Editorial

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Neuro-Oncology: Open Access
ISSN 2572-0376

2015
Vol. 1 No. 1:2

DOI: 10.21767/2572-0376.10001

A New Perspective on Gliomas: The Nucleolar Point of View

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Received: Nov 02, 2015, **Accepted:** Nov 04, 2015, **Published:** Nov 09, 2015

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Citation: Calogero A. A New Perspective on Gliomas: The Nucleolar Point of View. Neurooncol Open Access 2015, 1:1.

Editorial

The link between nucleolus and cancer begun with the recognition by the pathologist that there is not a constant number of nucleoli per cells, and that nucleoli either enlarged or increased in number correlate with aggressiveness in many cancers [1,2]. Later on, it was established in gliomas that the tumor grade correlates with the morphological nucleolar alterations [3]. Nevertheless, the involvement of this organelle in cancer biology has been largely neglected for many years.

The biological basis of drug resistance in these tumors is complex, being dependent to some extent on the genetic make-up of the tumor and its high tumor cell heterogeneity. As it happened for other tumors, the therapeutic options for the treatment of gliomas have become gradually dependent on the individual molecular profile of the patient. Representative molecular markers have been extensively investigated, such as the p53 gene status, the presence of deletions in the INK4a/INK4b locus coding for the tumor suppressors and cell cycle regulators p16, p15 andp14ARF, the MGMT (O6 -methylguanine DNA methyltransferase) levels, the EGFR receptor family, IDH1, IDH2 and hTERT promoter methylation. The level of expression for several players and regulators of apoptosis were all studied to predict the prognosis and response of the tumor to specific drugs [4].

Several of the above molecular markers are involved in nucleolar functions and many authors working on the tumor biology of gliomas have highlight the role of nucleolar proteins by demostrating that cancer nucleoli are altered as a consequence of hyperactive rDNA transcription [5,6].

The most widely function of the nucleolus is the ribosome biogenesis. This process can be studied by monitoring ribosomal RNA (rRNA) transcription by the RNA polimerase I [1]. For long time the RNA polimerase I transcription was considered a "house-keeping process". However, in the last decade there has been increasing evidence of active regulation of RNA polimerase I by a protein involved in cancer development. The central role of regulation of RNA polimerase I is underscored by the recent discovery that small molecules such as CX-5461 can interfere with the RNA polimerase I activity, and control ribosomal biogenesis and cell growth [7].

Proteomic studies have reported that over 4500 proteins can be found in the nucleolus, and that only about a thirty percent of them are directly involved in ribosome synthesis. These data seem to provide a nucleolus' view as of a dynamic and adaptable organelle. Nucleoli can be subjected to different types of "stress" such as those induced by nutritional deprivation, UV and ionizing radiations, and anti-neoplastic drugs. Such stimuli arouse responses leading to the activation of the so called "ribosomal surveillance pathway", involving C-MYC, NPM1 and the main players of the ARF-MDM2-P53 axis, among others [8-11]. These nuclear proteins have in common the fact that they are significantly involved in gliomagenesis and cancer progression, some playing an oncogenic role while others having a clear suppressor function, they shuttle forth and back from the nucleus to the nucleolus, all interact with each other to contribute either directly or indirectly to the ribosomal biogenesis regulation [1,3]. My colleagues and I are focusing our attention on clarifying the role of nucleolar proteins in the ARF-MDM2-P53 pathway and how they contribute to its alteration in gliomas.

ARF, following activation under nucleolar stress, binds to MDM2 allowing P53 to be released from the MDM2 control and to become stable and active. Also the ribosomal proteins RPL5 and 11 are involved in the control of MDM2 contributing to P53 activation. However, to become operative P53 needs also to undergo different types of post-translational modifications as well as the joining with a number of co-factors, both of which are required for P53 to be directed toward its transcriptional targets and acquire the ability to control the cell cycle progression, to promote the apoptosis or activate the senescence program. The inhibition of the RNA Polymerase I transcription by P53 makes no exception to

this paradigm of action and it is set off through the binding to SL1, which as a result prevents the interaction of SL1 with UBF. A further contribution to the inhibition of RNA Polymerase I transcription comes from ARF by negatively interacting with the transcription factors UBF and TFF-I, both of which are in turn necessary for the regulation of RNA Polymerase I. In conclusion, the activity of RNA Polymerase I is strictly controlled by tumor suppressors which have gained a nucleolar function and are operative within the ARF-MDM2-P53 pathway [8, 9]. More, in neoplastic cells and in glial tumor cells as well the above mechanisms of control are frequently disregulated by inactivating mutations of the p53 and ARF genes, and by overespression of MDM2 [12]. According to recent observations, several nucleolar partners of ARF such as MYC and NPM1 are involved in the control of tumor growth and underline the pivotal role of ARF for triggering the cell-cycle arrest and the apoptotic programmes after oncogenic cues. The stability of ARF is significantly increased in cells that overexpress exogenous NPM1. It associates with ARF within the nucleolus, delaying its turnover. As a consequence, the inhibition of NPM1 by shRNA has destabilizing effects over ARF stability [13,14].

In the last decade we found that the early growth response gene EGR-1 behaves as a suppressor gene that is down-regulated in fresh human gliomas, and is independent of ARF/Mdm2 but not p53 alterations. Suymolation of EGR-1 is mediated by ARF and is necessary for getting EGR-1 to activate PTEN, a tumor suppressor gene frequently deleted in gliomas [15]. The presence of a nucleolar localization sequence in the EGR-1 protein and its association with ARF have lead us to demonstrate that EGR-1 goes into the nucleolus under nucleolar stress conditions in different cell types including glial tumor cells, and that EGR-1 colocalizes with the nucleolar markers fibrillarin and NPM1 in presence of ARF. EGR-1 is present in the nucleolus mainly as the 100 kDa sumoylated form. We also showed that the level of the ribosomal RNA precursor 47S is inversely correlated to the level of EGR-1 transcripts and that EGR-1 is effective to regulate the synthesis of the 47S rRNA precursor. Finally we showed that EGR-1 binds to UBF. This allowed us to hypothesize that the inhibiting activity of EGR-1 on the synthesis of the 47S rRNA precursor is consistent with its interaction with UBF within the transcriptional complex of RNA polymerase I, and that this may have severe consequences on the ribosomal metabolism [16].

NPM1 has clearly showed growth promoting characteristics, as testified by the overexpression of NPM1 that stimulates the growth in vitro of glioma cell lines. In addition, NPM1 correlates with the proliferation markers PCNA and Cyclin A in glioma tumor tissue, and with a poorer prognosis [17,18]. However, different works favor NPM1 also as a tumor suppressive protein. In glial tumor cells ARF protein has been shown to interact with NPM1, which colocalizes with EGR-1. Since the activity of nucleolar EGR-1 is hampered in ARF-/-cells, and ARF transcription is regulated by EGR-1 while the turnover of ARF protein is under the control of NPM1, we speculated that some sort of cooperation between EGR-1 and NPM1 might also be present. At this point it would be important to know whether the expression of NPM1 is somehow correlated to that of EGR-1, and whether this correlation applies to different cellular types and stress conditions. Finally, we would like to know whether, in analogy to ARF, NPM1 contributes to the EGR-1 stability within the nucleolus.

As can be seen from the above discussion, we are just beginning to elucidate the complex role of nucleolus in tumor biology, and what can be learnt from tumor biology to uncover the multi-faceted reality of the nucleolus.

We hope that more adequate tissue models will be adopted for the future, such as freshly derived primary tumor cell lines and that tumor heterogeneity will be taken somehow in consideration in the analysis of this already complex matter.

Finally, in view of the emerging role of nucleolus in brain cancer we expect that for the future these investigations will bring new ideas for a renewing cancer therapy and a more appropriate tumor classification.

References

1 Quin JE, Devlin JR, Cameron D, Hannan KM, Pearson RB, et al. (2014) Targeting the nucleolus for cancer intervention. Biochim Biophys Acta 1842: 802-816.

2 Maggi LB Jr, Weber JD (2005) Nucleolar adaptation in human cancer. Cancer Invest 23: 599-608.

3 Hara A, Hirayama H, Sakai N, Yamada H, Tanaka T, et al. (1990) Correlation between nucleolar organizer region staining and Ki-67 immunostaining in human gliomas. Surg Neurol 33: 320-324.

4 Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, et al. (2015) Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. N Engl J Med 372: 2499-2508.

5 Xu Z, Joshi N, Agarwal A, Dahiya S, Bittner P, et al. (2012) Knocking down nucleolin expression in gliomas inhibits tumor growth and induces cell cycle arrest. J Neurooncol 108: 59-67.

6 Gil-Ranedo J, Mendiburu-Eliçabe M, García-Villanueva M, Medina D, del Álamo M, et al. (2011) An off-target nucleostemin RNAi inhibits growth in human glioblastoma-derived cancer stem cells. PLoS One 6: e28753.

7 Bywater MJ, Poortinga G, Sanij E, Hein N, Peck A, et al. (2012) Inhibition of RNA polymerase I as a therapeutic strategy to promote cancer-specific activation of p53. Cancer Cell 22: 51-65.

8 Ayrault O, Andrique L, Fauvin D, Eymin B, Gazzeri S, et al. (2006) Human tumor suppressor p14ARF negatively regulates rRNA transcription and inhibits UBF1 transcription factor phosphorylation. Oncogene 25: 7577-7586.

9 Lessard F, Morin F, Ivanchuk S, Langlois F, Stefanovsky V, et al. (2010) The ARF tumor suppressor controls ribosome biogenesis by regulating the RNA polymerase I transcription factor TTF-I. Mol Cell 38: 539-550.

10 Krüger T, Scheer U (2010) p53 localizes to intranucleolar regions distinct from the ribosome production compartments. J Cell Sci 123: 1203-1208.

11 Kim TH, Leslie P, Zhang Y (2014) Ribosomal proteins as unrevealed caretakers for cellular stress and genomic instability. Oncotarget 5: 860-871.

12 Calogero A, Arcella A, De Gregorio G, Porcellini A, Mercola D, et al. (2001) The early growth response gene EGR-1 behaves as a suppressor gene that is down-regulated independent of ARF/Mdm2 but not p53 alterations in fresh human gliomas. Clin Cancer Res 7: 2788-2796.

13 Lindström MS (2011) NPM1/B23: A Multifunctional Chaperone in Ribosome Biogenesis and Chromatin Remodeling. Biochem Res Int 2011: 195209.

14 Brady SN, Yu Y, Maggi LB Jr, Weber JD (2004) ARF impedes NPM/B23 shuttling in an Mdm2-sensitive tumor suppressor pathway. Mol Cell Biol 24: 9327-9338.

15 Yu J, Zhang SS, Saito K, Williams S, Arimura Y, et al. (2009) PTEN regulation by Akt-EGR1-ARF-PTEN axis. EMBO J 28: 21-33.

16 Ponti D, Bellenchi GC, Puca R, Bastianelli D, Maroder M, et al. (2014) The transcription factor EGR1 localizes to the nucleolus and is linked to suppression of ribosomal precursor synthesis. PLoS One 9: e96037.

17 Chen J, Sun J, Yang L, Yan Y, Shi W, et al. (2015) Upregulation of B23 promotes tumor cell proliferation and predicts poor prognosis in glioma. Biochem Biophys Res Commun 466: 124-130.

18 Holmberg Olausson K, Nistér M, Lindström MS (2014) Loss of nucleolar histone chaperone NPM1 triggers rearrangement of heterochromatin and synergizes with a deficiency in DNA methyltransferase DNMT3A to drive ribosomal DNA transcription. J Biol Chem 289: 34601-34619.