Vitamin C Reduces IGF-1 and VEGF Signaling in Retinal Endothelial Cells

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Purpose

Glucose acts as a competitive inhibitor for vitamin C, an important cofactor for DNA methylation, when crossing the blood retinal barrier. The purpose is to investigate potential role of vitamin C in gene expression pathways that may lead to the development of diabetic retinopathy.

Methods

- Primary, human retinal endothelial cells were treated either with or without 50 µM vitamin C.
- RNA was extracted and RNA-seq was used to determine transcription changes.
- Pathway analysis was performed using EnrichR, Gorilla, and Gene Set Enrichment Analysis (GSEA).

Results

437 genes upregulated and 308 genes downregulated transcription after treatment with vitamin C. Several pathways that may contribute to the pathogenesis of diabetic retinopathy were down regulated including IGF-1 and VEGF signaling in retinal endothelial cells.

Discussion

Although the contribution of IGF-1 to diabetic retinopathy has been largely attributed to stimulation of production of vascular endothelial growth factor A (VEGFA) in retinal pigment epithelial cells (RPE), knockout of IGF-1 receptors in retinal vascular endothelial cells was shown to reduce neovascularization in an oxygen-induced retinopathy mouse model. New blood vessels from proliferative diabetic retinopathy have been found to regress after anti-VEGF treatments, and anti-VEGF is similar in efficiency to panretinal photocoagulation of the blood retinal barrier in diabetic retinopathy.

Conclusion

Local vitamin C deficiencies in the eyes of diabetics affect signaling in the retinal endothelial cells which may contribute to the breakdown of the blood-retinal barrier in diabetic retinopathy.

Works Cited

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Vitamin C regulates pathways related to diabetic retinopathy

Term	Database	Database ID	EnrichR	GSEA	GOrilla
Cellular response to vascular endothelial growth factor stimulus	GO Bio Process	GO:0035924	0.036	0.052	N/A
Leukocyte adhesion to vascular endothelial cell	GO Bio Process	GO:0061756	0.046	0.053	0.019
Leukocyte tethering or rolling	GO Bio Process	GO:0050901	0.042	0.020	0.016
Negative regulation of endothelial cell migration	GO Bio Process	GO:0010596	0.045	0.000	N/A
Transport across blood-brain barrier	GO Bio Process	GO:0150104	0.040	0.036	N/A
Insulin-like growth factor binding	GO Molecular Function	GO:0005520	0.008	0.005	2.16E-04
Insulin-like growth factor I binding	GO Molecular Function	GO:0031994	0.032	0.008	0.003
VEGF-A complex	Jensen Compartments		2.69E-06	0.000	N/A
Diabetic retinopathy	Jensen Diseases		0.015	0.005	N/A
Hypoxia	MSigDB Hallmark 2020	M5891	2.15E-04	0.006	N/A
Inflammatory Response	MSigDB Hallmark 2020	M5932	0.035	0.121	N/A
Neovascularisation processes WP4331	WIKI	WP4331	3.54E-04	0.016	N/A
VEGFA-VEGFR2 Signaling Pathway	WIKI	WP3888	3.95E-04	0.000	N/A
Regulation of endothelial cell migration	GO Bio Process	GO:0010594	0.015	0.000	0.004

Table 1. Table of pathways significantly downregulated in expression after treatment with vitamin c. All p-values are adjusted with the Banjamini-Hocherberg method.

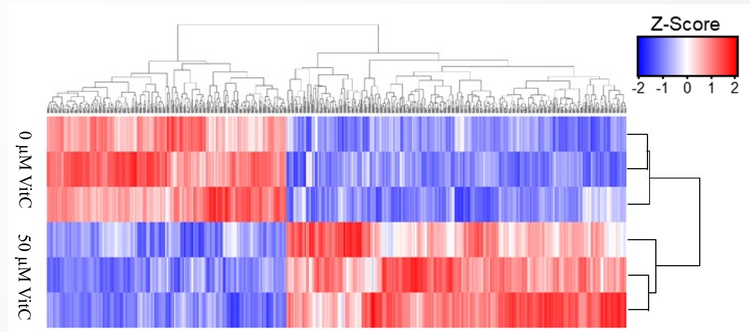

Figure 1. Heatmap showing the relative expression of differential genes. Red represents upregulated expression and blue represents downregulated expression.

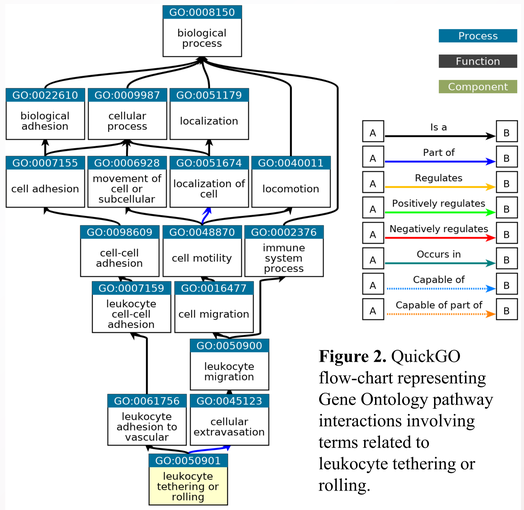

Figure 2. QuickGO flow-chart representing Gene Ontology pathway interactions involving terms related to leukocyte tethering or rolling.

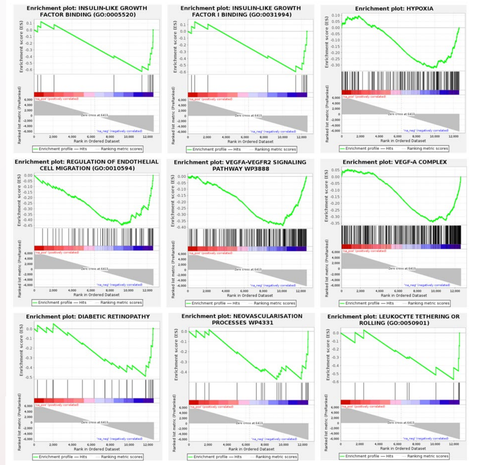

Figure 3. GSEA Traces from selected differential pathways.

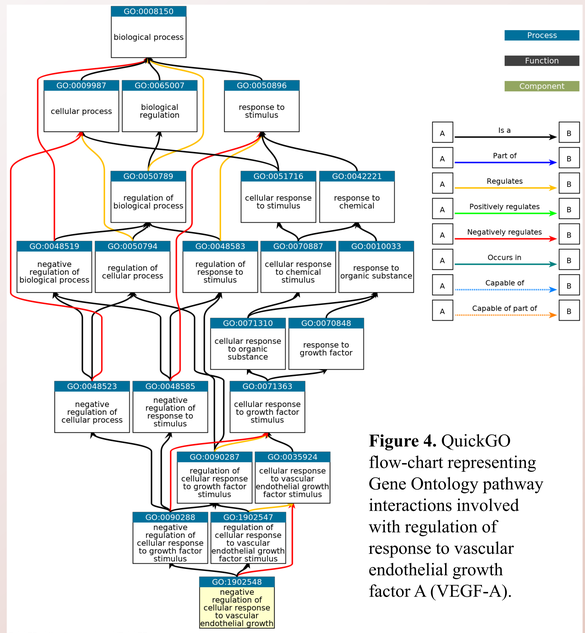

Figure 4. QuickGO flow-chart representing Gene Ontology pathway interactions involved with regulation of response to vascular endothelial growth factor A (VEGF-A).

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