Karolinska Institutet

Institutionen för mikrobiologi, tumör- och cellbiologi

Basis for Reclassification of Nasopharyngeal Carcinoma

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i MTC lecture hall, Theorells väg 1

Torsdag 12 april, 2012 kl 09:00

av

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Stockholm 2012

ABSTRACT

Nasopharyngeal carcinoma (NPC) shows broad differences in racial and geographical distribution, radiosensitivity, and a multifactorial etiology. This thesis aims to identify molecular biomarkers with potentially valuable for prognostic implications in NPC.

This thesis involved a series of studies which were performed on cohorts of patients with NPC to investigate the genetic alterations, Epstein-Barr virus (EBV) infection, and gene expression profiles, and to assess their correlations with clinicopathological parameters and survival of NPC patients. The results indicated that overexpression of caveolin-1 (Cav-1) and extracellular matrix metalloproteinase inducer (EMMPRIN/CD147) in NPC were significantly associated with TNM stage, metastasis, and poor prognosis (Paper I). Loss of heterozygosity (LOH) on 9p21, 16q and 19q13 may be responsible for tumor aggression behavior and progression of NPC, with a possible interaction between allelic loss and EBV infection in the etiology of NPC (Paper II). EBV latent membrane protein (LMP) 1 overexpression was significantly correlated with p53 accumulation in NPC, $CD8^+$ T cell infiltration, and matrix metalloproteinase (MMP) 9 overexpression in NPC cells. Moreover, plasma EBV DNA was detectable at a high frequency in primary NPC (96%). Higher plasma EBV-DNA levels were positively correlated with advanced TNM stages, lymph node metastasis, and NPC relapses (Papers III-V). Overexpression of LMP1 regulated the mTOR signaling pathway in NPC, possibly through phosphorylation of AKT/mammalian target of rapamycin (mTOR)/phospho-P70S6 kinase (P70S6K)/4EBP1. LMP1 expression was closely correlated with expression of p-mTOR, p-P70S6K and p-4EBP1 in NPC tumors, while expression levels of p-P70S6K, p-4EBP1 and LMP1 were significantly correlated with overall survival in NPC patients (Paper V).

Paper VI presents a new molecular NPC-space vector modulation (SVM) classifier, which integrates sex and seven genes, including LMP1, CD147, Cav-1, p-P70S6K, MMP11, survivin, and secreted protein acidic and rich in cysteine (SPARC). This NPC-SVM classifier could refine the classification of NPC patients into high- and low-risk groups, which demonstrated significant differences in 5-year disease-specific survival (DSS) rates in a group of 411 validation patients (86.2% *vs.* 37.6%, $p<0.001$). Paper VII presents a new histological classification study, which was developed mainly on the basis of morphological characteristics and tumor cell differentiation. Of 3,839 tumors, 2,057 (53.6%) were histologically classified as undifferentiated epithelial cell carcinoma (UECC), 942 (24.5%) as undifferentiated mixed epithelial-sarcomatoid cell carcinoma (UESCC), 640 (16.7%) as undifferentiated sarcomatoid cell carcinoma (USCC), and 200 (5.2%) as squamous cell carcinoma (SCC). Based on the new histological classification system, the 5-year DSS rates were 76.4% for UECC, 66.0% for UESCC, 56.0% for USCC, and 32.7% for SCC. Stratified according to the new classification, patients with UECC and UESCC who received radiochemotherapy (RCT) showed better 5-year DSS rates than those who received radiotherapy (RT) alone.

In summary, the results of these studies indicate that LOH, differentially-expressed genes, and EBV markers can act as prognostic biomarkers in NPC patients. The NPC-SVM classifier and the new proposed histopathological classification provide better discriminative prediction of NPC prognosis than the current WHO classification, as well as a means of monitoring the therapeutic efficacy of RCT and RT in advanced-stage NPC patients.

ISBN: 978-91-7457-699-3