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.
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, STA R conference, UGA, Athens
(2014) Travel award, STA R conference, UGA, Athens
(2015) Best poster presentation, STA R conference, UGA, Athens
(2016) Best poster presentation (2nd place), VA research day
(2016) Travel award, UGA graduate school, ARVO conference
(2016) Travel award, STA R conference, UGA, Athens

Abstracts (Selected)

3. “Modulation of p75NTR receptor protects against ischemic retinopathy: possible contribution of mesenchymal stem cells (MSCs)”. ARVO conference- Seattle, WA, 2016.
4. Deletion of p75NTR protects against peripheral and retinal ischemia: Possible contribution of mesenchymal stem cells (MSCs). STA R conference- Athens, GA, 2015.

Publications

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.

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)
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)