MicroRNAs in Human Retinal Endothelial Cells as Therapeutic Targets for Diabetic Retinopathy #4049649

OU WB EYE RESEARCH CENTER

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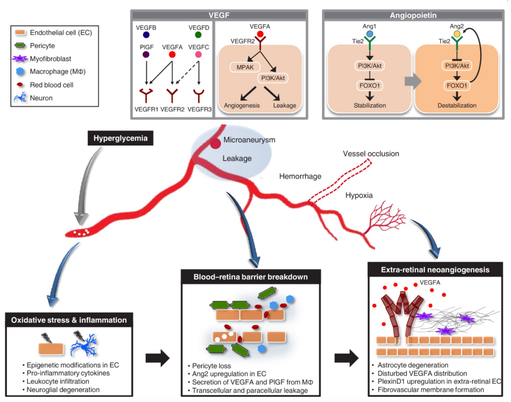
BACKGROUND

Diabetic Retinopathy (DR), a microvascular complication of diabetes, stands as the leading cause of vision impairment among middle-aged adults. Current treatments primarily focus on symptom management and preventing further damage, including intravitreal injection of anti-VEGF agents, laser photocoagulation, and vitreous surgery. However, these interventions are invasive and often only stabilize visual acuity rather than improve it.

MiRNAs (MicroRNAs) have recently emerged as significant regulators of gene expression and are implicated in the pathogenesis of various diseases, including DR. Several miRNA profiling studies have been conducted to identify dysregulated miRNAs associated with DR. The altered expression of specific miRNAs has been linked to crucial processes such as angiogenesis, inflammation, and oxidative stress, which are critical contributors to the development of diabetic retinopathy.



Kusuhara, S., Fukushima, Y., Ogura, S., Inoue, N., & Uemura, A. Pathophysiology of Diabetic Retinopathy: The Old and the New. *Diabetes & Metabolism Journal, 42*, 364 - 376 (2018).

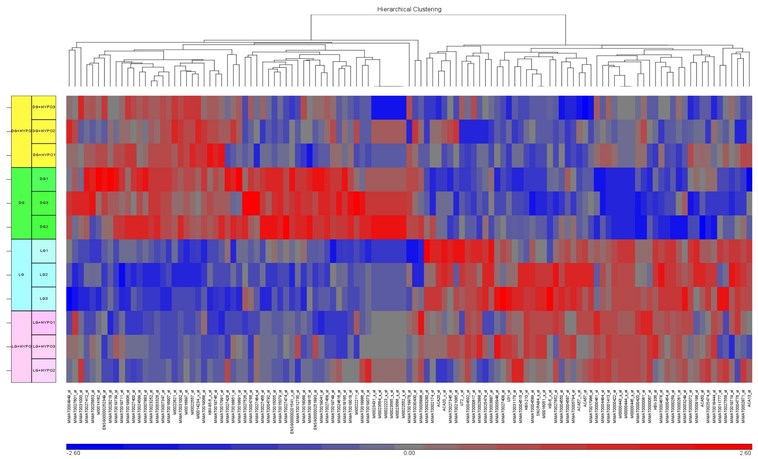
PURPOSE

Epigenetic modifications, especially miR alterations, play a crucial role in driving retinal endothelial cell dysfunction and subsequent angiogenesis in DR. This study aims to explore the impact of hyperglycemia and hypoxia on miRNA expression in Human Retinal Endothelial Cells (HRECs) to identify potential targets for DR treatment.

METHODS

HRECs were treated with high glucose (HG, 25mM D-glucose), hypoxia (1% oxygen), or a combination of HG and hypoxia for 5 days. Osmotic control (OC, 5 mM D-glycose + 20mM L-glucose) and normoxia (21% O2) served as control conditions.

ALTERATIONS OF miRNA DIFFERENTIAL PROFILE UNDER MULTIPLE CONDITIONS



Effect of High Glucose compared to Osmotic Control

Transcript ID	p-value	Fold-Change(HG vs. OC)
hsa-miR-124-3p	5.42576E-06	-22.3641
hsa-mir-124-1	3.18813E-06	-12.6373
hsa-mir-124-2	3.18813E-06	-12.6373
hsa-mir-124-3	3.18813E-06	-12.6373
hsa-miR-183-5p	0.0132162	-5.09566
hsa-miR-99b-3p	0.00594927	-3.63081
hsa-miR-30b-5p	0.0161553	-2.71616
hsa-miR-505-5p	0.00893086	-2.67664
hsa-miR-184	0.000560798	-2.57545
hsa-let-7d-3p	0.00601898	-2.51255
hsa-miR-30c-2-3p	0.0148683	-2.43018
hsa-miR-27b-5p	0.00735847	-2.42614
hsa-miR-20b-5p	0.0308006	-2.37318
hsa-miR-25-3p	0.00306777	-2.0272
hsa-miR-18a-5p	0.0181514	-2.01464
hsa-miR-8075	0.0138536	2.12494
hsa-miR-4710	0.000715855	2.24883
hsa-miR-4668-5p	0.00182959	2.29957
hsa-mir-4530	0.00493836	2.42153

Effect of Hypoxia compared to Normoxia

Transcript ID	p-value	Fold-Change(HYPO vs. Normoxia)
hsa-miR-4284	0.000928847	-3.6126
hsa-miR-145-5p	0.02478	-3.06222
hsa-miR-1301-3p	0.0206949	-2.6587
hsa-miR-99b-3p	0.0147022	-2.3881
hsa-miR-296-3p	0.00310225	-2.32097
hsa-miR-128-3p	0.00911593	2.04293
hsa-miR-619-5p	0.0271116	2.27355

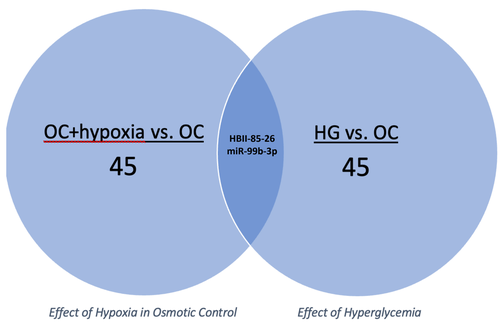
Effect of High Glucose + Hypoxia compared to High glucose

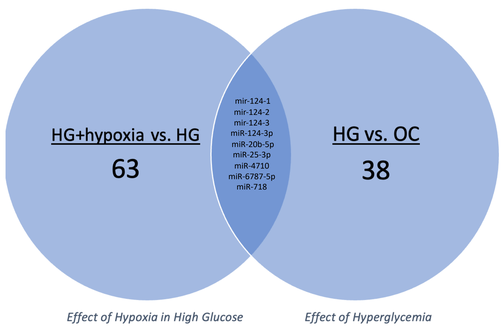
Transcript ID	p-value	Fold-Change(HG+HYPO vs. HG)
hsa-miR-328-3p	0.0356648	-3.19753
hsa-miR-339-5p	0.00192865	-2.41427
hsa-miR-6813-5p	0.026034	-2.39662
hsa-miR-4443	0.00212588	-2.3297
hsa-miR-25-5p	0.0278626	-2.02045
hsa-miR-93-3p	0.0418656	-2.00048
hsa-miR-4776-5p	0.0203907	2.0046
hsa-mir-124-1	0.00704811	3.1611
hsa-mir-124-2	0.00704811	3.1611
hsa-mir-124-3	0.00704811	3.1611
hsa-miR-124-3p	0.00307205	4.12363

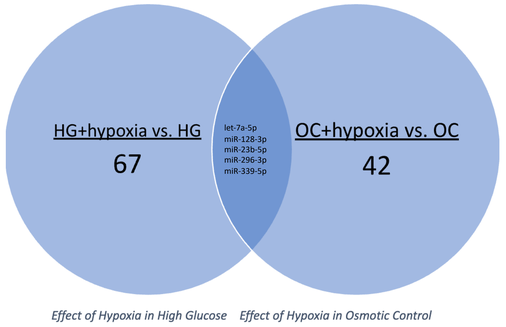
Effect of High Glucose + Hypoxia Compared to Hypoxia

Transcript ID	p-value	Fold-Change(HG+HYPO vs. HYPO)
hsa-miR-619-5p	0.00421437	-3.95706
hsa-miR-124-3p	0.0160349	-3.31291
hsa-miR-93-3p	0.00794435	-3.04852
hsa-miR-7975	0.000926826	-2.82183
hsa-miR-671-3p	0.00273357	-2.78203
ACA3-2	0.0326311	-2.49769
hsa-miR-3607-5p	0.0200195	-2.4199
hsa-miR-1296-5p	0.0223985	-2.40811
hsa-miR-125a-3p	0.00535701	-2.36875
hsa-miR-501-3p	0.0325452	-2.3557
hsa-miR-628-3p	0.0377146	-2.29164
ACA8	0.0226883	-2.26455
hsa-miR-2467-3p	0.0306876	-2.24756
hsa-miR-330-3p	0.0354936	-2.21875
hsa-miR-4485	0.04258	-2.19499
hsa-miR-181a-3p	0.00516402	-2.19402
hsa-miR-1290	0.019665	-2.13676
hsa-miR-23b-5p	0.00141749	-2.11608
hsa-miR-4646-5p	0.0146858	-2.09489
hsa-let-7f-5p	0.00303312	-2.08505
hsa-mir-6876	0.0216511	-2.07035
U31	0.00698021	-2.05215
hsa-mir-124-1	0.0373991	-2.03487
hsa-mir-124-2	0.0373991	-2.03487
hsa-mir-124-3	0.0373991	-2.03487
hsa-miR-6737-5p	0.0104671	-2.03
hsa-miR-6849-5p	0.00138173	-2.01314
HBII-85-6	0.0271733	2.0053
hsa-miR-8075	9.98016E-05	2.05239
hsa-miR-6750-5p	0.0226518	2.07579
hsa-mir-6722	0.0018439	2.09119
hsa-miR-4668-5p	0.0162327	2.23391
hsa-miR-1184	0.012028	2.97018

miRNA's MUTUALLY AFFECTED UNDER MULTIPLE CONDITIONS







GENES RELATED TO DIABETIC RETINOPATHY

Top MiRs Hypoxia+HG	P-value	Fold Change	Genes Related to Diabetic Retinopathy
miR-124-3p	1.20E-04	4.1	CCL2, CTGF, EDN1, IL6, PRKCB, PTGS2, ROCK2, SERPINE1, SP1, TIMP3
mir-20b-5p	7.54E-05	2.0	HIF1A, PPARG, VEGFA, ITGA2, SOD2, PRKCB
miR-25-3p	2.40E-04	1.7	FGF2
miR-718	0.003	-1.7	VEGFA
miR-4710	-0.03	-1.8	EDN1, SPARK
miR-296-3p	0.003	-1.8	ICAM1
miR-145-5p	0.05	-2.0	HIF1A, SERPINE1, CTGF, AKR1B10, SP1, VCAM1
miR-339-5p	3.58E-05	-2.4	SOD2
miR-4284	5.40E-04	-3.6	HIF1A, GDNF, SOD2

Dweep, H et al. miRWalk2.0: a comprehensive atlas of microRNA-target interactions, Nature Methods, 12(8): 697-697 (2015). (Nature Methods, Pubmed)

CONCLUSION

Pathological neovascularization in hyperglycemic conditions is significantly influenced by hypoxia. Exposure to high glucose and hypoxia induces substantial dysregulation of multiple miRNAs in HRECs, with some demonstrating distinct effects while others respond similarly, all crucial in angiogenesis regulation. This highlights the role of aberrant miRNA expression in the mechanisms underlying diabetic retinopathy (DR) pathogenesis. Particularly noteworthy is the upregulation of miR-124-3p, exhibiting the highest fold change (+4.1) under HG + hypoxia conditions. Previous studies have associated this miRNA with numerous genes implicated in diabetic retinopathy, suggesting it as a promising target for future DR treatment development.

ACKNOWLEDGEMENT

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