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Rectifying the Epigenetic Field Defect in Gastric Carcinogenesis

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Comment on Epigenetic Silencing of GDF1 Disrupts SMAD Signaling to Reinforce Gastric Cancer Development. [Oncogene 2015]

Gastric cancer is undoubtedly a fatal malignancy worldwide with high incidence and dismal prognosis. Its formation and development can be driven by genetic defects, dietary factors, alcohol consumption, viral infection, etc. Despite the multifactorial nature, more than 80% of gastric cancers are closely related to *Helicobacter pylori* (*H. pylori*) infection [1]. It is believed that *H. pylori* triggers chronic gastritis that results in gastric atrophy, intestinal metaplasia and dysplasia, and then finally to adenocarcinoma. Such microbial infection is associated with strong host response such as cytokine stimulation and neutrophil activation which play an important driver role in gastric carcinogenesis. The stimulated cytokines include pro-inflammatory interleukin-1β (IL-1β), IL-2, IL-6, IL-8 and tumor necrosis factor alpha (TNF-α), of which the IL-8 action in stimulating neutrophils is significantly enhanced upon infection by CagA-positive *H. pylori* [2]. In addition to immune system, *H. pylori* is known to perturb the expression of host genes by different mechanisms. For examples, *H. pylori* can cause promoter hypermethylation and silencing of *FOXD3*, leading to decreased levels of cell death modulators CYFIP2 and RARB to favor the proliferation of gastric cancer cells [3]. Moreover, *H. pylori* can epigenetically down-regulate the transcription of miR-490-3p, thereby resume the expression of its direct target SMARCD1 which is a member of the SWItch/SucroseNonFermentable (SWI/SNF) chromatin remodeling family with oncogenic functional roles [4]. The *H. Pylori* deregulated host genes are of clinical significance as demonstrated by their respective correlations with various clinic-pathological features of gastric cancer patients [3,4].

Based on the deteriorating effects of *H. pylori*, different first- and second-line therapies have been developed for elimination of *H. pylori* in patients. Common regimens include proton-pump inhibitors, ranitidine bismuth citrate and bismuth, which are often applied in combination to increase the therapeutic response [5]. In patients free of precancerous lesions, removal of *H. pylori* can significantly reduce the risk of stomach cancer formation. Nevertheless, the efficacy of *H. pylori* eradication in treating gastric cancer remains obscure, if not unsatisfactory [6]. Such outcome is apparently due to the irreversible *H. pylori*-triggered damages to gastric mucosa, implicating the carcinogenic effect of this organism is mainly exerted at early stage of infection. To find an alternative approach for gastric cancer therapy, extensive research had previously been performed to characterize the molecular deregulations induced by *H. pylori* infection, among which epigenetic alternation has emerged as a potential therapeutic target owning to its reversible nature by exogenous agents. Importantly, pathogenic epigenetic changes are not confined to *H. pylori*-associated gastric cancers, but are also found in other non-microbial subtypes, suggesting that such abnormalities exist in the majority of stomach cancers and are subject to amendment.

The notion of epigenetic therapy is supported by the availability of highly specific drugs, such asromidepsin and entinostat, which can target epigenetic regulatory proteins and have demonstrated promising effects in lymphoma and lung cancer patients under phase II clinical trials [7]. In particular, 5-aza-2'-deoxycytidine (5-aza-dC), a DNA demethylating agent, has been approved by Food and Drug administration (FDA) to treat myelodysplasia and acute myelogenousleukaemia (AML), and it also improved the survival of ovarian cancer patients when combined with carboplatin in phase II clinical trial [7,8]. Recent evidence further indicates that a low-dose, dose-intensive schedule of epigenetic drug produces superior clinical efficacy. Nonetheless, epigenetic drugs have yet been tested in gastric cancer patients primarily due to scarce *in vivo* evidence from relevant animal models. To this end, we have recently examined the effect of 5-aza-dC in a well-established gastric cancer mouse model [9]. We discovered that 5-aza-dC treatment effectively neutralized the carcinogenic effect of *N*-nitroso-*N*-methylurea (MNU) and significantly lowered the resulting gastric cancer incidence. Using genome-wide analysis, we pinpointed *Gdf1* as the key promoter-hypermethylated and drug-targeted gene in the murine gastric cancer tissues. Importantly, the human *GDF1* was also subject to promoter hypermethylation which could be demethylated by 5-aza-dC in gastric cancer cell lines. Following *in vitro* and *in vivo* assays consistently demonstrated that GDF1 played a tumor suppressor role by inhibiting cell proliferation and restricting cell cycle progression. Such functional effects were caused by induced expression of phosphorylated (p)-SMAD2/3 and nuclear accumulation of SMAD4, which in turn activated the transcription of cell cycle regulators *p15* and *p21*, and down-regulated the oncogenic *c-Myc* and p-retinoblastoma (Rb). This GDF1-SMAD signaling cascade is of clinical relevance as *GDF1* hypermethylation was significantly associated with poor survival, and GDF1 silencing paralleled with p-SMAD2/3 down-regulation in an Asian gastric cancer cohort.

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Our mechanistic finding, together with a previous study reporting the chemo-preventive effect of 5-aza-dC in a *H. pylori*-infected and MNU-treated gerbil model [10], demonstrate the effectiveness of epigenetic drug in suppressing gastric cancer development. Given the approved application in myelodysplasia and AML patients, 5-aza-dC could be further evaluated for management of gastric cancer. To substantiate such proposal, future validation of 5-aza-dC effect, together with molecular profiling of the drug-treated tissues, in other gastric cancer animal models is warranted. Based on the 5-aza-dC-induced global demethylation that can reactivate an array of functional genes, we anticipate that the consequential tumor suppression is mediated by a complex signaling network wherein the GDF1-SMAD axis only represents one of the core pathways. Delineation of additional 5-aza-dC-related mechanisms would be beneficial for identification of gastric cancer subtypes with potential susceptibility or resistance to such epigenetic therapy. Of note, a recent multicenter prospective cohort study showed that the methylation levels of three pre-selected genes (*miR-124a-3*, *EMX1* and *NKX6-1*) can predict the risk of developing metachronous gastric cancer [11]. It will be of future interest to evaluate such epigenetic field effect in 5-aza-dC-treated gastric cancer, and further mechanistic studies of these epigenetically-regulated genes may reveal crucial pathways protective against gastric carcinogenesis.

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