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EDITORIAL

Drivers of Esophageal Adenocarcinoma and Opportunities for Cancer Interception

Barrett's esophagus (BE) is a precancerous condition that can lead to esophageal adenocarcinoma (EAC), a particularly aggressive malignancy with a low survival rate. Molecular approaches to stratifying BE risk offer intriguing opportunities for cancer interception, defined as active intervention to reduce cancer risk.[1] In the paper by Gotovac et al,[2] the investigators model progression from dysplastic BE to EAC to better understand the functional significance of SMAD4 loss. Their experiments, focused on alterations in SMAD4, provide insights into how molecular alterations resulting in genomic instability can lead to rapid progression to cancer and metastasis. Detecting and understanding critical early molecular events that drive esophageal carcinogenesis may ultimately provide more effective ways to identify and treat the patients with BE at highest risk for EAC.

Current BE screening and surveillance focuses clinical endoscopic resources on a subset of patients identified based on clinical risk factors for BE. Once BE is identified, long-term endoscopic surveillance of BE is recommended. However, BE is a premalignant clinical condition with low rates of progression overall.[3] Indeed, a major challenge in EAC prevention is the heterogenous landscape of premalignant disease; although most cases of BE remain relatively stable over many years, others may progress rapidly or even catastrophically.[4] In addition, most patients with EAC present only after the cancer has developed; 93% of patients with EAC present with advanced disease having never undergone screening or related cancer prevention strategies.[5]

Unfortunately, the molecular mechanisms underlying progression to EAC have been difficult to discern and translate into clinical practice. In 2010, as the American Gastroenterological Association was preparing a position statement and technical review on BE, an adjunct paper by Spechler et al[6] noted progression of molecular events within BE. These events included early CDKN2A (P16) loss or methylation in nondysplastic BE and subsequent loss of P53 in progression to cancer.[6,7] Since then, in patients with BE, CDKN2A/B loss has been identified in 88% of progressors versus 24% of nonprogressors to dysplasia and EAC.[8] Altered P53 has been even more widely accepted as a marker of progression, and may be detected before dysplasia has occurred.[9] Nonetheless, current clinical practice in the United States still relies on histologic assessment of BE biopsies to determine risk while molecular markers undergo further development.

Rather than focusing on specific mutations, a model based on genomic copy number assessment has also been proposed as a way to predict progression in BE.[10] As with P53 abnormalities, it is notable that the copy-number approach provides insights into risk of progression that transcend histologic dysplasia assessment and suggests genomic instability serves as an important marker for progression risk.[10]

The current study by Gotovac et al[2] provides a deeper understanding of the underlying mechanism for the development of genomic instability and aggressive cancer.[2] Using an established BE cell line (CP-B) from a patient with BE dysplasia, CRISPR/Cas9 technology was used to knockout the SMAD4 gene. Lentiviral vectors were also used for RNAi-mediated SMAD4 knockdown. Comparison of the wild-type and SMAD4 knockdown revealed SMAD4 loss was associated with increased expression of CDC6,[2] a gene with proto-oncogenic activity. Gotovac et al[2] also demonstrated that the increased CDC6 was associated with loss of tumor suppressor CDKN2A/B, a factor already associated with BE. To assess the role of SMAD4 in malignant transformation, wild-type CP-B cells were then compared with SMAD4 knockout and knockdown lines in a tumor-formation assay using a xenograft model.[2] Although only 1 of 17 mice injected with control cells formed a tumor, all of the SMAD4 knockdown and many of the SMAD4 knockout cell lines established tumors in the xenograft model, illustrating that SMAD4 loss, in the context of a dysplastic cell line, was sufficient to form tumors.[2] Furthermore, xenografts were used to rederive cell lines that were reinjected into mice resulting in rapid development of metastatic disease.[2] The progression to metastases is a particularly compelling finding given the observation that in patients with EAC, SMAD4 alterations are 1 of the molecular drivers associated with worse overall survival.[11] Indeed, although SMAD4 loss is only found in 13% of EACs, it is identified in 44% of metastatic EAC.[12]

In summary, the findings reported by Gotovac et al[2] suggest that, in the setting of dysplastic BE, identification of SMAD4 loss could be considered a call to action. Although SMAD4 loss is associated with only a subset of EAC cases, this study offers a clear example of how a full panel of driver genes could be identified, validated, and translated into clinical practice. Similar panels are being developed to assess other premalignant disease in organs, such as pancreas, for which 6 markers (including P53 and SMAD4) have been identified.[13] It is possible that such a panel could broaden screening efficacy when combined with newer less invasive sampling strategies, such as the Cytosponge.[14] Such strategies are compelling because ablative strategies already exist for high-risk premalignant esophageal disease. Current guidelines suggest using ablative therapy for BE with high-grade dysplasia, although treatment for LDG remains less clear.[15] The presence of molecular markers, such as SMAD4

loss, associated with high risk of progression could help identify patients who would benefit the most from ablative strategies. To advance clinical practice, once molecular markers are identified, clinical trials will be necessary. As the rapid progression reported by Gotovac et al[2] makes clear, such trials need to be mindful of the speed of progression associated with some of the molecular drivers, leaving a narrow and critically important window for intervention and cancer interception.

KATHERINE S. GARMAN, MD
Department of Medicine
Duke University
Durham, North Carolina

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Correspondence
Address correspondence to: Katherine S. Garman, MD, Duke University, Division of Gastroenterology, Department of Medicine, Box 3913 DUMC, Durham, North Carolina 27710. e-mail: katherine.garman@duke.edu.

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