Title of Dissertation

MODULATING NEUROTROPHIN RECEPTOR; P75^{NTR} EXERTS VASCULAR PROTECTION IN ISCHEMIC RETINOPATHY

Abstract

Achieving reparative angiogenesis remains an unrealized goal in cardiovascular diseases. We have previously shown that deletion of the neurotrophin death receptor; p75^{NTR} increased activation of the survival receptor; TrkA in bovine retinal endothelial cell cultures.

The overall goal of this project is to examine the impact and elucidate the molecular mechanisms by which deletion of p75^{NTR} enhances vascular repair in ischemic tissues. Using oxygen-induced retinopathy mouse model, we demonstrated that expression of p75^{NTR} was upregulated during vaso-obliteration phase, which was accompanied by marked central vascular cell death and pathological neovascularization in WT pups. Deletion of p75^{NTR} receptor attenuated both manifestations, a vascular protective effect that was accompanied by increased activation and expression of TrkA receptor, preservation of mature neurotrophin levels (NGF and BDNF) as well as enhanced VEGF signal. Vascular protection was reversed by intravitreal injection of the staurosporine kinase inhibitor; K-252a. Next, we assessed the impact of deleting p75^{NTR} receptor on increasing vascular homing of mesenchymal stem cells (MSCs), using retinal ischemia-reperfusion (IR) mouse model. Trypsin-digested retinas showed that, deletion of p75^{NTR} protected against ischemia manifested by decreased number of acellular capillaries 10 days after IR insult. Vascular protection was enhanced by intra-vitreal injection of MSCs 48 hours after IR induction. Knocking down p75^{NTR} receptor on the surface of MSCs increased their vascular homing to ischemic vasculature 7 days after intravitreal injection and increased SDF-1α/CXCR-4& -7 signaling axis.

In summary, our results showed deletion of p75^{NTR} receptor is protective in different retinal ischemic models. The underlying mechanism involves, at least in part, activation of the survival receptor; TrkA and increased vascular homing of MSCs. Our findings identified p75^{NTR} receptor as novel therapeutic target for ischemic ocular diseases.

The University of Georgia

College of Pharmacy

Program in Clinical & Experimental Therapeutics

Final Defense of the Dissertation For

Sally L. Elshaer, B.Pharm, M.Sc.

For the Degree of
DOCTOR OF PHILOSOPHY

Monday, November 28, 2016
12:05 PM
Augusta: Room HM-135
Athens: Room 265-G

Committee Members:

Major Professor: Azza B. El-Remessy, PhD, RPh, FAHA

Bradley G. Phillips, Pharm.D., BCPS, FCCP

Randall Tackett, Ph.D.

William Hill, Ph.D.

Anilkumar R. Pillai, Ph.D.

Education

(2001-2006)	Bachelor of Pharmaceutical Sciences (B. Pharm), Mansoura University, School of Pharmacy, Mansoura, Egypt.
(2006-2010)	Master of Science (Pharmacology Major), Mansoura University, School of Pharmacy, Mansoura, Egypt.

Honors and Awards

(2006)	Honor graduate (top of class of ~800 students), Pharmacy School, Mansoura University.
(2012-2016)	Full PhD Scholarship, Egyptian Ministry of Higher Education
(2014-2016)	American Heart Association predoctoral fellowship, GSA
(2014)	Best poster presentation, STaR conference, UGA, Athens
(2014)	Travel award, STaR conference, UGA, Athens
(2015)	Best poster presentation, STaR conference, UGA, Athens
(2015)	Best poster presentation (2nd place), VA research day
(2016)	Travel award, UGA graduate school, ARVO conference
(2016)	Travel award, STaR conference, UGA, Athens

Abstracts (Selected)

1. "Deletion of TXNIP improved high fat diet-impaired vascular recovery in hind limb ischemia model". STaR conference- Athens, GA, 2016

2. "Modulation of $P75^{NTR}$ Restores Reparative Angiogenesis and Prevents Retinal Neovascularization in Ischemic Retinopathy". NGF meeting- Monterey, CA, 2016.

3. "Modulation of $p75^{NTR}$ receptor protects against ischemic retinopathy: possible contribution of mesenchymal stem cells (MSCs)". ARVO conference- Seattle, WA, 2016.

4. Deletion of $p75^{NTR}$ protects against peripheral and retinal ischemia: Possible contribution of mesenchymal stem cells (MSCs)". STaR conference- Athens, GA, 2015.

5. Modulation of $P75^{NTR}$ Restores Reparative Angiogenesis and Prevents Retinal Neovascularization in Ischemic Retinopathy. Angiogenesis meeting- Boston, MA, 2015.

6. Modulating $p75^{NTR}$ as a Therapeutic Target in Preventing Diabetes-induced Retinal Vascular Permeability. American diabetes association (ADA)- Boston, MA, 2015.

7. Modulation of $P75^{NTR}$ Restores Reparative Angiogenesis and Prevents Retinal Neovascularization in Ischemic Retinopathy. ARVO conference- Orlando, FL, 2014.

Publications

1. El-Sayed M. Ammar, Shehta A. Said, Ghada M. Suddek and Sally L. El-Damarawy (Elshaer) (2011): Amelioration of doxorubicin-induced cardiotoxicity by deferiprone in rats. Can. J. Physiol. Pharmacol., 89: 269-76.

2. El-Sayed M. Ammar, Shehta A. Said, Sally L. El-Damarawy *(Elshaer)* and Ghada M. Suddek (2013): Cardioprotective effect of Grape-seed proanthocyanidins on Doxorubicin-induced Cardiac Toxicity in Rats. Pharm Biol. 51(3): 339-44.

3. Sally L. Elshaer*, Mohammed A. Abdelsaid*, Ahmad Al-Azayzih*, Parag Kumar, Suraporn Matragoon, Julian J. Nussbaum and Azza B. El-Remessy: Pronerve Growth Factor Induces Angiogenesis via Activation of TrkA: Possible Role in Proliferative Diabetic Retinopathy. J Diabetes Res., 2013. *Equal contribution.

4. Barbara A Mysona, Ahmed Y Shanab, Sally L Elshaer and Azza B El-Remessy: Nerve growth factor in diabetic retinopathy: beyond neurons. Expert Rev. Ophthalmol. 9(2), 99–107 (2014).

5. Ahmed Y. Shanab, Sally L. Elshaer, Mona F. El-Azab, Sahar Soliman, Harika Sabbineni, Suraporn Matragoon, Susan C. Fagan and Azza B. El-Remessy: Candesartan stimulates reparative angiogenesis in ischemic retinopathy model: role of hemeoxygenase-1 (HO-1). Angiogenesis. 2015 Apr;18(2):137-50.

6. Maha Coucha, Sally L. Elshaer, Wael S. Eldahshan, Barbara A. Mysona, Azza B. El-Remessy: Molecular Mechanisms of Diabetic Retinopathy: Potential Therapeutic Targets. Middle East Afr J Ophthalmol. 2015 Apr-Jun;22(2):135-44.

7. Sally L. Elshaer, Renee E. Lorys, Azza B. El-Remessy: Cell Therapy and critical limb ischemia: Evidence and window of opportunity in obesity. Obes Control Ther 3(1): 1-8.

8. Sally L. Elshaer and Azza B. El-Remessy: Implications of the neurotrophin receptor $p75^{NTR}$ in ischemic microvascular diseases: Beyond the eye. Expert Rev Ophthalmol, 2016 (Accepted)

9. Maha Coucha, Islam N. Mohamed, Sally L. Elshaer, Osinakachuk Mbata, Megan L. Bartasis and Azza B. El-Remessy. High fat diet dysregulates microRNA-17-5p and triggers retinal inflammation: Role of ER-stress. World J diabetes, 2016 (Accepted)

Publications (In Communication/In Preparation)

10. Riyaz Mohamed, Maha Coucha, Sally L. Elshaer, Sandeep Artham and Azza B. El-Remessy: Inducible overexpression of endothelial proNGF as a mouse model to study microvascular dysfunction: Beyond the eye. (Submitted, Scientific reports)

11. Sally L. Elshaer*, Maha Coucha*, Islam Mohamed*, Sara Altantawi, Wael Eldahshan, Renee Lorys, M. Nusrul Hoda, Azza B. El-Remessy. Deletion of TXNIP improves high fat diet-impaired vascular recovery in hind limb ischemia model (Manuscript in preparation, to be submitted to Redox biology). *Equal contribution

12. Sally L. Elshaer, Azza B. El-Remessy. Modulation of P75NTR Restores Reparative Angiogenesis and Prevents Retinal Neovascularization in Ischemic Retinopathy: Possible contribution of TrkA receptor. (Submitted to Angiogenesis)

13. Sally L. Elshaer, William D. Hill and Azza B. El-Remessy. Modulation of p75NTR on mesenchymal stem cells increases their vascular protection in retinal ischemia-reperfusion mouse model. (Manuscript in preparation)

14. Riyaz Mohamed, Ahmed Y. Shanab, Sally L. Elshaer, Abdelrahman Alwahaibi, Frank Longo, Azza B. El-Remessy. Modulating $p75^{NTR}$ axis prevents diabetes-induced retinal vascular permeability and acellular capillaries in a STZ induced diabetic model. (Manuscript in preparation)