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Extra cellular matrix derived endogenous angioinhibitor tumstatin and its mechanism(s) of action

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Cancer is currently one of the most prevalent causes of human deaths in the world. Current therapeutic options aim only to slow the progression of cancer disease. Therefore, a renewed effort must be made to identify relevant endogenous cancer inhibitors that could be exploited as therapeutic drugs. We identified several endogenous anti-cancer molecules, which are released from extracellular matrix (ECM) into the blood circulation of cancer patients. Several of these endogenous circulating molecules were cloned and identified as angioinhibitors of tumor growth. These endogenous angioinhibitory proteins bind to the cell surface integrins and transduce the signalling mechanisms & regulate angiogenesis. Thus, integrins serve as transmembrane linkers between the ECM and cytoskeleton for outside-in signalling. One such endogenous circulating molecule, tumstatin, a 28-kDa protein from the C-terminal non-collagenous (NC1) domain of alpha3 type IV collagen was identified by us as an inhibitor of angiogenesis (Science 2002; PNAS 2003). Tumstatin interacting with alphaVbeta3 integrin and inhibits activation of focal adhesion kinase (FAK), phosphatidylinositol 3-kinase (PI-3K), serine/threonine kinase (Akt/protein kinase B), mammalian target of rapamycin (mTOR) and prevents dissociation of eukaryotic translation initiation factor 4E (eIF4E) from 4E binding protein (4E-BP1) leading to the inhibition of Cap-dependent translation in proliferating endothelial cells. Recently, we also demonstrated that tumstatin inhibits hypoxia induced pro-inflammatory cyclo-oxygenase-2 (COX-2) expression via FAK/Akt/NFkB pathway, leading to decreased tumor angiogenesis and tumor growth in an alpha3beta1 integrin dependent manner (Blood 2007; J Canc Sci Ther 2009). At present my laboratory is studying to understand four such endogenous angioinhibitor molecules derived from type IV collagen that include tumstatin, arresten, combostatin and hexastatin which are involved in cell signalling and the way these proteins control adhesion and migration of endothelial cells in pathological processes including tumor angiogenesis.

Biography

Sudhakar Akulapalli (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, JCST etc. He is serving as an Executive Editor, Editor and Editorial board member of reputed journals and is serving as a reviewer for 21 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.