学 位 論 文 の 要 旨

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主論文の題名

RERG suppresses cell proliferation, migration and angiogenesis through ERK/NF-κB signaling pathway in nasopharyngeal carcinoma

主論文の要旨

Background:

Nasopharyngeal carcinoma (NPC) is a malignancy of the head and neck that is prevalent in Southeast Asia and southern China. Recent studies in epigenetics suggest that DNA methylation plays a pivotal role in the onset and progression of cancer. Combining the methyl-DNA binding domain capture technique and cDNA microarray analysis, we identified a unique hypermethylated gene, RERG (Ras-like estrogen-regulated growth inhibitor), that was down-regulated in NPC tissues. RERG is a tumor suppressor gene that was first reported in breast cancer. However, the functions of RERG are largely unknown in other tumor types.

Methods:

RERG expression was assessed in human subjects (NPC primary tissues and non-cancer tissues) and cell lines (NPC cell lines and an immortalized epithelial cell line NP460). Further, we investigated the methylation rate of RERG in both human subject and cell lines. 5-Aza-2'-deoxycytidine (Aza) or combined with trichostatin A (TSA) were treated to three NPC cell lines (HK1, C666-1 and HK1_EBV). In addition, the role of RERG in NPC cells and its underlying mechanisms were explored by overexpression RERG in NPC cell lines.

Results:

RERG was significantly down-regulated in NPC cancer nests compared to normal nasopharyngeal epithelium cells. Furthermore, the RERG promoter was frequently methylated in NPC tissues and cell lines. The RERG methylation rate yielded an area under the curve (AUC) of receiver operating characteristic (ROC) curve was 0.897 (95%CI: 0.818–0.976). The down-regulation of RERG was restored in NPC cells treated with Aza and

TSA. In addition, ectopic expression of RERG in NPC cell lines resulted in a significant suppression of cell proliferation, clonogenicity, migration and invasion. RERG-overexpressing cells showed significantly slower growth and less angiogenesis in tumor xenografts in nude mice. RERG suppressed the ERK/NF-κB signaling pathway and inhibited tumor growth and angiogenesis with down-regulation of MMPs and IL8 in tumors of nude mouse xenografts.

Conclusions:

Our results suggest that RERG is frequently silenced by promoter CpG methylation in NPC, and acts as a functional tumor suppressor by suppressing the ERK/NF-κB signaling pathway. These findings support the potential use of RERG as a novel molecular target in NPC therapy.