Non-Coding RNAs in Glioblastoma

Non-coding RNAs have been implicated as master regulators of several biological processes, their expression being strictly regulated under physiological conditions. In recent years, particularly in the last decade, substantial effort has been made to investigate the function of ncRNAs in several human diseases, including cancer. The aim of this review is to guide the reader through important aspects of miRNA and lncRNA biology, focusing on the molecular mechanism associated with glioblastoma onset/progression.

1. Introduction

For decades, it has been believed that the central dogma of Molecular Biology (DNA → mRNA → Protein) was unidirectional, with all the complex cellular processes of an organism being solely due to the structural and catalytic functions of proteins [1]. Currently, it is widely accepted that this biological complexity is derived from the non-coding DNA portion of the genome, which was once thought of as 'junk DNA' (non-codifying DNA). Non-coding RNA (ncRNA) is a class of RNAs which has no potential for translation into proteins. The DNA sequence from which a functional ncRNA is transcribed is often called an RNA gene. The number of ncRNAs within the human genome is unknown; however, massive expansion of global transcriptome datasets from genomics consortia have been demonstrating that most of the human genome is transcribed into non-coding RNAs [2][3][4]. According to the Encyclopedia of DNA elements (ENCODE) project, approximately 75% of the human genome is actively transcribed into ncRNAs [2][5], only 2% of which code for known protein-coding genes [5]. Importantly, ncRNAs have been revealed to be functional and to form complex regulatory networks associated with several biological processes. Disruption of key components of these networks leads to deregulated cell function and contributes to human disease states, including cancer [6][7][8].

2. Glioblastoma

Glioblastoma is the most aggressive type of brain cancer in adults, accounting for about half of all primary brain tumors [9]. Despite the multimodal treatment procedure, which consists of maximal resection followed by radiotherapy and chemotherapy, the overall survival rate remains only 12–15 months, highlighting the urgent need for more effective targeted therapy [10].

New insights into the molecular subtypes of diffuse gliomas have led to unprecedented discoveries of potential prognostic and predictive markers [11]. The latest classification system announced by the World Health Organization (WHO) [12] combines the classical histomorphological analysis with molecular genetic tests, allowing more precise diagnosis and guidance for therapeutic interventions [13]. Further studies in this direction should provide the basis for the development of novel therapeutic strategies targeting unique molecular signatures for patient-tailored treatment.

3. Non-coding RNAs

Non-coding RNAs have increasingly been described as biomarkers of various human diseases [14][15][16][17][18] and/or suggested as therapeutic targets [19][20][21][22][23]. In this context, the aim of this article is to review the exciting progress towards elucidating the multifunctional facet of ncRNAs, with special focus on glioblastoma-associated miRNAs and lncRNAs. Finally, we also discuss the limitations and obstacles to translate these findings into the clinical practice.

LncRNAs play a central role in transcriptional and post-transcriptional regulation of protein-coding genes and may be categorized into different archetypes, such as: ceRNAs/miRNA sponges, guides, scaffolds, or enhancers. MiRNAs act at the post-transcriptional level by mRNA cleavage, blocking mRNA translation and/or mRNA stability.

LncRNAs and miRNAs are critical ncRNAs inserted in a complex regulatory network, with abnormal expression of these molecules having a direct impact on several aspects of gliomagenesis.

In conclusion, the lncRNA–miRNA–mRNA crosstalk represents a master regulatory key for maintenance of cellular homeostasis. The lncRNA-miRNA co-expression network provides an extra layer of complexity into how these molecules can contribute to glioblastoma onset, progression, and maintenance. This complex network of lncRNA-miRNA interactions is a prominent field of research, which may reveal potential therapeutic options for patient-tailored treatment.

References

1. Kathryn A. Haynes; Thuy K. Smith; Collin J. Preston; Ashok N. Hegde; Proteasome Inhibition Augments New Protein Accumulation Early in Long-Term Synaptic Plasticity and Rescues Adverse Aβ Effects on Protein Synthesis. *ACS Chemical Neuroscience* **2015**, *6*, 695-700, 10.1021/acschemneuro.5b00068.

2. Barbara L. Kee; A comprehensive transcriptional landscape of human hematopoiesis.. *Cell Stem Cell* **2011**, *8*, 122-4, 10.1016/j.stem.2011.01.006.

3. The FANTOM Consortium and the RIKEN PMI and CLST (DGT); FANTOM Consortium and the RIKEN PMI and CLST (DGT); Alistair R. R. Forrest; Hideya Kawaji; Michael Rehli; J. Kenneth Baillie; Michiel J. L. De Hoon; Vanja Haberle; Timo Lassmann; Ivan V. Kulakovskiy; et al. A promoter-level mammalian expression atlas. *Nature* **2014**, *507*, 462-470, 10.1038/nature13182.

4. Justin W. Halloran; Dakai Zhu; David C. Qian; Jinyoung Byun; Olga Y. Gorlova; Christopher I Amos; Ivan Gorlov; Prediction of the gene expression in normal lung tissue by the gene expression in blood.. *BMC Medical Genomics* **2015**, *8*, 77, 10.1186/s12920-015-0152-7.

5. The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature 2012, 489, 57–74.

6. Felix Y. Feng; Bhavna Malik; Long noncoding RNAs in prostate cancer: overview and clinical implications. *Asian Journal of Andrology* **2016**, *18*, 568-574, 10.4103/1008-682X.177123.

7. E.M. Reis; Sergio Verjovski-Almeida; Perspectives of Long Non-Coding RNAs in Cancer Diagnostics. *Frontiers in Genetics* **2012**, *3*, 32, 10.3389/fgene.2012.00032.

8. Hai Zou; Chu-Xiao Shao; Qin-Yun Zhou; Gui-Qi Zhu; Ke-Qing Shi; Martin Braddock; Dongsheng Huang; Ming-Hua Zheng; The role of lncRNAs in hepatocellular carcinoma: opportunities as novel targets for pharmacological intervention. *Expert Review of Gastroenterology & Hepatology* **2015**, *10*, 331-340, 10.1586/17474124.2016.1116382.

9. Jigisha P. Thakkar; Therese A. Dolecek; Craig Horbinski; Quinn T Ostrom; Donita D. Lightner; Jill S. Barnholtz-Sloan; John L. Villano; Epidemiologic and molecular prognostic review of glioblastoma.. *Cancer Epidemiology Biomarkers & Prevention* **2014**, *23*, 1985-96, 10.1158/1055-9965.EPI-14-0275.

10. Talita Glaser; Inbo Han; Liquan Wu; Xiang Zeng; Targeted Nanotechnology in Glioblastoma Multiforme. *Frontiers in Pharmacology* **2017**, *8*, 13, 10.3389/fphar.2017.00166.

11. Guido Reifenberger; Hans-Georg Wirsching; Christiane B. Knobbe-Thomsen; Michael Weller; Advances in the molecular genetics of gliomas — implications for classification and therapy. *Nature Reviews Clinical Oncology* **2016**, *14*, 434-452, 10.1038/nrclinonc.2016.204.

12. Guido Reifenberger; Ingmar Blümcke; Pieter Wesseling; Torsten Pietsch; Werner Paulus; Pathology and Classification of Tumors of the Central Nervous System. *Oncology of CNS Tumors* **2019**, , 3-89, 10.1007/978-3-030-04152-6_1.

13. Michael Weller; Emilie Le Rhun; Matthias Preusser; Jörg-Christian Tonn; Michael Weller; How we treat glioblastoma.. *ESMO Open* **2019**, *4*, e000520, 10.1136/esmoopen-2019-000520.

14. Kun-Yu Teng; Kalpana Ghoshal; Role of Noncoding RNAs as Biomarker and Therapeutic Targets for Liver Fibrosis.. *Gene Expression* **2015**, *16*, 155-62, 10.3727/105221615X14399878166078.

15. Janika Viereck; Thomas Thum; Circulating Noncoding RNAs as Biomarkers of Cardiovascular Disease and Injury. *Circulation Research* **2017**, *120*, 381-399, 10.1161/circresaha.116.308434.

16. Guangle Zhang; Cong Pian; Zhi Chen; Jin Zhang; Mingmin Xu; Liang-Yun Zhang; Yuanyuan Chen; Identification of cancer-related miRNA-lncRNA biomarkers using a basic miRNA-lncRNA network. *PLOS ONE* **2018**, *13*, e0196681, 10.1371/journal.pone.0196681.

17. Manuela Lanzafame; Gaia Bianco; Luigi Terracciano; Charlotte K. Y. Ng; Salvatore Piscuoglio; The Role of Long Non-Coding RNAs in Hepatocarcinogenesis. *International Journal of Molecular Sciences* **2018**, *19*, 682, 10.3390/ijms19030682.

18. Evelyn Kelemen; Judit Danis; Anikó Göblös; Zsuzsanna Bata-Csörgő; Márta Széll; Exosomal long non-coding RNAs as biomarkers in human diseases. *EJIFCC* **2019**, *30*, 224-236, .

19. Carlos Deocesano-Pereira; Raquel Arminda Carvalho Machado; Henrique Cesar De Jesus-Ferreira; Thiago Marchini; Tulio Felipe Pereira; Ana Claudia Oliveira Carreira; Mari Cleide Sogayar; Functional impact of the long non-coding RNA MEG3 deletion by CRISPR/Cas9 in the human triple negative metastatic Hs578T cancer cell line. *Oncology Letters* **2019**, , , 10.3892/ol.2019.10969.

20. Ondrej Slaby; Richard Laga; Ondrej Sedlacek; Therapeutic targeting of non-coding RNAs in cancer. *Biochemical Journal* **2017**, *474*, 4219-4251, 10.1042/bcj20170079.

21. Claire Fletcher; Eric Sulpice; Stephanie Combe; Akifumi Shibakawa; Damien A. Leach; Mark P. Hamilton; Stelios L. Chrysostomou; Adam Sharp; Jon Welti; Wei Yuan; et al. Androgen receptor-modulatory microRNAs provide insight into therapy resistance and therapeutic targets in advanced prostate cancer.. *Oncogene* **2019**, *38*, 5700-5724, 10.1038/s41388-019-0823-5.

22. D. R. Corey; S. Dimmeler; J.-W. Kornfeld; Targeting Noncoding RNAs in Disease: Challenges and Opportunities. *Science* **2013**, *341*, 1021-1021, 10.1126/science.341.6149.1021-c.

23. Masayuki Matsui; David R. Corey; Non-coding RNAs as drug targets. *Nature Reviews Drug Discovery* **2016**, *16*, 167-179, 10.1038/nrd.2016.117.