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Altered transcriptional regulatory proteins in glioblastoma and YBX1 as a potential regulator of tumor invasion

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Manoj Kumar Gupta[1,2], Ravindra Varma Polisetty[3], Rakesh Sharma[1], Raksha A. Ganesh[4], Harsha Gowda[1], Aniruddh K. Purohit[5], Praveen Ankathi[5], Komal Prasad[6], Kiran Mariswamappa[6], Akhila Lakshmikantha[6], Megha S. Uppin[5], Challa Sundaram[5], Poonam Gautam[7] & Ravi Sirdeshmukh[1,2,4]

We have studied differentially regulated nuclear proteome of the clinical tissue specimens of glioblastoma (GBM, WHO Grade IV) and lower grades of gliomas (Grade II and III) using high resolution mass spectrometry- based quantitative proteomics approach. The results showed altered expression of many regulatory proteins from the nucleus such as DNA binding proteins, transcription and post transcriptional processing factors and also included enrichment of nuclear proteins that are targets of granzyme signaling – an immune surveillance pathway. Protein - protein interaction network analysis using integrated proteomics and transcriptomics data of transcription factors and proteins for cell invasion process (drawn from another GBM dataset) revealed YBX1, a ubiquitous RNA and DNA-binding protein and a transcription factor, as a key interactor of major cell invasion-associated proteins from GBM. To verify the regulatory link between them, the co-expression of YBX1 and six of the interacting proteins (EGFR, MAPK1, CD44, SOX2, TNC and MMP13) involved in cell invasion network was examined by immunohistochemistry on tissue micro arrays. Our analysis suggests YBX1 as a potential regulator of these key molecules involved in tumor invasion and thus as a promising target for development of new therapeutic strategies for GBM.

Glioblastoma multiforme (GBM) belongs to a group of tumors, namely, gliomas which are predominant primary brain tumors[1]. Gliomas are clinically and histologically classified into four different grades (I-IV) as per WHO guidelines. Grade I (pilocytic astrocytoma) and II (diffused astrocytoma) are relatively slow growing and are considered as low-grade gliomas. Grade III (anaplastic astrocytoma) and Grade IV (Glioblastoma multiforme, GBM) are associated with poor survival and are considered as high-grade gliomas. GBM is the most aggressive form of all and is characterized by extreme proliferation, invasiveness, vascularization and necrosis[1]. GBM exhibits further heterogeneity with additional molecular subclasses - Neural, Pro-neural, Classical and Mesenchymal[2] suggesting complexity of the disease. As per WHO guidelines (WHO 2016), they are now evaluated on the basis of both histological and molecular features for the purpose of clinical diagnosis and outcome prediction[3].

The nucleus of the cells is a prime area of focus in the determination of malignancy. The signaling pathways involved in malignant transformation and progression are regulated by nuclear proteins and their post-translational modifications (PTMs). Earlier work on altered nuclear proteins from other tumors, revealed the role of oxidative stress response pathway, proteins involved in chromosome integrity, RNA processing or mRNA metabolism[4,5] making them a promising source as therapeutic targets or biomarkers for clinical

[1]Institute of Bioinformatics, International Tech Park, Bangalore, 560066, India. [2]Manipal Academy of Higher Education, Madhav Nagar, Manipal, 576104, India. [3]Department of Biochemistry, Sri Venkateswara College, University of Delhi, New Delhi, 110021, India. [4]Neuro-Oncology, Mazumdar Shaw Center for Translational Research, Bangalore, 560099, India. [5]Nizam's Institute of Medical Sciences, Hyderabad, 500082, India. [6]Mazumdar Shaw Medical Center, Narayana Health, Bangalore, 560099, India. [7]ICMR-National Institute of Pathology, Safdarjung Hospital Campus, New Delhi, 110029, India. Correspondence and requests for materials should be addressed to P.G. (email: gautam.poonam@gmail.com) or R.S. (email: ravisirdeshmukh@gmail.com)