MINI REVIEW: MICRO RNA IN NASOPHARYNGEAL CARCINOMA

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is a highly invasive and malignant tumor of the nasopharynx, the uppermost region of the pharynx, gravitating toward Southeast Asia, especially Vietnam. The etiology of NPC is suggested to be involved to several genetic susceptibility and environmental factors. miRNAs (microRNA), the short non-coding RNA molecular, have been reported that played important roles, as oncogene and/or tumor suppressor gene, in progression and development of NPC. In this review, we summarized the role of miRNAs in NPC and their potential use as biomarkers for early prognosis and diagnosis of NPC as well as therapeutic agent of NPC in future.

Keywords: *miRNA; nasopharyngeal carcinoma; biomarkers; therapeutic agents.*

1. Introduction

miRNAs (Mirco RNA), originally discovered in *Caenorhabditis elegans*, are the short non-coding RNA molecular within about 20-23 nucleotides (nts) in length that involved in post-transcriptional gene regulation (Chuang, Jones, 2007; Macfarlane, Murphy, 2010; Sata *et al*., 2011; Jeff, Fei-Fei, 2014). miRNAs have been shown to provide insight into both biological and clinical behavior of numerous human cancers, including nasopharyngeal carcinoma (NPC). miRNAs have been found to play important roles in cellular processing, including signal pathways related to cancer progression functioning as tumor suppressor genes and/or oncogenes (Esquela-Kerscher, Slack, 2006; Sata *et al.*, 2011; Jeff, Fei-Fei, 2014). miRNAs regulate gene expression by binding to sequence in 3' UTR (untranslated region) of target mRNA leading to the repression or degradation of mRNA (Ventura, Jacks, 2009; Liu *et al.*, 2014).

miRNA could be detected in a wide range of body fluids, including blood, serum, plasma, saliva, etc. and secreted as a stable extracellular form (Zheng *et al.*, 2011; Cortez *et al*., 2011). The detection of circulating miRNA could be served as biomarkers for various cancer, including lung cancer, hepatocellular carcinoma, nasopharyngeal cancer, etc. has been widely reported (Chen *et al*., 2008; Mitchell *et al*., 2008; Jeffrey, 2008; Yu *et al*., 2011; Jeff, Fei-Fei, 2014). The highly stable circulating miRNAs in body fluid has attributed to mainly mechanisms: their resistance to RNase activity, or their incorporation into exosomes, or formation of

a protein-miRNA complex with high-density lipo-proteins (Esquela-Kerscher, Slack, 2006; Chen *et al*., 2008; Tan *et al*., 2015). Many studies has been demonstrated that the potential of miRNA, especially circulating miRNA, could be used as biomarkers in diagnosis and prognosis to human cancers (Esquela-Kerscher, Slack, 2006; Chen *et al*., 2008; Tan *et al*., 2015).

2. MiRNA functions as tumor suppressor in regulating of NPC

Cancer is a multi-steps, in which the dysregulation of genes involved in cell proliferation, cell cycle, and/or apoptosis are associated with the expression of many miRNAs, characterized as oncogenes and tumor suppressor genes (Esquela-Kerscher, Slack, 2006). In the role of tumor suppressor genes, they are often downregulated in many human tumor tissues. In NPC, the common tumor suppressor gene are miR-9, miR-26a, miR-29, miR-30, miR-200 family, and Let-7 family, etc. (Jeff *et al*., 2014; Tan *et al*., 2015). Of that, miR-29 is one of the most important miRNA which is commonly downregulated in NPC. According to Lu et al. (2014), they reported that the level of miR-9 was declined in NPC specimens and NPC cell lines with important functional sequences (Lu *et al*., 2014). miR-9 is known to regulate cell proliferation, epithelial-mesenchymal transition, invasion, metastasis, apoptosis and angiogenesis in many human cancers, including NPC (Luo *et al*., 2009; Ma *et al*., 2010; Lu *et al*., 2014). The tumor suppressive effect is mediated by repressing CXCR4 and downstream p38 mitogen-activated protein kinase (MAPK) pathway (Lu *et al*., 2014). Mechanistically, miR-9 interacts and binds to the CXCR4 leading to its downregulation, inhibits cell growth, migration and cell invasion. Whereas many studies showed that overexpression of CXCR4 promoted cell proliferation, invasion and migration. It demonstrated that miR-9 was consistently downregulated in NPC specimens and significant associated with progression and metastasis in NPC (Ma *et al*., 2010; Lu *et al*., 2014; Tan *et al*., 2015). The role of miR-26a is considered as suppressor of cell proliferation and colony formation by inducing G1 cell-cycle arrest. In NPC cell line, it suppresses the expression of several onco-proteins, such as EZH2 (Zeste homolog 2), c-Myc, cyclins D3, E2 and cyclin-dependent kinases, and enhance the expression of CDK inhibitor p14 (ARF), p21 (CIP1) (Lu *et al*., 2011; Tan *et al*., 2015). The downregulation of EZH2 leads to the inhibition of cell growth and cell cycle progression (Lu *et al*., 2011; Yu *et al*., 2013). Studies have confirmed the expression of miR-26c is declined and significant correlated to cell growth and tumorigenesis of nasopharyngeal carcinoma (Lu *et al*., 2011; Yu *et al.*, 2013; Tan *et al*., 2015). The role of miR-200a was reported as the tumor suppressor gene that inhibits nasopharyngeal carcinoma cell growth, migration and invasion by mediated downregulation of ZEB2 and CTNNB1 (Xia *et al*., 2010). The downregulation of miR-200a was significantly associated to the nasopharyngeal tumorigenesis (Xia *et al*., 2010; Tan *et al.*, 2015). Other member of miR-200 family, miR-200b suppresses cell growth, migration and invasion by targeting Notch1 in NPC. According to Yang et al. (2013), miR-200b was significantly downregulated in NPC tissues and cell lines. *In vivo* studies indicate that overexpression of miR-200b effectively inhibits the growth of tumor in nude mouse models (Yang *et al*., 2013). Let-7 family is a tumor suppressing miRNAs and its downregulation in many human malignancies, including NPC (Wong *et al*., 2011). It regulates numerous oncogenes such as RAS, c-Myc, and HMGA2 (Büssing *et al*., 2008). Mechanically, high let-7 levels suppresses the expression of c-Myc. Its declination leads to the inhibition of NPC cell

proliferation (Büssing *et al*., 2008; Tan *et al*., 2015). Therefore, NPC cell exhibits reduced levels of miRNA Let-7 family, including Let-7a, b, c, d, e, g and i (Büssing *et al*., 2008; Wong *et al.*, 2011; Tan *et al*., 2015).

3. MiRNA functions as oncogene in regulating of NPC

Functionally active miRNAs in NPC tumorigenesis include miR-16, miR-18, miR-214, miR-218, miR-155, miR-141, miR-144, miR-155, etc. represent oncogenic effects called Onco-miRNAs (Jeffrey, *et al.*, 2008; Tan *et al*., 2015). Studies have indicated that onco-miRNAs is aberrant overexpression and significantly correlated to NPC tumorigenesis. According to research of Liu *et al.* 2013, they found that miR-16, miR-21, miR-24 and miR-155 significant increase in NPC patients, especially, combination of those miRNAs giving the high sensitivity and specificity for NPC diagnosis (Liu *et al.*, 2013). miR-141 is involved in a nasopharyngeal carcinoma. According to Zhang *et al*., miR-141 was upregulated in NPC specimens in comparison with normal nasopharyngeal epithelium. BRD3, UBAP1, and PTEN are potential targets of miR-141. BRD3 and UBAP1 are both involved in NPC tumorigenesis, in which, BRD3 is involved in the regulation of the Rb/E2f pathway (Zhang *et al*., 2010). miR-155 is proved to be upregulated in many human tumors, including NPC. The overexpression of miR-155 could be induced by the infection of EBV, in which modulated EBV-regulated pathways (Du *et al*., 2011). LMP-1 and EBNA-2 are responsible for the upregulation of miR-155 after EBV infection. Furthermore, LMP1 also trans-activates miR-155 expression through the NF-κB and AP1 pathway (Flemington *et al*., 2008; Gatto *et al*., 2008). Additionally, miR-155 expression is upregulated and correlated with plasma DNA copies of LMP1. Upregulated level of miR-155 is considered to stimulate NPC cell proliferation, colony formation, cell migration, and invasion (Zhu *et al*., 2014). miR-214 is known to be upregulated in NPC cell lines and cell tissues through promotes NPC cell proliferation and invasion, tumor formation and lung metastasis. According to Zhang *et al*. (2014), they reported that silencing of miR-214 by LNA-antimiR-214 (locked-nucleic-acid–anti-miR-214) in NPC cells resulted in promoting apoptosis and suppressing cell proliferation *in vitro*, and suppressed tumor growth in nude mice *in vivo*. miR-214 was considered to be important role in NPC tumorigenesis (Zhang *et al*., 2014). miR-378 stimulated tumor cell colony formation, migration, cell invasion *in vitro*, as well as tumor growth *in vivo*. Upregulated or downregulated miR-378 enhances or represses the expression of tumor inhibition TOB2 (ERBB2), which is widely repressed in tumor tissues (Yu *et al.*, 2014). High level of miR-663 is also observed in NPC cell. Inhibition of miR-663 represses NPC cell proliferation *in vitro* and tumor cell growth in nude mice. miR-663 directly targets p21, regulating cell cycle through G1/S transition (Yi *et al.*, 2012).

4. MiRNAs and NPC metastasis

NPC is considered having high invasion and metastasis, which caused round 90% of cancer death. In NPC miRNA study, several miRNAs have been reported that having roles in cancer metastasis regulation. According to Wang *et al*. (2014), miRNA-30a has been showed to regulate cancer metastasis, and is identified to be down-regulated in NPC primary tumors (Wang *et al*., 2014). In the case of NPC, the molecular mechanism has not been clearly elucidated, otherwise, by computational algorithms, E-cadherin was screened as a putative target gene of miR-30a (Wang *et al.*, 2014). miR-34c was also indicated to be significant downregulated in NPC cell line and clinical NPC tissues. MET proto-oncogene was identified as a direct target of miR-34c, the overexpression of miR-

34c was proved as suppressed NPC proliferation, migration and invasion. Taken together, it indicated that the downregulation of miR-34c had an important role in the development, invasion and migration of NPC (Li *et al*. 2015). In NPC specimens and cell lines, miR-144 was frequently upregulated and recognized as an important mechanism of NPC tumorigenesis. Repression of expression of miR-144 significant decreased cell proliferation, clonogenicity, migration and invasion. miR-144 is inversely correlated with the expression of TSGs phosphate and tensin homolog (PTEN) in NPC specimens and cell lines, as the result, miR-144 suppressed the PTEN expression to increase the expression of pAKt (phosphorylated protein kinase B) and Cyclin D1 and promote G(1)-phase transition and then decreased the expression of E-cadherin to promote migration and invasion (Zhang *et al.,* 2013). miR-149 may be involved in the invasion and metastasis of NPC through regulation of epithelial-mesenchymal transition (EMT) and by downregulating the expression of E-cadherin (Luo *et al.,* 2011; Tan *et al*., 2015). The effect of miR-10b has been reported to play an important action in metastasis of NPC cells. Inhibitors of miR-10b reduced the ability of NPC cell lines to migrate and invade. The expression of miR-10b related to migration and invasion related gene as E-cadherin, vimentin, and MMP-9. The overexpression of miR-10b was observed in NPC (Sun *et al*., 2013; Tan *et al*., 2015). miR-200a acted as a metastasis, growth, migration and invasion inhibitor which was observed in C666-1 cells. By targeting TIAM1, miR-29c suppressed NPC cell invasion and metastasis in nasopharyngeal carcinoma (Liu *et al*., 2012).

5. EBV-encoded miRNA in NPC

The prior infection with EBV (Epstein-Barr Virus) has been considered as an etiologic factor for NPC. Novel EBV-miRNA genes from NPC was reported by Zhu *et al.* (2009). They reported the miRNA profile of EBV-positive NPC tissue samples characterized by cloning and sequencing. EBV miRNA genes originating from BART region that found in NPC tissues. Among EBV-miRNAs, high levels of EBV-miR-BART1, EBV-miR-BART4, EBV-miR-BART6, EBV-miR-BART7, EBV-miR-BART11, EBV-miR-BART12, EBV-miR-BART19, EBV-miR-BART21, and EBV-miR-BART22 (Zhu *et al.,* 2009; Tan *et al.,* 2015). Giving examples, EBV-miR-BART-1 was involved in regulating the metabolism-associated genes in NPC. EBV-miR-BART-7 was observed in high level in NPC cell within the enhancing the proliferation, migration, and invasion of NPC cell *in vitro* study (Chan *et al.,* 2012; Tan *et al.,* 2015).

6. MiRNA as the therapeutic and diagnosis of NPC

miRNAs have been applied as great potential therapeutic and diagnosis agents for NPC. The need for clinical biomarkers for early diagnosis and prognosis of NPC, it should be increased the survival and successful treatment of NPC patients. In many studies, miRNAs have been reported that played important roles in regulating diverse cellular processes, such as proliferation, apoptosis, migration, and invasion, etc. In NPC, it could be function as tumor suppressor or oncogenes (Yumei, *et al.*, 2014). According to Zheng *et al.* (2014), most of NPC patients with a poor outcome exhibited high expression (> median) of miR-548q (70.6%) and miR-483-5p (64.7%) in tissue samples. The higher expression levels of miR-548q and miR-483-5p were found in NPC cell lines (CNE1, CNE2, and HNE1), when compared to an immortalized NPC cell line (NP69) and clinical biopsy tissues. It was suggested that those miRNAs involved in NPC development (Zheng *et al.,* 2014). It indicated that their prognosis roles in NPC and should be explored as a potential biomarker in the future

(Zheng *et al.*, 2014). Furthermore, based on the results of their 50 microarrays, they found that 39 miRNAs exhibited significant expression difference in NPC, such as miR-122, miR-630, miR-135a, miR-572, miR-940, miR-29c, etc. (Zheng *et al*., 2014). The level of plasma miR-9 declined and significant correlated to increasing of lymphatic invasion and advanced TNM stage. Thus, miR-9 plasma may serve an useful biomarker to predict the NPC development (Lu *et al.*, 2014). Exponentially growing studies conferred that potential of miRNAs to modulate diverse biological process. Further, numerous studies had briefly approved the treatment of miRNA-based therapeutic strategies in various cancers, including nasopharyngeal cancer. miR-214 was identified to be significantly higher expression in NPC compared to control (Deng *et al.*, 2013; Zhang *et al.*, 2014). According to Zhang et al. (2014), knockdown of miR-214 promotes apoptosis and inhibits cell proliferation in NPC. They finding suggested that miR-214 played an important role in NPC, and might be potentially therapeutic target for NPC patients (Zhang *et al*., 2014).

7. Conclusion

In summary, miRNA had the vital roles contributing to the progression and development of NPC by regulating several cell processes. The observation of miRNAs expression in NPC, comparing with the non-cancer samples, indicates the useful of biomarkers to prognosis and diagnosis of NPC. Furthermore, promising results of miRNAs-based therapy had been also achieved by many studies. Together, miRNAs would be potential biomarkers of early prognosis and diagnosis, and therapeutic agents in future.

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