Investigating the Role of Sterol Regulatory-Element Binding Proteins (SREBPs) in Age-Related Macular Degeneration

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Background/Objective:
SREBPs are transcription factors involved in lipid biogenesis and are known to play a role in angiogenesis. Vascular endothelial growth factor (VEGF) also promotes angiogenesis, with VEGF inhibitors as the predominant treatment for Age-related macular degeneration (AMD). AMD is the leading cause of permanent vision loss in the elderly population and is characterized by choroidal neovascularization (CNV). We hypothesize that VEGF can activate SREBPs in a SCAP-dependent manner.

Methods:
Human retinal microvascular endothelial cells (HRECs) were grown in 5% media and treated at passage 7. Prior to treatment, cells were all starved for 1h in 0.5% media. To estimate the changes in SREBP activation - HRECs were treated with 50ng/ml VEGF for 1, 4, and 12h or with 20 μM fatostatin, an inhibitor of SREBP activation, translocation into the nucleus, and SREBP transcription for 6h and 12h. Post treatment cells were lysed and protein was collected in RIPA buffer and semi-quantitative changes in target proteins were analyzed using immunoblotting. Statistical analysis was done by t-test, with significance if $p<0.05$, and sample size of n=2-3.

Results:
HRECs treated with VEGF exhibited an increasing trend for SREBP-1 and SREBP-2 in the cytoplasmic and nuclear forms at all time points. SCAP did not show a clear trend. HRECs treated with fatostatin exhibited a decreasing trend for SREBP-1 and SREBP-2 in the cytoplasmic form and nuclear SREBP-1 form at both time points. The nuclear form of SREBP-2 increased at both time points.

Conclusion and Potential Impact:
VEGF has demonstrated a role in SREBP activation, with both playing a role in angiogenesis. Fatostatin inhibition of SREBP indicated a potential antiangiogenic property. The downregulation of SREBP could provide a novel target in controlling and preventing angiogenesis in AMD. Further studies using animal models should elucidate the role of SCAP in VEGF activation of SREBPs.