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EDITORIAL

Isakov V, Goncharov A. Breaking barriers in the first-line *Helicobacter pylori* treatment: Chinese multicenter trial validates vonoprazan-based triple therapy. *World J Gastroenterol* 2025; 31(40): 112312 [DOI: [10.3748/wjg.v31.i40.112312](https://doi.org/10.3748/wjg.v31.i40.112312)]

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ORIGINAL ARTICLE**Retrospective Cohort Study**

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Prognostic role of histone deacetylase 10 in colorectal cancer: Strengths and gaps

Ali Afzal, Chatchai Muanprasat, Muhammad Babar Khawar

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Abstract

Histone deacetylase 10 (HDAC10) is emerging as a critical modulator of tumor immunity, chemoresistance, and transcriptional plasticity in colorectal cancer. Its suppression has been linked to altered CD8⁺ T cell activity, increased p53 expression, and reduced programmed death ligand 1 levels, suggesting a potential role in immune evasion. However, mechanistic understanding of HDAC10's selective function, especially in shaping the tumor microenvironment, remains limited. We advocate for targeted investigations using isoform-selective inhibitors, functional *in vivo* studies, and immune subset profiling to clarify HDAC10's therapeutic relevance in colorectal cancer.

Key Words: Histone deacetylase 10; Colorectal cancer; Tumor microenvironment; Immunotherapy resistance; P53-programmed death ligand 1 axis

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Core Tip: Histone deacetylase 10 (HDAC10) plays a multifaceted role in colorectal cancer by modulating immune evasion, chemoresistance, and transcriptional regulation. Its suppression influences CD8⁺ T cell activation, enhances p53 expression, and reduces programmed death ligand 1 levels, suggesting critical involvement in tumor-immune interactions. Selective HDAC10 inhibition, unlike pan-HDAC blockade, may offer targeted therapeutic benefit, particularly in microsatellite-stable tumors. Further *in vivo* studies and mechanistic dissection of HDAC10-p53-programmed death ligand 1 signaling are essential to harness its full potential in reshaping the tumor microenvironment and improving immunotherapy outcomes.

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TO THE EDITOR

We read with great interest the recent study by Nie *et al*[1] published in *World Journal of Gastroenterology*. This study has provided valuable and appealing evidence on the role of histone deacetylase 10 (HDAC10) in shaping the tumor microenvironment (TME) and mediating immunotherapy resistance in colorectal cancer (CRC). The depth of the multi-modal approach opted in current study, and integrating transcriptomic analyses with functional assays are appreciable, and we wish to offer some of critical reflections and suggestions for further consideration.

Firstly, while the authors convincingly correlate higher expression of HDAC10 with poor prognosis, immunosuppressive TME, and chemoresistance, we are of the view that further functional *in vivo* validation will strengthen the findings of this study. We commend that the authors have acknowledged that the lack of animal models limits a comprehensive understanding of immunological dynamics in the TME. Prior studies have shown that CD8⁺ T cell infiltration is a critical determinant of response to immunotherapy in CRC, and HDAC modulation has been reported to influence cytotoxic T cell function *via* major histocompatibility class I upregulation and chemokine expression[2,3]. Future investigations should focus to explore how HDAC10 suppression influences CD8⁺ T cell activation and checkpoint blockade efficacy *in vivo*. Similarly, investigating specific immune cell subsets such as T-regulatory cells or myeloid-derived suppressor cells could clarify its impact on the TME (Figure 1A).

Secondly, even though the authors have reported associations between HDAC10 expression and chemotherapeutic sensitivity *via in silico* IC₅₀ predictions using the “oncoPredict” R package, we believe investigating the direct pharmacological inhibition of HDAC10 using selective inhibitors such as DKFZ-748 (Figure 1B) and subsequent biological response assessments would elucidate role of HDAC10 in chemoresistance and strengthen the therapeutic rationale for its selective targeting in CRC. Recent efforts toward class- and isoform-selective HDAC inhibitors, such as HDAC6 and HDAC10-selective compounds, have demonstrated distinct transcriptional and immune-modulatory effects compared to pan-HDAC inhibition[4]. Isoform-selective such as DKFZ-748 offers significant therapeutic advantages over pan-HDAC inhibitors. They provide higher therapeutic precision to minimize off-target effects and systemic toxicity associated with pan-HDAC inhibitors[1]. This target approach may improve clinical applicability and enhance patient safety. Therefore, we suggest *in vivo* studies to validate the oncogenic function of HDAC10 and evaluate its potential as a therapeutic target, which would provide critical mechanistic insights into its role in tumor progression and therapy resistance.

Thirdly, the study also links HDAC10 suppression to augmented p53 expression. Since p53 is a crucial modulator of immunogenicity and programmed death ligand 1 (PD-L1) regulation, investigating the HDAC10-p53-PD-L1 axis could clarify how HDAC10 modulates both tumor proliferation and immune escape, particularly through transcriptional and epigenetic regulation of PDL1 (Figure 1C). HDAC-mediated regulation of PD-L1 *via* p53 and signal transducer and activator of transcription-1/interferon regulatory factor 1 has been described in multiple cancer types[5] which suggests a broader transcriptional control mechanism beyond direct promoter binding. Lastly, genes like *REG1A* and *CLDN18* were downregulated in group with higher HDAC10 expression. Therefore, assessing whether *REG1A* and *CLDN18* expression correlates with specific CRC subtypes in clinical samples would strengthen the link between HDAC10-driven transcriptional changes and tumor heterogeneity. Moreover, CRCs are further classified into microsatellite instability-high (MSI-H) and microsatellite stable (MSS) subtypes based on DNA mismatch repair status[6]. MSI-H tumor responds well than MSS inhibitors to immune checkpoint inhibitors due to high neoantigen load[7]. The distinct immune landscapes of MSS and MSI-H CRC subtypes would be worthwhile to explore whether HDAC10 inhibition offers great therapeutic advantages in MSS tumors. In conclusion, we commend the authors for highlighting HDAC10 as a promising therapeutic target and biomarker in CRC. We hope future studies will build upon this work by incorporating *in vivo* models, targeted HDAC10 inhibition as suggested, and deeper mechanistic insights into how HDAC10 regulates tumor immunity.

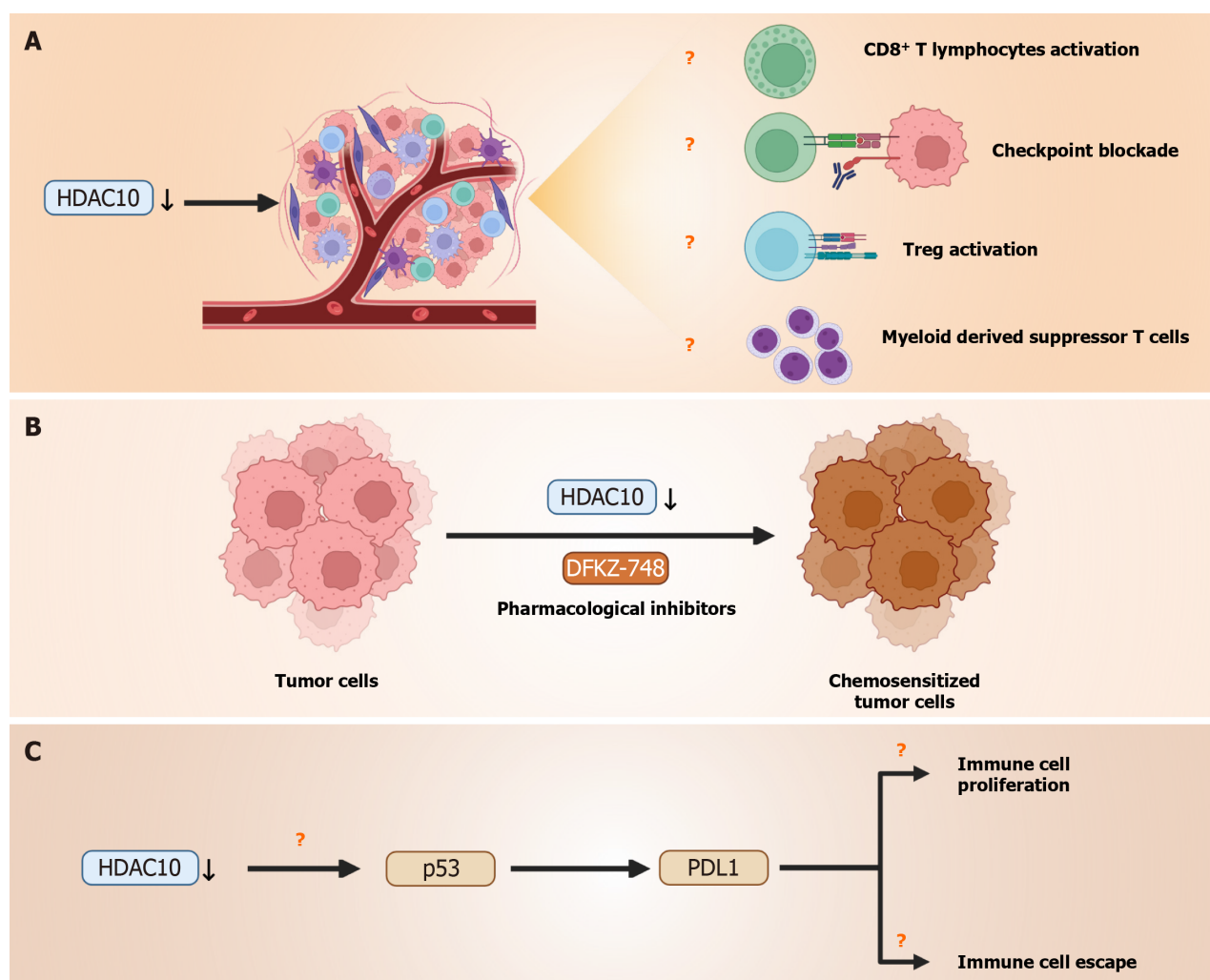


Figure 1 Schematic overview of histone deacetylase 10's multifaceted role in colorectal cancer progression and therapy response. A: Downregulation of histone deacetylase 10 (HDAC10) is proposed to reshape the tumor microenvironment, but its precise effects on CD8⁺ T cell activation, regulatory T cells, and myeloid-derived suppressor cells remain to be elucidated; B: Pharmacological inhibition of HDAC10 (e.g., DFKZ-748) leads to chemosensitization of colorectal cancer cells, yet the clinical benefit of this approach vs pan-HDAC inhibition is undetermined; C: HDAC10 suppression is associated with increased p53 and reduced programmed death ligand 1 expression; however, the mechanistic pathway remains unclear, especially in the context of immune cell proliferation and immune evasion. Orange question marks indicate hypothetical mechanisms that remain to be experimentally validated. HDAC10: Histone deacetylase 10; PDL1: Programmed death ligand 1.

FOOTNOTES

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