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Commentary

# Oncogenic potential of CHAF1A in gastric cancer: A novel link with Helicobacter pylori-driven carcinogenesis?

Vânia Camilo [a], Rui Henrique [a,b,c,*]

[a] Cancer Biology & Epigenetics Group – Research Center, Portuguese Oncology Institute of Porto (CI-IPOP), Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal
[b] Department of Pathology, Portuguese Oncology Institute of Porto, Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal
[c] Department of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar – University of Porto (ICBAS-UP), Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal

Gastric cancer remains one of the most commonly diagnosed malignancies and the 3rd leading cause of cancer-related death, worldwide [1]. Despite significant advances, gastric cancer patients are commonly diagnosed at an advanced stage, which severely limits treatment options. It is, thus, urgent to disclose novel molecular mechanisms that may assist therapeutic decisions and improve patient outcome.

*Helicobacter pylori* infection is widely acknowledged as the foremost risk factor for gastric cancer development. Indeed, this bacterium is estimated to colonize gastric epithelia of half of the world's population. Increasing evidence implicates Wnt/β-catenin signaling pathway as a critical mediator of *H. pylori*-induced gastric carcinogenesis [4]. Aberrant activation of the Wnt/β-catenin pathway is common in gastric cancer tissues (approximately 30% of cases) and cell lines, contributing to tumorigenicity by promoting diverse biological effects such as proliferation, invasion and angiogenesis [2].

Cancer is generally perceived as a genetic disease. However, convincing evidence supports the notion that cancers arise and progress not only due to cumulative alterations at the genetic level but also because of deregulation in epigenetic machinery. Epigenetic changes may condition DNA access by transcription factors and replication machinery, thus (re)shaping gene expression programs. In this setting, the study by Zheng and co-workers [6] unravels another layer of regulation of *H. pylori*-driven gastric carcinogenesis which relies on the cooperation between genetic and epigenetic mechanisms. The study is focused on the expression and mechanism of action of CHAF1A, a subunit of H3-H4 histone chaperone Chromatin Assembly Factor-1 (CAF-1), in gastric cancer. CHAF1A was found overexpressed in gastric cancer cell lines and tissue samples and its high expression was predictive of poor outcome. A finer dissection of the mechanisms of action of CHAF1A was achieved by the modulation of its expression *in vitro* and *in vivo*. Functional *in vitro* studies demonstrated that CHAF1A expression promoted gastric cancer cell proliferation by enhancing transcriptional activation of *c-MYC* and *CCND1* genes, through direct binding to their promoter regions. This activation was achieved in concert with TCF4, a mediator of Wnt signaling pathway, suggesting that CHAF1A may act as a co-activator of this important pathway. Interestingly, the authors also established a link between *H. pylori* infection and CHAF1A expression, which was dependent on Sp1 binding to *CHAF1A* promoter. Furthermore, *in vivo* studies reinforced the pro-tumoral effect of CHAF1A demonstrating that its overexpression promoted tumor growth. Overall, these findings suggest that CHAF1A may act as an oncogene in gastric cancer and, hence, constitute a novel therapeutic target.

In addition to further implicating the epigenetic machinery in cancer, this study highlights the functional versatility of CHAF1A, which now seems to extend beyond its conventional histone chaperone function. This versatility has already been demonstrated for another histone chaperone, ASF1A, in gastric and colorectal cancers [3]. Nevertheless, unlike CHAF1A, ASF1A disclosed a preferential binding to β-catenin. In the study by Zheng and co-workers [6], however, we are left to wonder whether β-catenin is also part of the CHAF1A/TCF4 complexes. We are led to assume so because *c-MYC* and *CCND1* are canonical targets of the TCF4/β-catenin complex, although no direct proof of association between β-catenin/TCF4/CHAF1A is provided. Furthermore, this study raises the question of whether, in the context of gastric carcinogenesis, CHAF1A may also interact with functional mediators of other signaling pathways and, if so, what is the biological outcome of such interactions. Finally, the role of the other subunits of CAF-1, namely CHAF1B, which interacts with CHAF1A and was similarly implicated in several cancer types [5] is also in need of further clarification.

From the clinical standpoint, the use of the Kaplan-Meier Plotter database, although informative, may restrict the analysis. Zheng and co-workers provide information concerning overall survival but other endpoints, such as disease-free and disease-specific survival, may be more relevant when considering the prognostic value of CHAF1A. The assessment of CHAF1A as an independent predictor of poor outcome is also lacking. Moreover, the analysis is based on the expression of CHAF1A in gastric cancer at the mRNA level. It would be, perhaps, equally relevant to assess CHAF1A protein expression in a cohort of gastric cancer patients for which clinicopathological data is available.

Overall, the work by Zheng and co-workers highlights the versatility of histone chaperones and opens new avenues for therapeutic

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* Corresponding author at: Department of Pathology, Portuguese Oncology Institute of Porto, Rua Dr. António Bernardino de Almeida, 4200-072 Porto, Portugal.
*URL's:* rmhenrique@icbas.up.pt, henrique@ipoporto.min-saude.pt (R. Henrique).

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intervention in the setting of *H. pylori*-driven gastric carcinogenesis. Undoubtedly, the study of epigenetic mediators as co-activators of aberrant genetic processes is only at its infancy and novel developments from this field are expected in the near future.

## Disclosure

The author declared no competing interests.

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