Sudhakar Akul Yakkanti, J Bioequiv Availab 2011, 3:7
doi: http://dx.doi.org/10.4172/0975-0851.1000109

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference & Exhibition on
Pharmaceutical Regulatory Affairs
6-7 September 2011 Baltimore, USA

Regulation of choroidal neovascularisation by tumstatin adenoviral gene delivery and its mechanism(s) action

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Purpose: Choroidal Neovascularization (CNV) leads to loss of vision in Age Related Macular Degeneration (AMD) that affects approximately 1 in 3 individuals over the age of 65. CNV of AMD is as common as cancer and one of the most prevalent causes of blindness in the world population. It has long been recognized that drugs targeting neovascularization may provide new and useful tools for the treatment of patients with CNV of AMD. The present available therapies in clinical trials come in the form of antibodies or antibody fragments that inhibit VEGF, which can only slow the progression of this eye disease. A renewed effort must therefore be made to identify efficient endogenous molecules that could be exploited as therapeutic agents to treat CNV of AMD. To achieve a better outcome, my laboratory research focused on angioinhibitory activity of tumstatin and was analyzed *in-vitro* by mouse choroidal endothelial cell proliferation, migration and tube formation. Recombinant adenovirus secreting Tumstatin was also tested *in-vivo* in laser-induced choroidal neovascularisation in a mouse model.

Methods: Mouse choroidal endothelial cells (MCEC) were prepared and treated with tumstatin, and *in-vitro* proliferation, migration and tube formation assays were performed. Matrix metalloproteinase-2 (MMP-2) activation and MMP-2/tumstatin complex formation was studied using gelatin zymography, Immunobloting and ISCO gradient analysis. Also the angioinhibitory effects of tumstatin were evaluated *in-vivo* using adenovirus secreting tumstatin in the laser induced choroidal neovascularisation in a mice model.

Results: Tumstatin demonstrated anti-proliferative activity and inhibited MCEC invasion, tube formation *in-vitro*. Tumstatin binds to collagen binding domain (CBD) of MMP-2 and inhibits its activation that is mediated by both membrane-type-1 MMP (MT1-MMP) and 4-amino-phenyl mercuric acetate (APMA) *in-vitro*. Adenovirus secreting tumstatin also exhibited significant inhibition of laser induced CNV in mice and MMP-2 activation *in-vivo*.

Conclusion: Angioinhibitory effect of tumstatin on choroidal neovascularisation was observed *in-vitro* and *in-vivo*. The identification of useful and potent endogenous angioinhibitors like tumstatin provides insight into the pathogenesis of choroidal neovascularisation. These results validate the potential of tumstatin in therapeutic applications for prevention of eye diseases.

Biography

Sudhakar Akul is the founder Director of Cell Signaling, Retinal and Tumor Angiogenesis Laboratory at Boys Town National Research Hospital, Associate Professor at Creighton University School of Medicine and University of Nebraska Medical Center, Omaha, NE, USA. He did his postdoctoral training at Harvard Medical School, Boston, MA, USA (2003). He has received Ph.D (2001), M.Phill (1997) and M.Sc (1995) degrees in life sciences from University of Hyderabad; and B.Sc in Biology from Silver Jubilee College (APRDC) Kurnool, SK University (1993) from India. He received President's fellowship (1992), GATE (1996) and CSIR (2007-2000) fellowships from Government of India. He received Mahindra & Mahindra Educational Award (2000) and Young Clinical Scientist Awards from Flight Attendant Medical Research Institute (FAMRI) in 2007 and 2010. He also received Bio-Bio Young Scientist Award from OMICS publishing group; Michael A. O'Connor Young Investigator Award; RO1 grant Award from NIH/NCI and Research Scholar Grant Award from ACS (2010). He is serving as AIBS/NIH-RO1 Grant reviewer for DT study section. He has published more than 35 research articles in several top journals including Science, Cancer Cell, JCI, Blood, PNAS, Gastroenterology, Cancer Research, JBC, IOVS, Mol Vision, J Clinical & Experimental ophthalmology, JCST etc. He is serving as an Executive Editor, Editor and Editorial board member of reputed journals and is serving as a reviewer for 20 scientific journals including JCI, Blood, Circulation, Circulation Research, Cancer research, Clinical Cancer research etc. He was honored by giving a position as Keynote Speaker, Chairman, Co-chairman and organizing committee member for several international conferences including Bio-Bio-2009; Bio-Bio-2010; Anal-Bio2010; Biomarkers & Clinical Research 2010; Diabetes & metabolism 2010 etc.