ARTICLE
Journal of Cellular Biochemistry 118:252–262 (2017)

Journal of Cellular Biochemistry

2-Deoxy Glucose Modulates Expression and Biological Activity of VEGF in a SIRT-1 Dependent Mechanism

Haritha Kunhiraman,[1] Lincy Edatt,[1] Sruthi Thekkeveedu,[1] Aswini Poyyakkara,[1] Viji Raveendran,[2,3†] Manikantan Syamala Kiran,[4] Perumana Sudhakaran,[3,5] and Sameer V.B. Kumar[1*]

[1]*Department of Biochemistry and Molecular Biology, Central University of Kerala, Kasargod, India*
[2]*Department of Plant Science, Central University of Kerala, Kasargod, India*
[3]*IUCGGT, University of Kerala, Karyavattom, Trivandrum, India*
[4]*Central Leather Research Institute, Chennai, India*
[5]*Department of Computational Biology and Bioinformatics, University of Kerala, Karyavattom, Trivandrum, India*

ABSTRACT

Reprogramming of energy metabolism particularly switching over of cells to aerobic glycolysis leading to accumulation of lactate is a hallmark of cancer. Lactate can induce angiogenesis, an important process underlying tumor growth and metastasis. VEGF is one of the most important cytokines which regulate this process and the present study was designed to examine if blocking glycolytic pathway in tumor cells can affect its angiogenic potency with respect to VEGF. For this, the expression and biological activity of VEGF synthesized and secreted by tumor derived cell lines in the presence or absence of 2-deoxy glucose (2-DG), an inhibitor of glycolysis was determined. The results suggested that inhibition of glycolysis using sub-lethal doses of 2-DG down-regulated the expression of VEGF and also significantly reduced its biological activity. Further mechanistic studies revealed that the down regulation of VEGF gene expression by 2-DG was due to an increase in SIRT-1 activity and the reduced biological activity was found to be due to an increase in the PAR modification of VEGF. Activity of SIRT-1 and PAR modification of VEGF in turn, was found to be correlated to the cellular NAD^+ levels. The results presented here therefore suggest that treatment of cancer cells with 2-DG can significantly reduce its overall angiogenic potency through transcriptional and post-translational mechanisms. J. Cell. Biochem. 118: 252–262, 2017.

KEY WORDS: ANGIOGENESIS; GLYCOLYSIS; VEGF; POLY ADP RIBOSYLATION; SIRT-1

Tumors cannot grow beyond 1–2 cubic millimeters because oxygen and nutrients do not efficiently diffuse to the cells in the center of the tumor, causing a state of cellular hypoxia [Folkman, 1995]. One of the important metabolic properties seen in such a situation is the increase in aerobic glycolysis and dependency of cells on glycolytic pathway for ATP generation referred to as the Warburg effect [Warburg et al., 1924; Warburg, 1956]. Increased glycolysis in tumors is mediated by activation of oncogenes, loss of tumor suppressors, or by adaptive responses to hypoxia in the tumor microenvironment [Kim and Dang, 2006]. Therefore, blocking glycolysis presents itself as a promising therapeutic strategy to manage cancer progression.

Further, tumors respond to a hypoxic environment by inducing angiogenesis, for which it secretes vascular endothelial growth factor (VEGF A), a key pro-angiogenic growth factor. Angiogenesis, the formation of new blood vessels from the pre existing vasculature, which plays important role in physiological process such as wound healing, embryo development and ovulation has also been implicated to play an important role in the growth, progression and metastasis of cancer apart from other pathological conditions such as diabetic retinopathy, arthritis, etc. [Pepper, 1997].

VEGF A is a 45 kDa, dimeric, disulphide bonded glycoprotein which acts through specific cell surface receptor-dependent signal transduction pathways. VEGF family of growth factors includes VEGF A, VEGF B, VEGF C, VEGF D, PIGF (Placental growth factor) and VEGF E. Among all the members, VEGF A is highly pro angiogenic and is the most studied factor [Roskoski et al., 2007; Shibuya, 2011]. Activity of VEGF A has been reported to be regulated at transcriptional, post-transcriptional, translational and post-translational levels [Xiong et al., 1998; Kumar et al., 2007].

†In memory (Deceased 05 March 2015)
*Correspondence to: Dr. Sameer V.B. Kumar, Asst. Professor, Department of Biochemistry and Molecular Biology, Central University of Kerala, Kasargod 671314, India. E-mail: sameerkumarvb@gmail.com; skumarvb@cukerala.edu.in
Manuscript Received: 10 June 2016; Manuscript Accepted: 13 June 2016
Accepted manuscript online in Wiley Online Library (wileyonlinelibrary.com): 15 June 2016
DOI 10.1002/jcb.25629 • © 2016 Wiley Periodicals, Inc.