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Original Article

The prognostic impact of RAP2A expression in patients with early and locoregionally advanced nasopharyngeal carcinoma in an endemic area

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Abstract: Background: By data mining from published transcriptomic databases, we identified *RAP2A* as a significantly upregulated gene in nasopharyngeal carcinoma (NPC) tissues. *RAP2A*, a member of the RAS oncogene family, is involved in the process of GTP binding and GTPase activity. The aim of this study was to evaluate the expression of RAP2A and its prognostic impact in patients with early and locoregionally advanced NPC. Methods: RAP2A immunohistochemistry was performed for 124 NPC patients who were receiving standard treatment and had no initial distal metastasis. We also performed Western blotting to evaluate the endogenous protein expression of RAP2A in NPC cells and non-neoplastic mucosal cells. The result of RAP2A expression was further correlated with clinicopathological variables, disease-specific survival (DSS), distant metastasis-free survival (DMeFS), and local recurrence-free survival (LRFS). Results: High expression of RAP2A was significantly associated with advanced primary tumor status ($P = 0.024$) and advanced TNM stage ($P = 0.006$). In univariate analysis, high expression of RAP2A served as a significant prognostic factor for inferior DSS ($P < 0.0001$), DMeFS ($P < 0.0001$), and LRFS ($P < 0.0001$). In multivariate analysis, RAP2A overexpression still independently predicted worse DSS (hazard ratio [HR] = 2.976, $P < 0.001$), DMeFS (HR = 4.233, $P < 0.001$), and LRFS (HR = 4.156, $P < 0.001$). Moreover, Both HONE1 and TW01 NPC cells, but not non-neoplastic DOK cells demonstrated significantly increased RAP2A expression. Conclusion: Overexpression of RAP2A is associated with advanced disease status and may therefore be an important prognosticator for poor outcomes in NPC, as well as a potential therapeutic target to aid in developing effective treatment modalities.

Keywords: RAP2A, nasopharyngeal carcinoma, NPC, GTPase

Introduction

There is a marked geographic variation in the incidence of nasopharyngeal carcinoma (NPC). It is rare in the United States and Western Europe, but is endemic in southern China and Taiwan. This tumor occurs more commonly in males, with the male: female ratio approaching 2-3:1 [1]. The geographic variation of NPC incidence suggests a multifactorial etiology, including Epstein-Barr virus (EBV) infection, genetic predisposition, and environmental factors such as smoking and high intake of preserved foods [2, 3]. In the endemic area, approximate 99% of cases are classified as non-keratinizing or undifferentiated carcinoma, showing strong association with EBV [4]. Radiotherapy is the mainstay of first-line local treatment for early stage NPC. For more advanced disease, concurrent cisplatin-based chemoradiotherapy improves local control and decreases the rate of distant metastasis [5]. Despite recent ad-