



**Karolinska
Institutet**

Institutionen för mikrobiologi, tumör- och cellbiologi

Biomarkers in Nasopharyngeal Carcinoma

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
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av

Zi-Ming Du

Huvudhandledare:

Professor Ingemar Ernberg
Karolinska Institutet
Institutionen för mikrobiologi, tumör- och
cellbiologi

Bihandledare:

Professor Jian-Yong Shao
Sun Yat-sen University Cancer Center,
Guangzhou, China
Department of Molecular Diagnostics

Docent Lifu Hu

Karolinska Institutet
Institutionen för mikrobiologi, tumör- och
cellbiologi

Fakultetsopponent:

Professor Jaap Middeldorp
Vrije Universitet Amsterdam, Netherland
Department of Pathology, Cancer Center

Betygsnämnd:

Docent Dawei Xu
Karolinska Institutet
Department of Medicine, Solna

Professor Ann-Beth Jonsson

Stockholm University
Department of Genetic, Microbiology, and
Toxicity

Professor Laszlo Szekely

Karolinska Institutet
Department of Microbiology, Tumor and Cell
Biology

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is one of the most common malignancies in certain areas of Southern China, Southeastern Asia and Northern Africa. Currently, evaluation of NPC prognosis is mainly based on the tumor-node-metastasis (TNM) staging system. However, NPC patients with the same clinical stage often present different clinical courses, suggesting that the TNM staging is insufficient to predict prognosis of this disease. Therefore, it is important to find molecular biomarkers, which can help clinicians to identify NPC patients with worse prognosis and develop therapeutic interventions in NPC patients.

This thesis presents the identification and investigation of mechanism of several novel markers in NPC. In the first paper, Caveolin-1 (Cav-1), a major structural component of caveolae, and CD147 (also known as extracellular matrix metalloproteinase inducer, EMMPRIN), a glycoprotein, were found to be overexpressed in NPC. Both Cav-1 and CD147 expression levels correlated significantly with metastasis and poor prognosis of NPC patients. Further studies revealed that Cav-1 and CD147 enhance NPC cell migration, which is associated with MMP-3 and MMP-11 (active) secretion.

The role of microRNA-155 (miR-155) is associated with oncogenesis of several human tumors. In the second paper, miR-155 was found to be upregulated in NPC cell lines and clinical samples. EBV encoded LMP1 and LMP2A could further enhance the expression of miR-155 in NPC CNE1 and TW03 cells. JMJD1A was identified as a direct target of miR-155 in NPC. Downregulation of JMJD1A was significantly correlated with N stage of the TNM classification, a lower five-year survival rate, and a lower five-year disease-free survival rate of NPC patients.

Spleen tyrosine kinase (Syk) is a nonreceptor tyrosine kinase and often aberrantly expressed in human cancers. In the third paper, high expression of Syk was detected in 24% of NPC cases. High expression of Syk, resulted partly from LMP2A expression in NPC, is associated with tumor recurrence and poor prognosis of NPC patients.

Human chromosome 3 (Chr. 3) contains clusters of tumor suppressor genes (TSGs) involved in many cancer types. In the fourth paper, using Not I Chr. 3 microarray, ten candidate TSGs were found in NPC. Among them, the CpG island in the promoter region of Wingless-type Mouse mammary tumor virus integration site family, member 7A (WNT7a) and the intron 1 region of Integrin α 9 (ITGA9) were confirmed to be hypermethylated in NPC by bisulfite sequencing and methylation specific PCR. Demethylating agent 5-aza-2'-deoxycytidine (5-aza-CdR) treatment could restore the expression of WNT7a and ITGA9 in NPC cell lines. Furthermore, WNT7a and ITGA9 were downregulated in NPC clinical samples. As both proteins execute significant functions related to the tumor cell biology, the potential of WNT7a and ITGA9 as diagnosis or therapeutic targets for NPC should be considered.