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Commentary

ASF1A in Gastric and Colorectal Cancer: On the Hinge Between Genetics and Epigenetics?

Rui Henrique

Department of Pathology and Cancer Biology and Epigenetics Group - Research Center (CI-IPOP), Portuguese Oncology Institute of Porto & Department of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal

Gastric cancer (GC) and colorectal cancer (CRC) are two of the most common human malignancies worldwide, ranking 5th and 3rd in incidence, and 3rd and 4th in mortality, respectively, in 2012 (Global Cancer Observatory). Over the last decade, a significant progress in CRC treatment resulted in improved patient survival and quality of life, whereas for GC such progress has not been apparent in the same extent. Thus, a more profound knowledge of the molecular alterations underlying neoplastic transformation and progression in GC and CRC is key for developing new tools for risk stratification and novel therapeutic strategies.

The canonical Wnt pathway has been implicated both in gastric and colorectal carcinogenesis. In the stomach, Helicobacter pylori-driven carcinogenesis promotes nuclear β-catenin accumulation, fostering cell proliferation (Song et al., 2015). On the other hand, the vast majority of CRCs (about 80%) displays Wnt pathway deregulation due to *APC* mutations, that render β-catenin free to translocate to the nucleus and activate its target genes (Huels and Sansom, 2015). Overall, Wnt deregulation results in uncontrolled proliferation and impaired cell differentiation, setting the stage for neoplastic transformation.

Both genetic and epigenetic events are implicated in gastrointestinal carcinogenesis, although the role of genetic aberrations has been more extensively and thoroughly investigated. Nevertheless, epigenetic deregulation, including aberrant DNA methylation patterns as well as histone onco modifications and altered chromatin remodeling, is being increasingly recognized as major contributor to cancer initiation and progression. In this setting, the study by Liang and co-workers (Liang et al., 2017) addresses the very interesting, but seldom explored, link between cancer genetics and epigenetics. This study is focused on the altered expression of histone H3–H4 chaperone ASF1A as a prognostic biomarker in GC and CRC, as well as its impact in cancer cell biology. In a small panel of GC and CRC cell lines, ASF1A was found overexpressed at protein level and this observation was confirmed in primary tumors, using immunohistochemistry. Interestingly, ASF1A expression gradually increased from normal to metaplastic to neoplastic tissues, suggesting a role in tumorigenesis. In CRC, higher ASF1A expression levels associated with worse overall survival. Functional studies demonstrated that ASF1A promotes cell cycle progression, clonogenicity, stemness and invasiveness, and these effects are likely mediated through its interaction with β-catenin, stimulating expression of its target genes, including *LGR5*, *CCND1*, *c-MYC* and *ZEB1*. Remarkably, an inverse correlation between ASF1A and E-Cadherin expression was disclosed, intermediated by β-catenin in an inhibitory loop involving ZEB1. Finally, in vivo experiments demonstrated that ASF1A overexpression promote tumor growth and metastasis. The authors conclude that in addition to its potential as prognostic biomarker, ASF1A might also constitute a therapeutic target (Liang et al., 2017).

The findings of Liang and co-workers add to current knowledge on gastric and colorectal carcinogenesis, uncovering the cooperation between deranged genetic and epigenetic mechanism in two extensively studied tumor models. In addition, novel CRC prognostic biomarkers might allow for improved patient risk stratification, assisting in therapeutic decision-making. Several issues, however, require further clarification. At molecular level, the mechanism underlying ASF1A overexpression remains elusive. Is it a cause or a consequence of neoplastic transformation? Although no mechanism was proposed, it is tempting to speculate whether this might be due to impaired ASF1A degradation, which is controlled by RAD6 (Wang et al., 2015). Furthermore, the association of ASF1A overexpression and tumor aggressiveness needs to be explored in more depth. An interesting hint derives from the observation that ASF1A expression was higher in the less differentiated cancer cell lines (Liang et al., 2017). In GC, poorly differentiated tumors, such as signet ring cell carcinomas, frequently display E-cadherin loss of expression, a feature that is associated with gene mutations, but that might be also related with ASF1A overexpression. Because detailed pathological information is lacking, inferences cannot be made regarding this possibility. The clinical relevance of Liang and co-workers' findings also demand additional investigation. The prognostic value of ASF1A overexpression in GC was not explored and it could be even more valuable than that in CRC, owing to globally worse prognosis of GC patients compared to CRC patients. Moreover, even in CRC, prognostic value was demonstrated only for overall survival. However, other equally or more relevant endpoints such as disease-specific and disease-free survival need to be considered. Importantly, multivariable analysis is also required, to determine whether ASF1A overexpression is an independent predictor of poor outcome. Finally, the recent identification of pyrimidine-2,4,6-trione derivative small molecules that inhibit Asf1 and H3K56 acetylation, without disturbing other histone modification (Seol et al., 2015), provides a support to

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E-mail addresses: henrique@ipoporto.min-saude.pt, rmhenrique@icbas.up.pt.

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Liang and co-workers' claim about the potential therapeutic implications of their results. Thus, like most scientific endeavors, this study not only provides some answers but it raises more profound questions that will certainly stimulate future research on the hinge between genetics and epigenetics in Cancer.

Disclosure

The author declared no competing interests.

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