Acta Pharmacologica Sinica (2012) 33: 981–982
 1671-4083/12 $32.00
www.nature.com/aps

Research Highlight

MicroRNAs: novel factors in clinical diagnosis and prognosis for nasopharyngeal carcinoma

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Acta Pharmacologica Sinica (2012) 33: 981–982; doi: 10.1038/aps.2012.98; published online 2 Jul 2012

Nasopharyngeal carcinoma (NPC) is a non-lymphomatous, squamous cell malignancy arising from the epithelial cells lining of the nasopharynx. Histologically, NPC has been classified into 3 types: keratinizing squamous cell carcinoma (WHO type I), differentiated non-keratinizing squamous cell carcinoma (WHO type II) and undifferentiated carcinomas (WHO type III). Compared to other malignant tumours of the upper aero digestive tract, NPC is a special type of head and neck cancer in terms of epidemiology, pathology and clinical presentation. The etiology of NPC involves multiple factors, including genetic susceptibility, exposure to chemical carcinogens and Epstein-Barr virus (EBV) infection[1]. In some regions, notably the southern parts of China, and parts of Southeast Asia, this cancer occurs in an endemic form with an incidence 10- to 30-fold higher than in the other regions and, histologically, usually belongs to WHO type II and III. In the west, however, NPC occurs sporadically and usually belongs to WHO type I. There is also increased incidence in northern Africa and the Inuit of Alaska[2, 3].

MicroRNAs (miRNAs) are a class of small non-coding RNA molecules, 19–25 nucleotides in length, that negatively regulate gene expression through binding the 3′-untranslated region (3′-UTR) of targeted transcripts, resulting in mRNA cleavage or translation repression[4]. About 30% of human genes are regulated by miRNAs. MicroRNAs are frequently deregulated in many types of cancers, and play critical roles in tumorigenesis, which regulate the expression of oncogenes or tumour suppressor genes.

In a recent issue of *Lancet Oncol*, Liu *et al*[5] reported that 41 miRNAs were differentially expressed between nasopharyngeal carcinoma and non-cancer nasopharyngitis tissues (fold change≥2.5, false discovery rate 0). Previous reports showed that miRNAs were aberrantly expressed in nasopharyngeal carcinoma compared with normal epithelial tissue, and promoted an aggressive tumour phenotype by changing the expression of their mRNA targets[6–8]. For instance, Sengupta *et al*[6] investigated the expressions of 207 miRNAs in 31 NPCs and 10 normal tissues with miRNA microarrays, and demonstrated the involvement of miR-29c in NPC metastasis by regulating mRNAs encoding extracellular matrix proteins. Chen *et al*[7] studied the expression of 270 human miRNAs in 13 NPC samples in comparison with 9 adjacent normal tissues using a stem-loop real-time PCR assay, and found the expressions of 35 miRNAs were significantly altered in NPC, thus inferred that some cancer-related pathways enriched with targets of down-regulated miRNAs. We also demonstrated with microarray that 34 miRNAs were differentially expressed between 8 NPC and 4 normal tissues[8]. Furthermore, we identified 2 novel pathways, targeted by the altered miRNAs, were strongly associated with NPC development, and a c-Myc centred miRNA regulatory network was inferred in NPC. These reports indicate that some important miRNAs can be used as markers for differential diagnosis of NPC from non-cancer nasopharyngitis patients. Interestingly, in all the 4 studies, miR-34c has been found under-expression in NPC specimens, suggesting that that this miRNA plays a crucial role in NPC development and progression. However, the functions of miR-34c were still unclear in NPC. Additionally, 3 out of the 4 reports showed that 3 miRNAs (miR-34b, miR-29c and miR-100) in NPC were down-regulated. Here, we pay attention to the miR-29 family because miR-29a and miR-29b were also under-expressed in NPC as shown in 2 of the 4 reports. We consider that the miR-29 family is important to judge the development and progression of NPC, at least in clinical NPC samples.

Furthermore, Liu and his colleagues established a signature of 5 miRNAs (miR-142-3p, miR-29c, miR-26a, miR-30e and miR-93) from the 41 differentially expressed miRNAs as independent prognostic factors and risk scores in NPC patients. Compared with patients with low-risk scores, patients with high-

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risk scores had shorter disease-free survival (DFS), distant metastasis-free survival (DMFS) and overall survival. This finding shows that the miRNAs have significant value for determing the survival prognosis, in addition to judgement of NPC development and progression. It reminds us that miRNAs may be used as makers in NPC classification and allowing clinicians to diagnose patients more early and accurately. In addition, the authors found that patients of TNM stages III–IV with low risk scores had a favourable response to concurrent chemotherapy, while patients of the same stages with high risk scores did not benefit from concurrent chemotherapy. This finding suggests that miRNA signature has more prognostic values in concurrent chemotherapy than TNM staging, although these two classification systems have same predictive ability of patient survival. The TNM staging system provides a useful benchmark for establishing the prognostic definition and treatment strategy. Usually, early-stage NPC patient should be treated with radiotherapy, whereas patient with advanced disease should receive chemoradiotherapy. However, large variations in the clinical outcomes were found in patients with the same stage and similar treatment regimens[9]. It is suggested that the present staging system is inadequate for definition of prognosis. Thus, a novel signature, independent of TNM staging, is needed for predictive of survival of patients with NPC and allowing clinicians to potentially identify candidates for aggressive therapy to improve treatment outcomes. Combination of the five-miRNA signature and TNM stage has a better prognostic value than did TNM stage alone in the NPC patients.

As the important roles of miRNAs in cancer are gradually revealed, their potential applications as predictive markers and treatment targets have generated great interest in cancer diagnosis, as well as classification, prognosis, risk factor evaluations and therapy strategies. The result of Liu *et al* provide a new insight into NPC development and progression, and have potential implication in NPC patients survival prognosis and personalised therapy.

1 Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 2005; 365: 2041–54.
2 Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol 2002; 12: 421–9.
3 Nielsen NH, Mikkelsen F, Hansen JP. Nasopharyngeal cancer in Greenland. The incidence in an Arctic Eskimo population. Acta Pathol Microbiol Scand A 1977; 85: 850–8.
4 Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009; 136: 215–33.
5 Liu N, Chen NY, Cui RX, Li WF, Li Y, Wei RR, *et al*. Prognostic value of a microRNA signature in nasopharyngeal carcinoma: a microRNA expression analysis. Lancet Oncol 2012; 13: 633–41.
6 Sengupta S, den Boon JA, Chen IH, Newton MA, Stanhope SA, Cheng YJ, *et al*. MicroRNA 29c is down-regulated in nasopharyngeal carcinomas, up-regulating mRNAs encoding extracellular matrix proteins. Proc Natl Acad Sci U S A 2008; 105: 5874–8.
7 Chen HC, Chen GH, Chen YH, Liao WL, Liu CY, Chang KP, *et al*. MicroRNA deregulation and pathway alterations in nasopharyngeal carcinoma. Br J Cancer 2009; 100: 1002–11.
8 Li T, Chen JX, Fu XP, Yang S, Zhang Z, Chen KhH, *et al*. microRNA expression profiling of nasopharyngeal carcinoma. Oncol Rep 2011; 25: 1353–63.
9 Mao YP, Xie FY, Liu LZ, Sun Y, Li L, Tang LL, *et al*. Re-evaluation of 6th edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement based on magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2009; 73: 1326–34.