

Altered miRNA Maturation in Ischemic Hearts: Implication of Hypoxia on XPO5 and DICER1

Dysregulation and RedoximiR State

Table S1. miRNAs regulating antioxidant responses and/or being regulated by ROS (redoximiRs) analysed.

miRNA	Molecular target	Function	Reference
miR-101-3p	Cul3	Hypoxia elevates the expression of miR-101 which inhibited the expression of cul3. A reduction in the level of Cul3 activates the Nrf2/HO-1 axis	[1]
miR-122-5p	CDK4-PSMD10 pathway	miR-122 negatively regulates the UPR through the CDK4-PSMD10 pathway	[2,3]
miR-124-3p	CYBB	miR-124-3p negatively regulate CYBB expression and NOX2 protein level. miR-124-5p/NOX2 axis modulates NOX-mediated ROS production	[4]

miR-125b-1-3p		miR-125b-1-3p acts as a cardioprotector in ischemia-reperfusion injury	[5,6]
miR-128-3p	MAFG	miR-128 expression is modulated by hypoxic conditions and negatively regulates the expression of MAFG and could affect MAFG-related genes such as HMOX-1 and x-CT	[7]
miR-130a-3p	APE1	Lower miR-130a could generate a more extensive response to oxidative stress, which in turn could elevate Ape1	[8]
miR-132	TGF- β 1 smad3	miR-132 inhibits oxidative stress and apoptosis and decreases the expression of TGF- β 1	[9]

		and smad3	
miR-141	ZEB1 targets miR-141	miR-141 is upregulated by oxidative stress and is inhibited by ZEB1	[10]
miR-144-3p	NFR2	miR-144 reduce nuclear factor-erythroid 2-related factor 2 (NRF2) and is also associated with decreased glutathione regeneration and attenuated antioxidant capacity	[11]
miR-145	SGK1	HIF-1a, under hypoxic conditions, induces overexpression of miR-145. miR-145 protects against hypoxic damage, inducing SGK1 expression	[12]
miR-146a	Catalase	miR-146a mediates catalase suppression	[13]

		in the absence of RIP1	
miR-153	Nrf2	miR-153 is up-regulated in oxidative stress conditions and represses Nrf2	[14]
miR-155-5p	Dicer targets miR-155 miR-155 targets HK2	miR-155 is regulated by Dicer during chronic hypoxia, and activates HK2 expression and glycolysis	[15]
miR-181a-5p	Bcl-2	miR-181a is induced by H ₂ O ₂ and suppresses Bcl-2 expression	[16]
miR-185-5p		Hypoxia induces miR-185 expression. miR-185 inhibits the DNA damage-induced 14-3-3 δ signalling pathway	[17]
miR-191-5p	C/EBP β	miR-191 is induced by hypoxia and represses	[18]

		CCAAT/enhancer binding protein β (C/EBP β)	
miR-196b-5p	Bach-1	miR-196 down-regulated Bach1 and up-regulated HMOX1 gene expression, and inhibited HCV expression	[19]
miR-199	Hif-1 α Sirt1	miR-199 is downregulated during hypoxia and inhibits Hif-1 α and Sirt1 expression	[20]
miR-200a-3p	keap1	miR-200a regulates the Keap1/Nrf2 pathway	[21]
miR-200b		miRNA-200b expression is decreases by hypoxia	[22]
miR-200c-3p	ZEB/miR-200 double-negative feedback loop	ZEB factors transcriptionally repress miR-200 family members and these inhibit ZEB	[23]

		expression at the post-transcriptional level. miR-200c is upregulated by oxidative stress	
miR-206	SOD1	miR-206 inhibits SOD1 expression, promoting ROS production	[24]
miR-21-5p	NF-κB targets miR-21 miR-21 targets PDCD4	NF-κB positively regulated miR-21 expression under oxidative stress, and PDCD4 was a direct target for miR-21	[25]
miR-210-3p	Several pathways related to the low cellular oxygen	miR-210-3p was highly up-regulated in the nuclear compartment after hypoxic stimulus	[26]
miR-212-3p	SOD2	miR-212-3p inhibits SOD2 expression, promoting ROS production	[27]
miR-23b-5p	POX	miR-23b-5p inhibits	[28]

		POX expression. POX induces apoptosis through the generation of ROS and decreasing HIF signalling	
miR-24-3p	HMOX-1 Cellular survival pathways (e.g., AKT and ERK)	miR-24 is a hypoxia-sensitive miRNA, represses HMOX-1 expression and induces apoptosis and oxidative stress	[29]
miR-25-3p	MITF SCF bFGF	Oxidative stress could induce the overexpression of miR-25 that reduced the expression of MITF, SCF and bFGF	[30]
miR-26a-5p	PTEN	miR-26a is inhibited by H ₂ O ₂ , protects against H ₂ O ₂ -induced injury by targeting PTEN and prevents H ₂ O ₂ -induced apoptosis through re-	[31]

		activation of the Akt/mTOR pathway	
miR-27a-3p miR-27b-3p	PHB1 Nrf2	miR27a and miR27b downregulate Nrf2 and PHB1 expression induced by c-Myc	[32]
miR-27b-5p	NF-kB	H ₂ O ₂ inhibits the expression of miR-27b and it supresses NF-kB pathway	[33]
miR-30b-5p	Catalase	H ₂ O ₂ upregulated the expression of miR-30b-5p, which inhibited the expression of endogenous catalase	[34]
miR-31-5p	SIRT3	miR-31 targets SIRT3 to repress its expression, being involved in ROS regulation	[35]
miR-34a-5p	Sirt1 Mgst1 Sp1 Nrf2	miR-34a represses expression, of Sirt1 and Mgst1 and its upstream	[36]

		transcription factors Sp1 and Nrf2	
miR-34b miR-34c-5p	DJ-1 PARKIN	miR-34b and miR-34c reduction results in a decreased expression of DJ1 and PARKIN, and is associated with mitochondrial dysfunction and reactive oxygen species production	[37]
miR-361-3p	caspase-2/-8/-9	Hypoxia decreased miR-361-3p expression, and it overexpression mitigated hypoxia injury by inhibiting apoptosis via targeting apoptosis initiators caspase-2/- 8/-9	[38]
miR-370-3p	MGMT	miR-370-3p downregulates MGMT gene expression and	[39]

		inhibits DNA repair	
miR-382-5p	PTEN	Hypoxia and HIF-1 α induce the expression of miR-382-5p. miR-382-5p inhibits PTEN levels and stimulates the AKT/mTOR signalling pathway	[40]
miR-424-5p	CUL2	Hypoxia increases miR-424 that targets cullin 2 (CUL2) stabilizing HIF- α	[41]
miR-429	HIF1A	miR-429 expression is induced by HIF-1 and by hypoxia. miR-429 inhibits HIF1A and indirectly affects VEGFA mRNA	[42]
miR-433-3p	γ -glutamyl-cysteine ligase	miR-433 decreases glutathione levels by targeting glutamate cysteine ligase; increases oxidative stress	[43]
miR-4673	OGG1	miR-4673	[44]

		downregulates OGG1 levels, inducing ROS production	
miR-506-3p	NF-κB p65 P53 targets miR-506-3p	miR-506 inhibits NF-κB p65 expression, induces ROS accumulation, and then activates p53. In addition, p53 promotes miR-506 expression level, indicating that miR-506 mediates cross-talk between p53, NF-κB p65 and ROS	[45]
miR-509-5p	SOD2	miR-509-5p inhibits SOD2	[46]
miR-551b-3p	Catalase	miR-551b-3p inhibited the expression of catalase and potentiated ROS accumulation	[47]
miR-765	VEGFA	miR-765 was severely downregulated after	[48]

		hypoxia and decreases the levels of VEGFA, AKT1 and SRC- α	
miR-9-5p	NOX4 TGFBR2	miR-9-5p is up-regulated in oxidative stress conditions and inhibits TGFBR2 and NOX4	[49]
miR-92b-3p	TSC1	miR-92b-3p is upregulated by hypoxia and suppresses TSC1 expression	[50]

miRNAs highlighted in bold have altered expression in patients with ischemic cardiomyopathy compared to the control group. The molecular target and functions described here are focused on those that relate miRNA, its biogenesis and oxidative stress.

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