Esophageal adenocarcinoma: Wanted—new models and better targets

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In this issue of the *Journal*, Dr Wang and members from the Lin Laboratory at the University of Michigan¹ report on the role of Dickkopf-3, a divergent member of the Wnt family of proteins, and its ability to increase invasion and migration in esophageal adenocarcinoma (EAC) cells. The authors perform an in vitro analysis of Dickkopf-3 in selected EAC cell lines and supplement this approach with an immunohistochemical analysis in 64 EAC patient specimens. The conclusion is that Dickkopf-3 overexpression is associated with EAC growth, invasion, and progression. The group at the University of Michigan have been leaders in the study of EAC, and this article describes some interesting preclinical observations, but also highlights the current challenges in studying this disease.

There are only 17,000 cases of EAC annually in the United States, and after a diagnosis of EAC the 5-year survival is a dismal 15%. Moreover, there are few relevant clinical trials open for accrual in NCI.gov clinical trials. Thus, the nature of the disease and its current treatment paradigms limit the advocacy for expanding research in the prevention, diagnosis, and treatment of EAC.

As demonstrated in this study,¹ the numbers of EAC cell lines currently available for study are limited. Despite the majority of EAC human tumors overexpressing Dickkopf-3, none of the EAC cell lines used in this study had any significant Dickkopf-3 expression. Therefore, Wang and colleagues¹ had to use an artificial, forced overexpression strategy to evaluate the EAC tumor biology. This is suboptimal from a stoichiometric perspective and from an inability to silence *Dickkopf-3* to determine whether it is sufficient or required to drive tumorigenesis or aggressiveness. Although this is concerning, a more glaring and overarching problem in performing transformative research regarding EAC is the lack of an adequate animal model. Wang and colleagues¹ used a traditional heterotopic xenograft flank model that may not recapitulate EAC tumorigenesis or metastases.

Currently, there are no well-characterized EAC genetically engineered mouse models that faithfully produce EAC. Orthotopic patient-derived xenografts may be difficult to establish but certainly need to be investigated. The lack of EAC animal models is a major barrier to the preclinical evaluation of novel therapies, target validation, and pathway discovery and confirmation.

Although the article by Wang and colleagues¹ suggests that Dickkopf-3 overexpression may be a negative prognostic factor in EAC, investigators have reported conflicting results in other solid tumors (ie, pancreatic cancer), suggesting a tumor- or organ-specific response.² If true, this may make any interpretation of targeting Dickkopf-3 in basket trials challenging. Recent genomic analysis of EAC using a combination of whole exome and whole genome sequencing revealed a mutational signature defined by a high prevalence of A to C transversions at AA dinucleotides.³ Several genes (*TP53*, *CDKN2A*, *SMAD4*, and *PIK3CA*) previously implicated in EAC were confirmed, but new highly mutated genes uncovered in this analysis include *ELMO1* and *DOCK2*, upstream modulators of the RAC1 GTPase. This signaling pathway is involved in cancer cell migration and invasion but is not typically thought of as a primary driver of carcinogenesis. Herein lies a fundamental problem in our ability to use precision or personalized medicine for patients with EAC—we do not know the genomic driver events for EAC carcinogenesis. Thus, we do not have good targets for therapy. The majority of clinical trials using targeted therapies have failed in EAC despite promising preclinical evaluation, precisely for this reason.

There remains much work to be done to move the diagnosis and treatment of EAC into the genomic era of modern oncologic care. Although advances in multimodality care for EAC have improved and patients are living longer, the next big advances will need to come from an improved understanding of tumor genomics, immunotherapies, and the development and validation of targeted therapies.

References

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