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CIP2A Is Overexpressed in Gastric Cancer and Its Depletion Leads to Impaired Clonogenicity, Senescence, or Differentiation of Tumor Cells

Wenjuan Li,1,3 Zheng Ge,3 Cheng Liu,3 Zhifang Liu,2 Magnus Björkholm,3 Jihui Jia,1 and Dawei Xu3

Abstract

Purpose: Cancerous inhibitor of protein phosphatase 2A (CIP2A) is an oncogenic factor stabilizing c-MYC protein and driving cellular transformation. We determine whether CIP2A expression can serve as a marker for gastric cancer and investigate the mechanism underlying CIP2A-mediated transformation and cell proliferation.

Experimental Design: Normal and malignant gastric tissues derived from 37 patients with gastric cancer were analyzed for CIP2A expression using reverse transcription-PCR and immunohistochemical staining. Gastric and other cell lines with different p53 and pRB backgrounds were used to inhibit CIP2A expression using small interfering RNA and then examined for clonogenic potentials, senescence, or differentiation.

Results: CIP2A mRNA was present in 34 of 37 (90%) of tumor specimens but absent in 27 of 37 (73%) of matched normal gastric mucosa. In 10 adjacent normal tissues with detectable CIP2A mRNA, 6 of them exhibited much weaker levels of CIP2A compared with their corresponding tumors. Thus, a total of 32 (87%) gastric cancer samples overexpressed CIP2A. CIP2A protein expression was readily detectable in the tumor tissues but absent in normal gastric mucosa. Depleting CIP2A expression substantially inhibited growth and clonogenic capabilities of tumor cell lines independently of p53 and pRB pathways. Gastric cancer–derived AGS cells underwent senescence following the inhibition of CIP2A expression. Moreover, CIP2A depletion triggered partial differentiation of leukemic HL60 cells.

Conclusion: CIP2A in tumor cells is required for sustained proliferation by preventing cell growth arrest, senescence, or differentiation and its expression is significantly (P < 0.001) discriminatory between normal and cancerous gastric tissue.

Gastric cancer is one of the most common malignancies worldwide and ranks second in terms of global cancer-related mortality (1, 2). Helicobacter pylori infection has been shown to initiate the pathogenesis of gastric cancer by causing a chronic gastritis, the precursor to all the pathophysiologic abnormalities characteristic of gastric carcinogenesis (1, 3, 4). However, these precursor lesions only develop in a proportion of infected subjects and do not necessarily progress into invasive cancers. The host genetic, bacterial virulence, environmental, and many other factors have been implicated in affecting the gastric oncogenic process, but the underlying molecular mechanism is poorly understood (1, 3). Moreover, because of lack of reliable early diagnostic markers, the prognosis of gastric cancer remains poor. Therefore, better defining the pathogenesis of gastric cancer, looking for useful biomarkers, and exploring novel therapeutic targets for treatment are urgently demanding tasks (1–3).

A hallmark of cancer is unlimited cellular proliferation due to the aberrant expression of key factors regulating cell cycle progression, apoptosis, senescence, and differentiation (5). One of these molecules, named cancerous inhibitor of protein phosphatase 2A (PP2A; CIP2A), has recently been identified to stabilize c-MYC protein by inhibiting its degradation mediated by PP2A in cancer cells and to be required for the malignant cell growth (6). When overexpressed, CIP2A transforms immortalized human cells. Furthermore, CIP2A was observed to be highly expressed in human neck and head carcinomas and colon cancers (6). Taken together, CIP2A functions as an oncoprotein contributing to malignant transformation of human cells. In the present study, we compared CIP2A expression between normal and malignant gastric tissues to determine whether CIP2A could serve as a diagnostic marker for gastric cancer; moreover, we sought to investigate the