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Characterization and Prognostic Significance of Methylthioadenosine Phosphorylase Deficiency in Nasopharyngeal Carcinoma

Hong-Lin He, MD, Ying-En Lee, MD, Yow-Ling Shiue, PhD, Sung-Wei Lee, MD, Tzu-Ju Chen, MD, and Chien-Feng Li, MD, PhD

Abstract: Identification of cancer-associated genes by genomic profiling contributes to the elucidation of tumor development and progression. The *methylthioadenosine phosphorylase* (*MTAP*) gene, located at chromosome 9p21, plays a critical role in tumorigenicity and disease progression in a wide variety of cancers. However, the prognostic impact of MTAP in patients with nasopharyngeal carcinoma (NPC) remains obscured. Through data mining from published transcriptomic database, *MTAP* was first identified as a differentially downregulated gene in NPC. In this study, our aim was to evaluate the expression of MTAP in NPC and to clarify its prognostic significance.

MTAP immunohistochemistry was retrospectively performed and analyzed in biopsy specimens from 124 NPC patients who received standard treatment without distant metastasis at initial diagnosis. The immunoexpression status was correlated with the clinicopathological variables, disease-specific survival (DSS), distant metastasis-free survival (DMFS), and local recurrence-free survival (LRFS). Real-time quantitative polymerase chain reaction (PCR) was used to measure *MTAP* gene dosage. In some cases, we also performed methylation-specific PCR and pyrosequencing to assess the status of promoter methylation.

MTAP deficiency was significantly associated with advanced tumor stages ($P = 0.023$) and univariately predictive of adverse outcomes for DSS, DMFS, and LRFS. In the multivariate comparison, MTAP deficiency still remained prognostically independent to portend worse DSS ($P = 0.021$, hazard ratio = 1.870) and DMFS ($P = 0.009$, hazard ratio = 2.154), together with advanced AJCC stages III to IV. Homozygous deletion or promoter methylation of *MTAP* gene were identified to be significantly associated with MTAP protein deficiency ($P < 0.001$).

MTAP deficiency was correlated with an aggressive phenotype and independently predictive of worse DSS and DMFS, suggesting its role in disease progression and as an independent prognostic biomarker of NPC, which potentially offers new strategy of targeted treatment for patients lacking MTAP expression.

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Abbreviations: 6-TG = 6-thioguanine, aCGH = array comparative genomic hybridization, DMFS = distant metastasis-free survival, DSS = disease-specific survival, EBV = Epstein–Barr virus, LRFS = local recurrence-free survival, MMP = matrix metalloproteinase (MMP), MTA = methylthioadenosine, MTAP = methylthioadenosine phosphorylase, NPC = Nasopharyngeal carcinoma, ODC = ornithine decarboxylase, PCR = polymerase chain reaction, PRPP = 5-phosphoribosyl-1-pyrophosphate, RT = radiotherapy.

INTRODUCTION

Nasopharyngeal carcinoma (NPC), a common head and neck malignancy in southeastern Asia and Taiwan, is caused by a combination of factors, including Epstein–Barr virus (EBV) infection, environmental influence, and genetic susceptibility.[1] In endemic areas, NPC is strongly associated with EBV infection.[2] However, little is known about the molecular mechanism underlying NPC pathogenesis. Although advances in concurrent chemoradiotherapy have led to better locoregional control and overall survival, treatment options for advanced disease are still limited.[3] Therefore, it would be of great value to work out molecular mechanisms of this cancer and to search for potential prognostic biomarkers. New biomarkers can help to stratify the risk of disease progression and to develop novel therapeutic strategies for NPC patients in a personalized manner.

Mounting evidence has suggested that DNA losses of chromosome 9 are identified in a variety of cancers, particularly 9p21 that harbors several candidate or established tumor suppressor genes, such as *CDKN2A* (also known as $p16^{INK4A}$/$p14^{ARF}$), *CDKN2B* (also known as $p15^{INK4B}$), and *MTAP* (*methylthioadenosine phosphorylase*).[4–10] The *MTAP* gene, which lies about 100 kb telomeric to *CDKN2A*, is frequently co-deleted with the *CDKN2A* and *CDKN2B* genes in many different cancers.[6,7,10–12] *MTAP* encodes a key enzyme in the catabolism of methylthioadenosine (MTA), which is generated during the biosynthesis of polyamines. MTAP is expressed abundantly in a wide range of normal cells and tissues. In normal cells, MTAP cleaves MTA into adenine and

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From the Department of Pathology, E-DA Hospital, I-Shou University, Kaohsiung, Taiwan (H-LH); Institute of Biomedical Science, National Sun Yat-Sen University, Kaohsiung, Taiwan (H-LH, Y-LS); Department of Anesthesiology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan (Y-EL); Department of Radiation Oncology, Chi-Mei Medical Center, Liouying, Tainan, Taiwan (S-WL); Department of Pathology, Chi-Mei Medical Center, Tainan, Taiwan (T-JC, C-FL); National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan (C-FL); Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan (C-FL); and Institute of Clinical Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan (C-FL).
Correspondence: Chien-Feng Li, Department of Pathology, Chi-Mei Medical Center, Tainan, Taiwan (email: angelo.p@yahoo.com.tw).
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