Alteration of DNA Methylation in Gastric Cancer with Chemotherapy

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Introduction

Epigenetic alterations such as DNA methylation, histone acetylation, and chromatin remodeling can control gene expression by regulating gene transcription. DNA methylation is one of the frequent epigenetic events that play important roles in cancer development. Cancer cells can gain significant resistance to anticancer drugs and escape programmed cell death through major epigenetic changes, including DNA methylation. To date, several research groups have identified instances of both (i) hypermethylation of tumor suppressor genes, and (ii) global hypomethylation of oncogenes. These changes in DNA methylation status could be used as biomarkers for the diagnosis and prognosis of cancer patients undergoing chemotherapies or other clinical therapies. Herein, we describe genes for which methylation is dependent upon anticancer drug resistance in patients with gastric cancer; we then suggest a significant epigenetic target to focus on for overcoming anticancer drug resistance.

Keywords: DNA methylation, gastric cancer, chemoresistance, cisplatin, 5-FU

Epigenetic alterations such as DNA methylation, histone acetylation, and chromatin remodeling are associated with gene transcription and other biological activities [1, 2]. DNA methylation generally occurs at the promoters of CpG-rich regions (CpG islands) and regulates gene expression [3]. Because alteration of DNA methylation is one of the major epigenetic changes that occur in cancer, aberrant DNA methylation profiling techniques have commonly been used as prognostic markers to monitor both (i) patient responses to therapy, and (ii) patient survival [2]. Global hypomethylation has been detected in many proto- and oncogene sequences where chromosome instability and gene activation were caused by DNA hypomethylation [3, 4]. Localized hypermethylation has also been identified in tumor suppressor genes for which low expression in cancer cells and patient tissues was highly correlated with DNA hypermethylation [4]. Moreover, upregulation and mutation of the DNA methyltransferase 1 gene (DNMT1) has frequently been found in many cancers, including gastric cancers [4, 5]. A member of the TET family, Ten-eleven translocation methylcytosine dioxygenase (TET1), which is responsible for DNA demethylation, was also highly methylated and downregulated in many cancers, including gastric carcinoma [6].

Although different types of chemotherapeutic anticancer drugs are deployed against several types of cancers, chemoresistance to anticancer drugs reduces chemotherapy efficiency and worsens survival rates for cancer patients. Cancer can regulate signaling pathways, cause genomic instability, alter gene expression, and trigger epigenetic alterations [7, 8]. Cancer can also cause large-scale phenotypic changes such as the process of epithelial-mesenchymal transition [7, 8]. These phenomena are well-known mechanisms that cancer cells utilize to escape programmed cell death and gain the chemoresistance to anticancer drugs (Fig. 1). Among
the epigenetic alterations involved, DNA methylation can silence apoptotic genes to induce anticancer drug resistance (Fig. 1) [7]. Several methylation alterations in apoptotic genes have been identified and used as epigenetic biomarkers in determining either chemoresistance or chemosensitivity to anticancer drugs (Fig. 1) [9].

Gastric cancer is still the fourth most common cancer and the second leading cause of cancer-related mortality worldwide [4, 10]. Despite improved lifestyles and advancements in medical technologies (enabling earlier diagnoses and therapies), the prognoses and 5-year survival rates for cancer patients remain poor [11]. Although surgery is a major and efficient therapy for treating gastric cancer patients, radiation therapy and chemotherapy are necessary adjuncts for ridding the patient’s body of gastric cancer [12]. Chemotherapies based on anticancer drugs such as 5-fluorouracil (5-FU) and cisplatin have been extensively used to cure gastric cancers for several decades. An analog of uracil, 5-FU can inhibit thymidylate synthase and can be incorporated into both RNA and DNA, inducing DNA damage and cytotoxicity [13, 14]. Cisplatin, a platinum-based complex, can induce cell death by directly interacting...