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EDITORIAL

RNF43: A Biomarker With Potential Ramifications for Therapeutic Intervention in Gastric Cancer

Gastric adenocarcinoma is the third leading cause of cancer-related mortality worldwide and accounts for greater than 780,000 deaths annually.[1] The strongest known risk factor for this malignancy is chronic gastritis induced by the bacterial pathogen *Helicobacter pylori*, and clinical trials have now clearly demonstrated the efficacy of *H pylori* eradication therapy in prevention of gastric cancer. However, most gastric cancer cases are not diagnosed until a more advanced stage, and although radiation and chemotherapy can improve outcomes, prognosis remains poor. Thus, there is a need for novel gastric cancer biomarkers to optimize the ability to improve prognostic outcomes.

To date, few biomarkers associated with gastric cancer have been translated into molecularly targeted therapies. HER-2 is one such therapeutic gastric cancer biomarker.[2] The trastuzumab for gastric cancer study, an open-label, phase III, randomized-controlled clinical trial, investigated the efficacy of trastuzumab, a monoclonal antibody against HER-2, in combination with chemotherapy for first-line treatment of HER-2-positive gastric cancers, and revealed that trastuzumab treatment significantly improved overall survival and disease-free survival times compared with chemotherapy alone.[3] Another biomarker for gastric cancer immunotherapy is PD-L1. The ATTRACTION-2 study, a phase III, randomized, double-blind, placebo-controlled clinical trial, compared the effectiveness of nivolumab, a monoclonal antibody against PD-L1, in patients with advanced gastric cancer and revealed that nivolumab significantly increased overall survival and reduced the risk of mortality compared with placebo control subjects.[4] However, the paucity of biomarkers that can be operationalized into actionable intervention trials is evidence of a clear gap in gastric cancer research that must be addressed.

Although a brute force approach for identification of novel biomarkers has resulted in an increase in the armamentarium of potential therapeutic regimens, this is no longer considered sufficient in the design of treatment strategies. Fortunately, the molecular characterization of gastric cancers has allowed for large-scale detection of many potential biomarkers simultaneously, thus making it substantially easier to tailor specific treatment regimens to an individuals' gastric cancer profile. The Cancer Genome Atlas analysis resulted in the identification of four different gastric cancer subtypes: (1) Epstein-Barr virus–positive, (2) microsatellite instability, (3) genomically stable, and (4) chromosomal instability.[5] The Asian Gastric Cancer Research Group analysis also identified four gastric cancer molecular subtypes, including microsatellite instability and the microsatellite stable tumor types associated with epithelial-mesenchymal transition, TP53 activity, or TP53 inactivity.[6] The gastric cancer subtypes identified from both of these analyses are distinguished by unique biomarkers, representing different gene mutations, thus, offering the opportunity for customized treatment strategies. These studies also reveal the complexity of gastric cancers and the fact that it is a multifaceted and highly heterogeneous disease.

Through these studies and others, mutations in RNF43 have been identified and are considered to represent driving mutations in gastric cancer,[7] which are frequently found in microsatellite instability gastric tumors.[5] DNA damage responses are critical for maintaining genomic stability, which is commonly lost in gastric tumors, and several E3 ubiquitin ligases have been reported to be involved in this response. Neumeyer et al[8] now demonstrate that the E3 ubiquitin ligase, RNF43, is a novel and important mediator of the DNA damage response in the stomach and importantly, that loss of RNF43 function directly contributes to gastric carcinogenesis. RNF43 depletion confers resistance to γ-radiation through attenuating DNA damage responses in vitro, thereby preventing apoptosis and increasing cellular proliferation. Furthermore, depletion of RNF43 confers resistance to DNA-damage-inducing chemotherapies, which are currently used in the treatment of gastric cancer, through reduced DNA damage responses and apoptosis, findings that were comprehensively validated in gastric cancer cells in vitro, a xenograft model in vivo, and both murine and human organoids ex vivo.

Because *H pylori* is the strongest known risk factor for the development of gastric cancer and induces DNA damage in gastric epithelial cells, Neumeyer et al[8] also demonstrated the importance of RNF43 in *H pylori*–induced DNA damage. Specifically, the authors found that *H pylori* upregulates RNF43 and that depletion of RNF43 attenuates DNA damage responses in the context of *H pylori* infection in vitro. *H pylori* similarly upregulates RNF43 expression in the stomach in wild-type mice and this directly corresponds to DNA damage responses. However, loss of RNF43 function in mice results in attenuation of DNA damage responses and reduced apoptosis, which is associated with increased severity of gastric inflammation. Extending these findings to humans, RNF43 expression was shown to significantly increase among *H pylori*–infected patients with gastritis; however, RNF43 expression decreased with premalignant and malignant lesions, again indicating the importance of RNF43 in DNA damage responses along the carcinogenic cascade. Finally, Neumeyer et al[8] assessed RNF43 mutations in human gastric tumors and demonstrated that RNF43 expression levels directly correlate with DNA damage

responses, and that *RNF43* mutations in gastric tumors conferred resistance to DNA damage.

Current treatment regimens for gastric cancer include adjuvant chemotherapy with cisplatin or 5-fluorouracil combined with irradiation, and the efficacy of these treatments relies heavily on the ability to induce DNA damage and thereby apoptosis. However, not all tumors respond appropriately to this therapeutic regimen. The current study raises the tantalizing premise that cells lacking RNF43 do not respond to either chemotherapeutic and irradiation treatments, and may also accumulate additional mutations that could further worsen disease outcomes and prognosis. Collectively, this significant study demonstrates that RNF43 could serve as an important gastric cancer biomarker to improve the ability to predict responses to adjuvant chemotherapy and thereby improve prognostic outcomes within the context of precision medicine.

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