apoptosis and pro-inflammatory effects [Mizuno et al., 2005; Hayama et al., 2011]. The role of HMOX1 in tumor development is highly debated [Boschetto et al., 2008; Tsai et al., 2012]. These controversial findings suggested that there may be unidentified mechanisms or regulatory factors involved in HMOX1 function. Recent studies have shown the existence of HMOX1 in the nuclei and mitochondria [Bindu et al., 2011; Gandini et al., 2012].

Abbreviations: AD, Alzheimer disease; CO, carbon monoxide; miRNA, microRNA.
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*Correspondence to: Department of Biochemistry and Molecular Biology, Harbin Medical University, Harbin 150081, China. E-mail: gaoxu_671227@163.com or maning2013@163.com

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These data suggest that HMOX1 or its products might play a role in the regulation of gene expression at the transcriptional level and cellular aerobic oxidation.

MicroRNAs (miRNAs) are small, non-coding RNAs that base-pair with specific mRNAs and inhibit translation or promote mRNA degradation. miRNAs control gene expression by binding to their target mRNA UTR, ORF, CDS, or even the target protein [Tay et al., 2008; Eiring et al., 2010; Qin et al., 2010]. Several studies have shown that miRNAs may regulate the expression of HMOX1, or HMOX1 may regulate the amount of miRNA directly or indirectly (Table I). These findings may provide a new avenue for the investigation of the roles of HMOX1.

Based on recent data on miRNAs and HMOX1, a regulatory feedback network between HMOX1 and miRNAs may exist that plays a crucial role in cells (Fig. 1).

## MICRORNAs–HMOX1 FEEDBACK LOOP

As is mentioned above, it is possible that HMOX1 may be a target of miRNAs, which is supported by experimental evidence. The question arises of whether miRNAs are mediated by HMOX1 and play a key role in enhancing or attenuating HMOX1 function. In the previous studies, contradictory results regarding the consequences of miRNAs on the function of HMOX1 have been reported. We hypothesize that some type of balance between HMOX1 and miRNAs expression has been overlooked and may contribute to the contradictory effects. The mechanism of the feedback between miRNAs and the targeted genes is being gradually revealed.

Therefore, the regulation of HMOX1 expression and the function by miRNAs is an important area of study. miRNAs are even more important as regulatory molecules for controling gene expression at the posttranscriptional level in response to stress.

### THE EXPRESSION OF HMOX1 MAY BE REGULATED BY miRNAs

microRNAs are very important regulators of gene expression. We observed that HMOX1 could be a potential target of many miRNAs based on a bioinformatic prediction. The known functions of these miRNAs are listed in the Table I. Recent studies showed that miRNAs regulated HMOX1 expression directly or indirectly (Table II). These data revealed that the expression of HMOX1 could be regulated by miRNAs at the posttranscriptional level.

On the other hand, HMOX1 could be regulated by miRNAs at the transcriptional level. The promotor of the *HMOX1* gene has an antioxidant-response element (ARE), which can bind the transcription factor Nrf2 to promote transcription. Furthermore, the transcription factor BACH1 can competitively bind to the ARE with Nrf2, inhibiting transcription. Studies have shown that miR-155 efficiently inhibited BACH1 protein translation, resulting in a concentration-dependent increase in HMOX1 mRNA and protein expression in human umbilical vein endothelial cells [Pulkkinen et al., 2011]. The let-7 miRNA enhances the expression of HMOX1 by suppressing Bach1 in human hepatocytes [Hou et al., 2012]. Moreover, miRNAs were reported to bind the promoter region to regulate gene transcription [Younger and Corey, 2011]. It is possible that some miRNAs bind to the promoter region of the *HMOX1* gene because of the polymorphism in the promoter of the *HMOX1* gene.

TABLE I. The List of miRNAs That Can Target HMOX1 Based on a Bioinformatic Prediction (http://www.microrna.org/microrna/getGeneForm.do)

| miRNAs | Stress | Tissue/organ | Function | Ref. (PMID) |
|---|---|---|---|---|
| 377 | Diabetes mellitus | Renal | Up-regulated, leading to increased fibronectin production | 18716020 |
| 217 | TGF-β treatment; cancer | Renal; pancreatic | Up-regulated, pro-fibrotic effects; Tumor suppressor | 21984124; 20675343 |
| 485-5p | Cancer | Ovarian; ependymal | Down-regulated | 22053178; 21083603 |
| miR-200b/c | TGF-β1 treatment | Renal | Up-regulated, pro-fibrosis | 21389977 |
| 429 | Cancer | Ovarian; gastric; colorectal | Down regulated, pro-migration; Down regulated, pro-migration; up-regulated, anti-apoptotic | 19501389; 21884154; 23111103 |
| 505 | MCF7-ADR | Breast | Down-regulated, tumor suppressor | 22051041 |
| 22 | Cancer; isoproterenol; aging | Lung/ovarian/colorectal; Heart | Down-regulated; pro-hypertrophic; promoting senescence | 22484852/22469921/22492279; 22847192; 22538858 |
| 218 | Cancer | Breast/Glia/oral/head and neck/colon/medullary/ lung/bladder/nasopharyngeal/cervical | Down-regulated, tumor suppressor | 22705304/22766851/22860003/ 21795477/23159910/20838434/ 21519788/21385904/17998904 |
| 873 | Cancer; HTLV-1 infection | Glia; T cells | Down-regulated; Down-regulated, | 21912681; 22496815 |
| 128 | Cancer; Sunitinib/Doxorubicin neurodegenerative | Glia/endometrial/prostate; Glia/breast tumor; neurons | Down-regulated, as tumor repressor; chemotherapeutic resistance; down-regulated | 21874051/20028871/19955085; 23201752/21953503; 18987751 |
| 338-3p | Hepatitis B virus X protein | Hepatic | Down regulated; inhibiting proliferation | 22942717 |
| 328 | Atrial fibrillation/acute myocardial infarction; cancer; Alzheimer's disease | Heart; Glia/colorectal/lung | Promoting atrial fibrillation/up-regulated; tumor suppressor; targeting BACE mRNA | 21098446/21881276; 23077581/ 22453125/21448905; 18986979 |

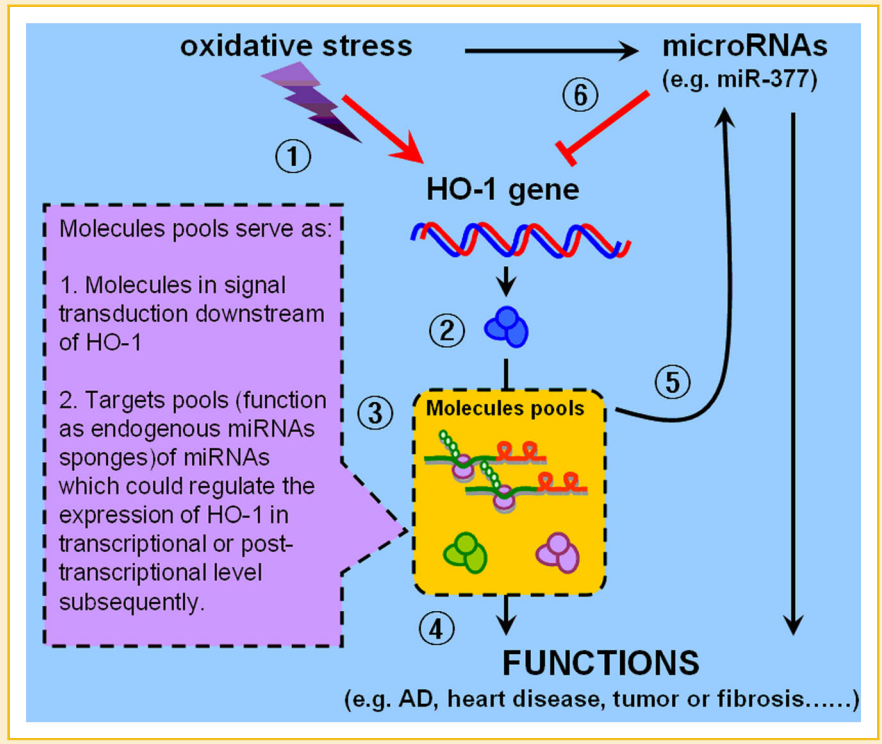


**Fig. 1.** ①1 Stress promotes HMOX1 expression. ②2 HMOX1protein. 3 ③ HMOX1or/and its products control gene expression or cell signaling pathways, and all of the regulated molecules form pools. ④4 HMOX1 exhibits direct or indirect biological functions. ⑤5 Molecular pools regulate miRNA expression by serving as endogenous miRNA sponges or transcription factors. ⑥6 miRNAs negatively regulate HMOX1 expression.

## HMOX1 REGULATED miRNAs EXPRESSION

**HMOX1 substrate may regulate miRNA expression.** Heme is the substrate of the HMOX1 enzyme. DGCR8, a heme-binding protein, is necessary for miRNA processing [Faller et al., 2007]. DGCR8, along with the RNase Drosha, cleaves pri-miRNAs into pre-miRNAs in the process of miRNA biosynthesis. Finally, the expression of the mature miRNA may be altered.

**HMOX1 products may regulate miRNAs expression.** HMOX1 expression is altered under stress, and its function may also change as a result of its products. Evidence suggested that carbon monoxide down-regulated the expression of miR-710 in colonic myofibroblast cells treated with CORM (supplied by the CO-releasing molecule) [Uchiyama et al., 2010]. Cytosolic iron could regulate the activity of the miRNA pathway through poly(C)-binding protein 2 (PCBP2), which is associated with Dicer and promotes the processing of miRNA precursors [Li et al., 2012].

**HMOX1 interferes miRNA target pools that regulate miRNAs.** A single miRNA can regulate multiple target genes, which could be referred to as "target pools." It has been reported that the target abundance could affect the role of miRNAs in the cells [Arvey et al., 2010]. Therefore, the HMOX1 mRNA abundance could interfere with the "target pools" of miRNAs, diluting the miRNAs activity.

**The cellular localization of HMOX1 suggests that it may regulate miRNA expression directly.** Investigations of the transcription level of miRNAs have been initiated. The data showed that the p53 protein stimulates miR-107 transcription levels in glioma cells, as miR-107 is the transcriptional target of the p53 protein [Chen et al., 2012]. Furthermore, c-myc transcriptionally represses miR-23a and miR-23b [Gao et al., 2009].

HMOX1 is a 32-kDa protein that is localized in microsomes [Ryter et al., 2006]; however, it has also been demonstrated to be present in the mitochondria and nucleus, which suggests that it may regulate

TABLE II. The Relationship Between HMOX1 and miRNAs Based on Data

| PMID | Species/cell | Treatment | Effects | miRNA:mRNA pairs |
|---|---|---|---|---|
| 21827279 | Mouse C2C12 myoblasts | HO-1 | Downregulates Lin28 and DGCR8, myomirs: miR-1, 133a/b, 206 ↓ | |
| 21982894 | Human HUVEC | TNF-α | TNF↑-(NF-kB)-miR-155↑-Bach1-HO-1↑ | |
| 21147878 | Human/rat 3T3-L1 | Insulin | HO-1↑; miR-155, 183, 872 ↓ | |
| 21106538 | Human | miR-217, 377 transfection | HO-1 protein ↓ | miR-217/377:HO-1 |
| 20633528 | Human HBV | miR-122 transfection | HO-1↓ | miR-122:HO-1 |
| 17919492 | Human HCV | miR-122 transfection | HO-1↓ | miR-122:HO-1 |
| 22698995 | Human Huh-7 HepG2 | Let-7 transfection | Let-7—Bach1↓-HO-1↑ Anti-oxidant injury | Let-7:Bach1 |

gene expression (coding genes or non-coding genes) at the transcriptional level as a transcriptional factor. Although it is not a canonical transcription factor, either HMOX1 itself or its products may regulate transcription through interaction with other transcription factors.

## FEEDBACK LOOPS BETWEEN miRNAs AND THEIR TARGET GENES

The concept of feedback loops between miRNAs and their target genes has been proposed in recent years. The mir-17-92 cluster modulates the translation of the E2F2 and E2F3 mRNAs via binding sites in their 3′-untranslated region, while the endogenous E2F2 and E2F3 directly bind the promoter of the mir-17-92 cluster, activating its transcription. It is suggested that there is an autoregulatory feedback loop between the E2F factors and the mir-17-92 cluster [Sylvestre et al., 2007]. MiR-9 inhibited the proliferation and promoted the migration of glioma cells by directly targeting cyclic AMP response element-binding protein (CREB). Furthermore, the transcription of miR-9-1 is under CREB′s control, forming a negative feedback mini-circuit. Taken together, miR-9 inhibits proliferation but promotes migration, whereas CREB plays a pro-proliferative and anti-migratory role, suggesting that the CREB-miR-9 negative feedback mini-circuit plays a critical role in the decision to "go or grow" in glioma cells [Tan et al., 2012]. Ectopic miR-34a induced the mesenchymal–epithelial-transition (MET) and down-regulation of SNAIL and ZEB1, which was mediated by a conserved miR-34a/b/c seed-matching sequence in the 3′-UTR. Conversely, the transcription factors SNAIL and ZEB1 were shown to bind to E-boxes in the miR-34a/b/c promoters, thereby repressing miR-34a and miR-34b/c expression [Siemens et al., 2011]. When miRNAs and their targets exhibit adverse effects, the balance may lead to contradictory results. The feedback loop between miRNA and HMOX1 may be an indicator of the complex function of HMOX1.

## THE FEEDBACK LOOP BETWEEN MIR-377 AND HMOX1 IN RENAL FIBROSIS

Fibrosis involves an excess accumulation of extracellular matrix (primarily composed of collagen) and usually results in the loss of function when normal tissue is replaced with scar tissue. The progressive fibrosis accompanies all chronic renal disease [Hewitson, 2012].

Transforming growth factor-β (TGF-β) is a key mediator in a variety of kidney diseases, including diabetic nephropathy. TGF-β exerts its biological functions largely via its downstream complex of signaling molecules, the Smad proteins. Paradoxically, TGF-β is also essential for normal homeostasis and suppression of inflammation. One feasible mechanism by which TGF-β may exert its beneficial properties is through the induction of HMOX1 [Zarjou and Agarwal, 2012], which is known to be cytoprotective through its potent antioxidant, anti-inflammatory, and anti-apoptotic properties in different conditions, including several kidney diseases. Up-regulation of HMOX1 expression was able to both prevent the progression of renal tubule-interstitial fibrosis and to reverse an established renal fibrosis in animals subjected to unilateral ureteral obstruction (UUO) [Correa-Costa et al., 2010].

MiR-377 was positively regulated by TGF-β, and elevated glucose concentrations mimicked diabetic nephropathy in vitro, as well as in mouse diabetic nephropathy models in vivo. Consistently, up-regulation of miR-377 led to reduced expression of p21-activated kinase and superoxide dismutase, which enhanced fibronectin protein production [Wang et al., 2008]. As fibronectin is a key matrix protein that accumulates in excess in diabetic nephropathy, miR-377 may have a critical role in the pathophysiology of diabetic nephropathy.

It has been confirmed that miR-377 can regulate HMOX1 expression [Beckman et al., 2011]. However, it remains to be determined whether HMOX1 is able to regulate the expression of miR-377. What is the mechanism? Does HMOX1 play a role as a transcription factor or does it interact with other transcription factor to regulate miR-377 expression? Perhaps HMOX1 mRNA molecules downstream serve as miRNA sponges that regulate miR-377 expression. However, the details of the mechanism remain unknown.

## THE FEEDBACK LOOP BETWEEN MIR-328 AND HMOX1 IN MITOCHONDRIA DYSFUNCTION DISEASE

Mitochondria are fundamental to survival and proper functioning of cells. These organelles play a key role in energy production, in maintaining homeostatic levels of second messengers (such as reactive oxygen species and calcium) and in the coordination of apoptotic cell death [Mayer and Oberbauer, 2003]. Dysfunction of the mitochondria is involved in a variety of diseases, including Alzheimer′s disease (AD) [Hauptmann et al., 2009].

AD is characterized by the accumulation of plaques formed of short β-amyloid (Aβ) peptides in the hippocampal region of the brain. Aβ peptides are produced upon proteolytic cleavage of β-site APP-cleaving enzyme 1 (BACE1), which contributes to the formation of these plaques [Cai et al., 2012]. Recent evidence suggests that mitochondrial dysfunction is a common early pathogenic mechanism in AD, integrating genetic factors related to enhanced Aβ production and tau-hyperphosphorylation with aging, as the most relevant sporadic risk factor [Calkins et al., 2012]. Oxidative damage to the mitochondrial DNA (mtDNA) as a determining event occurs during aging [Santos et al., 2012], which may cause or potentiate mitochondrial dysfunction and favor neurodegenerative events.

Recent evidence showed that miRNAs could regulate mitochondrial function. miR-484 can suppress translation of the mitochondrial fission protein Fis1 and inhibit Fis1-mediated fission and apoptosis during myocardial infarction [Wang et al., 2012]. miR-494 was shown to regulate mitochondrial biogenesis in skeletal muscle through mitochondrial transcription factor A [Yamamoto et al., 2012]. miR-499 was shown to regulate mitochondrial dynamics by targeting calcineurin and dynamin-related protein-1, inhibiting cardiomyocyte apoptosis [Wang et al., 2011].

miR-328 was shown to be down regulated in AD patients [Provost, 2010], while HMOX1 protein levels are significantly increased. Although a high level of HMOX1 was initially proposed as a neuroprotective system in the brains of AD patients, some groups proposed the observed increase of HMOX1 in AD brain as a possible neurotoxic mechanism [Schipper, 2011]. The hypothesis of the feedback loop between miR-328 and HMOX1 allows for the interpretation of the complex role of HMOX1 in AD. We proposed that miR-328 could regulate HMOX1 expression at the post-transcriptional level by targeting the HMOX1 3′UTR and up-regulating HMOX1 expression,

promoting its entry into the nucleus or mitochondria. HMOX1 may serve as a transcription factor or it may interact with other transcription factors to affect the expression of genes related to apoptosis. The investigation of these possibilities will give insight into whether HMOX1 regulates miR-328 directly or indirectly. Moreover, the mitochondrial genome includes miRNA and pre-miRNA coding sequences, and experiment data have confirmed that many pre-miRNAs and mature miRNAs (including miR-328) in exist in the human mitochondrial genome [Eric et al., 2011]. There may be some unidentified interaction or functional relationship between miR-328 and HMOX1 in the mitochondria.

A similar mechanism may exist in cancer, which is also a disease of mitochondrial dysfunction [de Moura et al., 2010]. The tumor repressors miR-128, miR-22, miR-218, and miR-328 were shown to be down-regulated in many malignant tumors (Table I), and HMOX1 is a potential target of these miRNAs. The balance of miRNAs and HMOX1 may contribute to the adverse effects of HMOX1 in different tumors.

## CONCLUSION

In summary, the balance between miRNAs and HMOX1 should not be ignored. This balance is an important component of HMOX1 function that involves a regulatory feedback loop between miRNA and HMOX1. However, the feedback loop may be limited by the diversity of tissues and species. Mitochondrial HO activity has been reported in the liver of rodents infected with *Plasmodium berghei* or treated with the HMOX1 inducer cobalt chloride, but this activity was absent in ox heart mitochondria [Converso et al., 2006], a discrepancy most likely explained on the basis of species and/or organ differences. The mechanism needs to be investigated in a specific context.

## REFERENCES


Arvey A, Larsson E, Sander C, Leslie CS, Marks DS. 2010. Target mRNA abundance dilutes microRNA and siRNA activity. Mol Syst Biol 6:363.

Beckman JD, Chen C, Nguyen J, Thayanithy V, Subramanian S, Steer CJ, Vercellotti GM. 2011. Regulation of heme oxygenase-1 protein expression by miR-377 in combination with miR-217. J Biol Chem 286(5):3194–3202.doi: 10.1074/jbc.M110.148726. Epub 2010 Nov 24.

Bindu S, Pal C, Dey S, Goyal M, Alam A, Iqbal MS, Dutta S, Sarkar S, Kumar R, Maity P, Bandyopadhyay U. 2011. Translocation of heme oxygenase-1 to mitochondria is a novel cytoprotective mechanism against non-steroidal anti-inflammatory drug-induced mitochondrial oxidative stress, apoptosis, and gastric mucosal injury. J Biol Chem 286(45):39387–39402.doi: 10.1074/jbc.M111.279893. Epub 2011 Sep 9.

Boschetto P, Zeni E, Mazzetti L, Miotto D, Lo Cascio N, Maestrelli P, Marian E, Querzoli P, Pedriali M, Murer B, De Rosa E, Fabbri LM, Mapp CE. 2008. Decreased heme-oxygenase (HO)-1 in the macrophages of non-small cell lung cancer. Lung Cancer 59(2):192–197.Epub 2007 Sep 27.

Cai Y, Zhang XM, Macklin LN, Cai H, Luo XG, Oddo S, Laferla FM, Struble RG, Rose GM, Patrylo PR, Yan XX. 2012. BACE1 elevation is involved in amyloid plaque development in the triple transgenic model of Alzheimer's disease: Differential Aβ antibody labeling of early-onset axon terminal pathology. Neurotox Res 21(2):160–174.doi: 10.1007/s12640-011-9256-9. Epub 2011 Jul 2.

Calkins MJ, Manczak M, Reddy PH. 2012. Mitochondria-targeted antioxidant SS31 prevents amyloid beta-induced mitochondrial abnormalities and synaptic degeneration in Alzheimer's disease. Pharmaceuticals (Basel) 5(10): 1103–1119.

Chen L, Zhang R, Li P, Liu Y, Qin K, Fa ZQ, Liu YJ, Ke YQ, Jiang XD. 2012. P53-induced microRNA-107 inhibits proliferation of glioma cells and down-regulates the expression of CDK6 and Notch-2. Neurosci Lett pii: S0304-3940 (12)01516-9. doi: 10.1016/j.neulet.2012.11.047. [Epub ahead of print].

Converso DP, Taillé C, Carreras MC, Jaitovich A, Poderoso JJ, Boczkowski J. 2006. HMOX1 is located in liver mitochondria and modulates mitochondrial heme content and metabolism. FASEB J 20(8):1236–1238.Epub 2006 May 3.

Correa-Costa M, Semedo P, Monteiro AP, Silva RC, Pereira RL, Gonçalves GM, Marques GD, Cenedeze MA, Faleiros AC, Keller AC, Shimizu MH, Seguro AC, Reis MA, Pacheco-Silva A, Câmara NO. 2010. Induction of heme oxygenase-1 can halt and even reverse renal tubule-interstitial fibrosis. PLoS ONE 5(12): e14298.doi: 10.1371/journal.pone.0014298

de Moura MB, dos Santos LS, Van Houten B. 2010. Mitochondrial dysfunction in neurodegenerative diseases and cancer. Environ Mol Mutagen 51(5):391–405.doi: 10.1002/em.20575

Eiring AM, Harb JG, Neviani P, Garton C, Oaks JJ, Spizzo R, Liu S, Schwind S, Santhanam R, Hickey CJ, Becker H, Chandler JC, Andino R, Cortes J, Hokland P, Huettner CS, Bhatia R, Roy DC, Liebhaber SA, Caligiuri MA, Marcucci G, Garzon R, Croce CM, Calin GA, Perrotti D. 2010. miR-328 functions as an RNA decoy to modulate hnRNP E2 regulation of mRNA translation in leukemic blasts. Cell 140(5):652–665.doi: 10.1016/j.cell.2010.01.007

Barrey E, Saint-Auret G, Bonnamy B, Damas D, Boyer O, Gidrol X. 2011. Pre-microRNA and mature microRNA in human mitochondria. PLoS ONE 6(5): e20220.doi: 10.1371/journal.pone.0020220

Faller M, Matsunaga M, Yin S, Loo JA, Guo F. 2007. Heme is involved in microRNA processing. Nat Struct Mol Biol 14(1):23–29.Epub 2006 Dec 10.

Gandini NA, Fermento ME, Salomón DG, Blasco J, Patel V, Gutkind JS, Molinolo AA, Facchinetti MM, Curino AC. 2012. Nuclear localization of heme oxygenase-1 is associated with tumor progression of head and neck squamous cell carcinomas. Exp Mol Pathol 93(2):237–245.doi: 10.1016/j.yexmp.2012.05.001. Epub 2012 May 8.

Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JT, Dang CV. 2009. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature 458(7239):762–765.doi: 10.1038/nature07823. Epub 2009 Feb 15.

Gong X, Zhang L, Jiang R, Ye M, Yin X, Wan J. 2012. Anti-inflammatory effects of mangiferin on sepsis-induced lung injury in mice via up-regulation of heme oxygenase-1. J Nutr Biochem doi: 10.1016/j.jnutbio.2012.09.003. [Epub ahead of print].

Hamedi-Asl P, Halabian R, Bahmani P, Mohammadipour M, Mohammadzadeh M, Roushandeh AM, Jahanian-Najafabadi A, Kuwahara Y, Roudkenar MH. 2012. Adenovirus-mediated expression of the HMOX1 protein within MSCs decreased cytotoxicity and inhibited apoptosis induced by oxidative stresses. Cell Stress Chaperones 17(2):181–190.doi: 10.1007/s12192-011-0298-y. Epub 2011 Oct 13.

Hauptmann S, Scherping I, Dröse S, Brandt U, Schulz KL, Jendrach M, Leuner K, Eckert A, Müller WE. 2009. Mitochondrial dysfunction: An early event in Alzheimer pathology accumulates with age in AD transgenic mice. Neurobiol Aging 30(10):1574–1586.doi: 10.1016/j.neurobiolaging.2007.12.005. Epub 2008 Mar 4.

Hayama T, Tabata K, Uchiyama T, Fujimoto Y, Suzuki T. 2011. Ferrearin C induces apoptosis via heme oxygenase-1 (HMOX1) induction in neuroblastoma. J Nat Med 65(3–4):431–439.doi: 10.1007/s11418-011-0514-1. Epub 2011 Feb 15.

Hewitson TD. 2012. Fibrosis in the kidney: Is a problem shared a problem halved? Fibrogenesis Tissue Repair 5(Suppl.1):S14 [Epub ahead of print].

Hou W, Tian Q, Steuerwald NM, Schrum LW, Bonkovsky HL. 2012. The let-7 microRNA enhances heme oxygenase-1 by suppressing Bach1 and attenuates oxidant injury in human hepatocytes. Biochim Biophys Acta 1819(11–12):1113–1122.doi: 10.1016/j.bbagrm.2012.06.001. [Epub ahead of print].

Jozkowicz A, Was H, Dulak J. 2007. Heme oxygenase-1 in tumors: Is it a false friend? Antioxid Redox Signal 9(12):2099–2117.

Li Y, Lin L, Li Z, Ye X, Xiong K, Aryal B, Xu Z, Paroo Z, Liu Q, He C, Jin P. 2012. Iron homeostasis regulates the activity of the microRNA pathway through poly(C)-binding protein 2. Cell Metab 15(6):895–904.doi: 10.1016/j.cmet.2012.04.021. Epub 2012 May 24.

Mayer B, Oberbauer R. 2003. Mitochondrial regulation of apoptosis. News Physiol Sci 18:89–94.

Mizuno K, Toma T, Tsukiji H, Okamoto H, Yamazaki H, Ohta K, Ohta K, Kasahara Y, Koizumi S, Yachie A. 2005. Selective expansion of CD16 high CCR2—Subpopulation of circulating monocytes with preferential production of heme oxygenase (HO)-1 in response to acute inflammation. Clin Exp Immunol 142(3):461–470.doi: 10.1111/j.1365-2249.2005.02932.x

Provost P. 2010. Interpretation and applicability of microRNA data to the context of Alzheimer's and age-related diseases. Aging (Albany NY) 2(3): 166–169.

Pulkkinen KH, Ylä-Herttuala S, Levonen AL. 2011. Heme oxygenase 1 is induced by miR-155 via reduced BACH1 translation in endothelial cells. Free Radic Biol Med 51(11):2124–2131.doi: 10.1016/j.freeradbiomed.2011.09.014. Epub 2011 Sep 17.

Qin W, Shi Y, Zhao B, Yao C, Jin L, Ma J, Jin Y. 2010. miR-24 regulates apoptosis by targeting the open reading frame (ORF) region of FAF1 in cancer cells. PLoS ONE 5(2):e9429.doi: 10.1371/journal.pone.0009429

Ryter SW, Alam J, Choi AM. 2006. Heme oxygenase-1/carbon monoxide: From basic science to therapeutic applications. Physiol Rev 86(2):583–650.

Santos RX, Correia SC, Zhu X, Smith MA, Moreira PI, Castellani RJ, Nunomura A, Perry G. 2013. Mitochondrial DNA oxidative damage and repair in aging and Alzheimer's disease. Antioxid Redox Signal. 18(18):2444–2457.

Schipper HM. 2011. Heme oxygenase-1 in Alzheimer disease: A tribute to Moussa Youdim. J Neural Transm 118(3):381–387.doi: 10.1007/s00702-010-0436-1. Epub 2010 Jun 20.

Siemens H, Jackstadt R, Hünten S, Kaller M, Menssen A, Götz U, Hermeking H. 2011. miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial–mesenchymal transitions. Cell Cycle 10(24):4256–4271.doi: 10.4161/cc.10.24.18552. Epub 2011 Dec 15.

Sylvestre Y, De Guire V, Querido E, Mukhopadhyay UK, Bourdeau V, Major F, Ferbeyre G, Chartrand P. 2007. An E2F/miR-20a autoregulatory feedback loop. J Biol Chem 282(4):2135–2143.Epub 2006 Nov 29.

Tan X, Wang S, Yang B, Zhu L, Yin B, Chao T, Zhao J, Yuan J, Qiang B, Peng X. 2012. The CREB-miR-9 Negative feedback minicircuitry coordinates the migration and proliferation of glioma cells. PLoS ONE 7(11):e49570.doi: 10.1371/journal.pone.0049570. Epub 2012 Nov 20.

Tay Y, Zhang J, Thomson AM, Lim B, Rigoutsos I. 2008. MicroRNAs to Nanog, Oct4 and Sox2 coding regions modulate embryonic stem cell differentiation. Nature 455(7216):1124–1128.doi: 10.1038/nature07299. Epub 2008 Sep 17.

Tsai JR, Wang HM, Liu PL, Chen YH, Yang MC, Chou SH, Cheng YJ, Yin WH, Hwang JJ, Chong IW. 2012. High expression of heme oxygenase-1 is associated with tumor invasiveness and poor clinical outcome in non-small cell lung cancer patients. Cell Oncol (Dordr) 35(6):461–471.doi: 10.1007/s13402-012-0105-5. Epub 2012 Oct 10.

Uchiyama K, Naito Y, Takagi T, Mizushima K, Hayashi N, Harusato A, Hirata I, Omatsu T, Handa O, Ishikawa T, Yagi N, Kokura S, Yoshikawa T. 2010. Carbon monoxide enhance colonic epithelial restitution via FGF15 derived from colonic myofibroblasts. Biochem Biophys Res Commun 391(1):1122–1126. doi: 10.1016/j.bbrc.2009.12.035. Epub 2009 Dec 11.

Wang Q, Wang Y, Minto AW, Wang J, Shi Q, Li X, Quigg RJ. 2008. MicroRNA-377 is up-regulated and can lead to increased fibronectin production in diabetic nephropathy. FASEB J 22(12):4126–4135.doi: 10.1096/fj.08-112326. Epub 2008 Aug 20.

Wang JX, Jiao JQ, Li Q, Long B, Wang K, Liu JP, Li YR, Li PF. 2011. miR-499 regulates mitochondrial dynamics by targeting calcineurin and dynamin-related protein-1. Nat Med 17(1):71–78.doi: 10.1038/nm.2282. Epub 2010 Dec 26.

Wang K, Long B, Jiao JQ, Wang JX, Liu JP, Li Q, Li PF. 2012. miR-484 regulates mitochondrial network through targeting Fis1. Nat Commun 3:781.doi: 10.1038/ncomms1770

Yamamoto H, Morino K, Nishio Y, Ugi S, Yoshizaki T, Kashiwagi A, Maegawa H. 2012. MicroRNA-494 regulates mitochondrial biogenesis in skeletal muscle through mitochondrial transcription factor A and Forkhead box j3. Am J Physiol Endocrinol Metab 303(12):E1419–E1427.doi: 10.1152/ajpendo.00097.2012. Epub 2012 Oct 9.

Younger ST, Corey DR. 2011. Transcriptional gene silencing in mammalian cells by miRNA mimics that target gene promoters. Nucleic Acids Res 39 (13):5682–5691.doi: 10.1093/nar/gkr155. Epub 2011 Mar 22.

Zarjou A, Agarwal A. 2012. Heme oxygenase-1 as a target for TGF-β in kidney disease. Semin Nephrol 32(3):277–286.doi: 10.1016/j.semnephrol.2012.04.007

Zhao J, Tan S, Liu F, Zhang Y, Su M, Sun D. 2012. Heme oxygenase and ocular disease: A review of the literature. Curr Eye Res 37(11):955–960.doi: 10.3109/02713683.2012.700753. Epub 2012 Jun 21.