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Targeting oncogenic acetyltransferase NAT10 to overcome anti-PD-1 resistance in nasopharyngeal carcinoma

Yue Zhao

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Department of General, Visceral, Thoracic and Transplantation Surgery, Uniklinik Köln, Cologne, Germany

Correspondence to
Dr Yue Zhao;
yue.zhao@uk-koeln.de

ABSTRACT

Targeted resistance to immune checkpoint therapy remains a clinical challenge, and a recent study reported by Xie *et al* provides novel insights into how RNA acetylation, particularly N4-acetylcytidine (ac^4C), plays a pivotal role in shaping the tumor immune microenvironment in nasopharyngeal carcinoma (NPC). Through elucidation of the NAT10/DDX5/high mobility group box 1 axis, the authors demonstrate that enhanced ac^4C modification suppresses $CD4^+$ and $CD8^+$ T-cell functionality, thereby facilitating tumor immune evasion and the resistance to anti-programmed cell death protein-1 therapy. This commentary evaluates the significance of these findings within the broader context of epitranscriptomic regulation research in oncology, identifies critical knowledge gaps regarding the equilibrium between immunosuppression and immune activation, and examines the therapeutic potential of NAT10 inhibition as a potential combinatorial approach in cancer immunotherapy. This work advances our understanding of how post-transcriptional RNA modifications influence tumor-immune interactions, establishing a conceptual framework for future investigations aimed at optimizing immunotherapeutic approaches in NPC and potentially other malignancies.

INTRODUCTION

Immune checkpoint inhibitors (ICIs), particularly anti-programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) agents, have demonstrated significant therapeutic potential in nasopharyngeal carcinoma (NPC). However, the immunosuppressive tumor microenvironment (TME) in advanced-stage NPC remains a critical barrier to achieving durable clinical responses.[1] The phase III CONTINUUM trial highlighted the efficacy of combining PD-1 blockade with chemoradiotherapy, yet resistance persists in many patients, underscoring the need to unravel mechanisms driving immune evasion.[2] Xie *et al* provide pivotal insights into this challenge by identifying NAT10, the sole known acetyltransferase for N4-acetylcytidine (ac^4C) RNA modification, as a key mediator of TME immunosuppression via the DDX5/high mobility group box 1 (HMGB1) axis. This commentary contextualizes their findings, explores implications for cancer immunology, and discusses therapeutic opportunities to overcome ICI resistance in NPC.

Mechanistic insight: the role of NAT10 and ac4C modification

Xie *et al* used lentiviral vectors to achieve overexpression of NAT10 and CRISPR-Cas9 technology to construct NAT10 knockout cell lines (NAT10 Cas9). By disrupting the NAT10 gene with sgRNA, they significantly reduced its expression and the downstream ac^4C modification level. They treated cells with the small molecule inhibitor remodelin to inhibit the acetyltransferase activity of NAT10 through pharmacological means and verified its impact on downstream target genes, complementing the results of gene knockout. Xie *et al* delineated a novel NAT10/DDX5/HMGB1 pathway central to immune suppression in NPC. NAT10-mediated ac^4C modification stabilizes transcripts of CEBPG, DDX5, and helicase-like transcription factor (HLTF), enhancing their translational efficiency. Particularly, elevated DDX5, an RNA helicase, promotes HMGB1 expression—a multifunctional protein that recruits immunosuppressive cells, impairs antigen presentation, and induces T-cell exhaustion.[3 4] Furthermore, a positive feedback loop between HLTF and NAT10 was identified. The transcriptional co-factor HLTF (helicase-like transcription factor) is a member of the SWI/SNF family, possessing helicase and ATPase activities, which regulates the transcription of certain genes by altering the chromatin structure around the genes. HLTF is also implicated in tumor cell survival, proliferation and migration. Crucially, ac^4C modification directly links epitranscriptomic regulation to T-cell dysfunction, as NAT10 inhibition restores effector T-cell activity and synergizes with anti-PD-1 therapy. In addition, ac^4C enhances proliferation and antiviral immunity in T

cells by stabilizing key messenger RNAs such as MYC and promoting their translation, and its decline with age is associated with decreased T-cell function.[5] ac^4C also affects the metabolic processes and inflammatory responses of immune cells, affecting their activity and cytokine release.[6] These findings highlight ac4C as a promising target for immunotherapy and anticancer strategies.

Implications for tumor immunology and therapy

This study bridges RNA acetylation with immune evasion, expanding the paradigm of epitranscriptomic control in cancer. While m6A modifications are well-documented in immune regulation, ac^4C represents an underexplored axis with unique therapeutic potential. Unlike m^6A methyltransferase, NAT10's role in acetylating RNA introduces a novel layer of post-transcriptional regulation. The current study redirects focus to ac^4C acetylation, with Guo *et al* previously revealing that NAT10-mediated ac4C modification promotes glycolysis and regulatory T-cell infiltration in cervical cancer, thereby inducing immunosuppression. Notably, NAT10 inhibition synergizes with anti-PD-L1 therapy to enhance treatment efficacy.[7] Xie *et al* extend these findings to NPC, proving that NAT10-mediated ac^4C modification stabilizes and enhances translational efficiency of key transcripts (CEBPG, DDX5, and HLTF), mechanistically linking ac^4C modification to TME regulation. These molecular alterations elevate HMGB1 expression, ultimately inducing effector T-cell dysfunction.[8] Xie *et al* demonstrated in preclinical studies using transgenic mouse models that validate the role of NAT10 in NPC. The mechanism was established by creating C57BL/6 NAT10em1Smoc mice, and by combining the NPC cell or Lewis lung cancer cell transplantation model. Remarkably, NAT10 triggers immune microenvironment disorders and disrupts T-cell homeostasis through a series of acetylation modifications on its target genes, ultimately influencing the therapeutic response to PD-1 inhibition. The discovery that NAT10 inhibition sensitizes tumors to PD-1 blockade in NPC, cervical cancer, and hepatocellular carcinoma underscores its broad relevance. In the study conducted by Xie and colleagues, remodelin was employed as a small-molecule inhibitor of NAT10. Its effects were mainly observed in vitro, where it significantly reduced ac4C modification levels in downstream targets like DDX5 and HLTF, closely mimicking NAT10 knockout. This pharmacological inhibition complemented the CRISPR-Cas9 gene knockout results, confirming that NAT10's acetyltransferase activity is crucial for regulating NPC progression. Although remodelin is the well-known NAT10 inhibitor and shows promise for cancer therapy, the authors have not tested its effectiveness in animal models. Overall, understanding

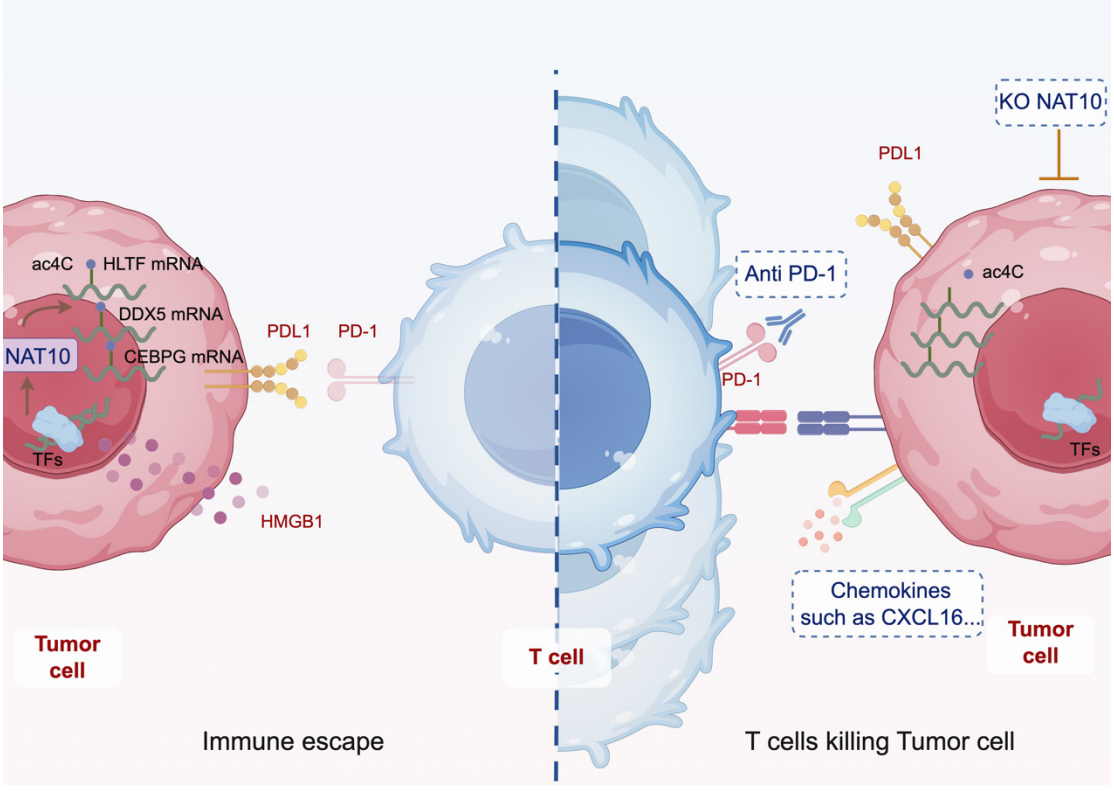

Figure 1 Proposed mechanism of targeting NAT10 in combination with anti-PD-1 therapy for nasopharyngeal carcinoma. Anti PD-1 and anti NAT10 promote chemokine release in the tumor microenvironment to enhance the recruitment of T cells, which restore the ability of T cells to kill tumor cells. (The schematic overview was created by Figdraw). ac4C, N4-acetylcytidine; HLTF, helicase-like transcription factor; HMGB1, high mobility group box 1; mRNA, messenger RNA; PD-1, programmed cell death protein; PD-L1, programmed death-ligand 1.

NAT10's role in modulating the tumor immune microenvironment provides new insights for developing immunotherapeutic strategies, particularly in cancers with low immunotherapy response rates.

Therapeutic outlook and unanswered questions

NAT10 presents promise as a drug target, with small-molecule inhibitors like remodelin showing preclinical efficacy in reducing ac^4C levels and reversing immunosuppression. Former studies have shown that NAT10-targeting therapies do not exhibit significant toxicity in multiple cancer models. Wang *et al* found that targeting NAT10 could effectively inhibit liver metastasis of gastric cancer, and H&E staining showed no observable toxicity to major organs such as heart, liver, lung, and kidney.[9] Similarly, Tao *et al* found that remodelin significantly inhibited tumor growth in a patient-derived xenograft model of head and neck squamous cell carcinoma, while well tolerated without significant toxicity to normal tissues was observed.[10] However, NAT10 is a widely expressed acetyltransferase, systemic toxicity from targeting it remains a concern.

Strong evidence supports the therapeutic potential of targeting NAT10 and its ac4C modification in various cancers. However, cancers with low NAT10 expression or tumors with alternative activation pathways may have limited response. Currently, there remains a lack of clinical strategies for patients with stratifying tumor based on the ac4C modification profile, and effective screening of targeted beneficiaries is helpful to achieve precise treatment and response to efficacy.

Several questions remain unanswered: the interplay between NAT10 acetylation and other RNA modifications in shaping the TME, the optimal timing for NAT10 inhibition (neoadjuvant, concurrent, or post-ICI resistance), and whether combinational strategies can enhance antitumor immunity without causing toxicity. Moreover, Xie *et al* appropriately caution that NAT10-mediated T-cell dysfunction exists in delicate equilibrium with HMGB1/CXCL16 homeostasis. Achieving therapeutic balance between immune activation and cytokine storm prevention remains a critical challenge requiring further investigation before clinical translation.

CONCLUSION

Xie *et al* re-define the role of RNA acetylation in cancer immunity, positioning the NAT10/DDX5/HMGB1 axis as a master regulator of TME immunosuppression in NPC (figure 1). Their work not only elucidates a mechanism of ICI resistance but also offers an actionable strategy to restore T-cell function through NAT10 inhibition. As epitranscriptomic research advances, targeting ac^4C modification represents a promising frontier for overcoming immunotherapy resistance in NPC and other solid tumors. Future efforts must prioritize biomarker-driven clinical trials and multi-target approaches to optimize therapeutic outcomes while mitigating risks.

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ORCID iD

Yue Zhao http://orcid.org/0000-0002-6790-3402

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