Pathology & Oncology Research (2020) 26:1347–1348
https://doi.org/10.1007/s12253-019-00631-2

LETTER TO THE EDITOR

# Epstein-Barr Virus MicroRNAs in Nasopharyngeal Carcinoma

Evangelos Tsiambas[1,2] · Nicholas S. Mastronikolis[1,3] · Panagiotis P. Fotiades[4] · Vasileios Ragos[5] · Nikolaos Kavantzas[2] · Andreas C. Lazaris[2]

Received: 19 November 2018 / Accepted: 4 March 2019 / Published online: 9 March 2019


Dear Editor,

Nasopharyngeal Carcinoma (NPC) is a unique, aggressive pathological entity included in the Head and Neck Carcinoma (HNC) family of malignancies. Geographically its prevalence is observed in East Asia and Africa with its highest incidence rate in China. Concerning its histological origin, the malignancy is derived from the nasopharyngeal epithelia demonstrating a high invasive and metastatic potential mainly correlated with poor prognosis. Keratinizing, non-keratinizing and Basaloid carcinoma represent its pathological variants. Epstein-Barr virus (EBV) latent but persistent infection is predominantly implicated in its development and progression. In fact, EBV's oncogenic activity is mediated by the aberrant expression of specific critical proteins including LMPs and EBNA1 [1]. Concerning the therapeutic strategies that are applied in patients diagnosed with NPC, radiotherapy is still the eligible treatment for them, but the corresponding response rates depend on specific genetic signatures, including gross chromosome (polysomy/aneuploidy), gene (mutations, deletions), and also epigenetic (promoter CpG methylation, specific RNA aberrations) abnormalities.

micro-RNAs (miRs) are considered as novel significant markers for discriminating patients suffering from cancer based on their molecular characteristics. miRs are short, non-coding RNAs consisting of 20–25 nucleotides located at intra- or intergenic regions. Functional miRs mediate a crucial positive regulation of posttranscriptional gene silencing. Based on this activity, they enhance normal cell functions, including proliferation, apoptosis, and tissue differentiation. Their deregulation in cancerous cells due to genetic (mutations, translocations), epigenetic (DNA hypermethylation of tumour suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations leads to a loss of miRs-mediated repression of target mRNA. Interestingly, a biphasic role of miRs in cancers of different histogenetic origin has been confirmed. In some of them, their up regulation correlates with an increased ongogenic activity, whereas in others the same miR type acts as a suppressor agent [2].

Referring to the endogenous EBV-miRs involvement in NPC development and biological behaviour, many study groups have analyzed their alterations supporting the idea that there are distinct molecular patterns affecting the prognosis of the patients. One study group suggested that three molecular and clinical distinct histo-genetic profiles (immunogenic, classical and mesenchymal) should be discriminated based on a panel of miRs (miR-142, miR-26a, miR-141 and let-7i characterizes the mesenchymal sub type) affecting prognosis in the corresponding patients [3]. Additionally, EBV endogenous miRs were also analyzed. Another study group analyzed exactly the role of EBV depended BamH1-A rightward transcripts (BARTs) known as miR-BART4, a specific non-coding region which is also observed to be over expressed in lymphoepithelioma-like carcinomas. Focused on miR-BART4 aberrant expression they observed that this was correlated with development and progression of NPC due to PTEN inhibition affecting also negatively response rates to radiotherapy [4]. Similarly, another study based on small RNA sequencing analysis concluded that a panel of miRs (BART5-5p, BART7-3p, BART9-3p, and BART14-3p) over activation was responsible for down regulation of critical

✉ Evangelos Tsiambas
tsiambasecyto@yahoo.gr

1 Department of Pathology-Cytology, 401 General Army Hospital, Athens, Greece

2 Department of Pathology, Medical School, University of Athens, Athens, Greece

3 Department of Otorhinolaryngology, Head and Neck Surgery, Medical School, University of Patras, Patras, Greece

4 Department of Surgery, 424 General Army Hospital, Thesaloniki, Greece

5 Department of Maxillofacial and Department of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

suppressor genes such as ataxia telangiectasia mutated (ATM), by binding to its multiple sites [5]. Because miR-BARTs seem to control critical functions inside the EBV genome including viral latency and host cell immune response potential, their aberrant expression enhances EBV oncogenic activity in the host cells of nasopharyngeal epithelia during carcinogenetic process. Interestingly, this mechanism of gene deregulation is observed in dysplastic epithelia, an evidence of early micro-genetic abnormality.



## References

1. Lo KW, Chung GT, To KF (2012) Deciphering the molecular genetic basis of NPC through molecular, cytogenetic, and epigenetic approaches. Semin Cancer Biol 22:79–86
2. Hiromu S, Maruyama R, Yamamoto E, Masahiro K (2012) DNA methylation and microRNA dysregulation in cancer. Mol Oncol 6: 567–578
3. Zhao L, Fong AHW, Liu N, Cho WCS (2018) Molecular subtyping of nasopharyngeal carcinoma (NPC) and a microRNA-based prognostic model for distant metastasis. J Biomed Sci 25(1):16–28
4. Wu Q, Han T, Sheng X, Zhang N, Wang P (2018) Downregulation of EB virus miR-BART4 inhibits proliferation and aggressiveness while promoting radiosensitivity of nasopharyngeal carcinoma. Biomed Pharmacother 108:741–751
5. Lung RW, Hau PM, Yu KH et al (2018) EBV-encoded miRNAs target ATM-mediated response in nasopharyngeal carcinoma. J Pathol 244(4):394–407