JEM Journal of Experimental Medicine

INSIGHTS

Testing the mettle of RNA methylation in T cell exhaustion

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Song et al. (https://doi.org/10.1084/jem.20250424) identify Mettl8 as a regulator of progenitor exhausted CD8⁺ T cells, stabilizing Tcf7 transcripts and shaping chromatin programs. Mettl8 loss drives effector differentiation and improves tumor control, underscoring RNA methylation as a key layer of T cell fate regulation.

T cell exhaustion is a barrier to durable antitumor immunity (McLane et al., 2019; Hashimoto et al., 2018). Song et al. (2026) identify an unexpected role of the RNA methyltransferase Mettl8 as a regulator of progenitor exhausted CD8⁺ T cells through stabilization of *Tcf7* transcripts and modulation of chromatin organization. Targeting this pathway reshapes the exhausted T cell subset distribution by enhancing effector-like cell differentiation and improves responses to PD-1 blockade treatment of cancer.

The ability of cytotoxic T lymphocytes to sustain antitumor responses is limited by the progressive acquisition of T cell exhaustion, a differentiation state characterized by diminished effector function and high inhibitory receptor expression (Baitsch et al., 2011; Sakuishi et al., 2010; Blackburn et al., 2009). Exhausted CD8⁺ T cells are a heterogeneous population composed of multiple differentiation states (Zheng et al., 2021; Paley et al., 2012). Stem-like progenitor exhausted T cells (Tpex) retain proliferative potential and self-renewal capacity and give rise to terminally exhausted populations (Miller et al., 2019; Utzschneider et al., 2016). Checkpoint inhibitors primarily act on this progenitor pool, enabling their proliferation and differentiation into effector populations that are capable of tumor control (Im et al., 2016; Sade-Feldman et al., 2018).

The transcription factor Tcf1, encoded by the gene *Tcf7*, is a defining regulator of the progenitor exhausted state (Im et al., 2016; Utzschneider et al., 2016; Sade-Feldman et al., 2018; Miller et al., 2019). Tcf1 promotes the maintenance of stem-like properties and establishes transcriptional programs that support long-term persistence of T cells during chronic antigen exposure (Wu et al., 2016; Kratchmarov et al., 2018). Despite its central importance, however, the molecular mechanisms that regulate Tcf1 expression and stability during T cell exhaustion remain incompletely understood. Song et al. (2026) address this question by examining the role of RNA methylation in controlling the Tcf1 network.

Through a combination of genetic, molecular, and tumor models, the authors identify Mettl8 as a key regulator of CD8⁺ T cell–mediated antitumor immunity. Mettl8 expression is enriched in Tpex and decreases following PD-1 blockade, suggesting that it participates in maintaining the progenitor exhaustion state. Deletion of Mettl8 in T cells leads to a pronounced shift in the exhausted T cell landscape. Instead of maintaining a stable progenitor population, Mettl8-deficient CD8⁺ T cells preferentially differentiate toward effector-like intermediate and terminally exhausted states, coupled with enhanced production of effector molecules and improved tumor control. By identifying Mettl8 as a regulator of Tpex, the authors shed light on a previously uncovered mechanism that integrates RNA modification with transcriptional control of T cell differentiation.

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Mechanistically, the study reveals a dual mode of regulation. First, Mettl8 binds *Tcf7* mRNA and promotes m^3C RNA methylation, which stabilizes the transcript and supports sustained expression of Tcf1. Second, Mettl8 interacts with the Tcf1 protein to influence chromatin organization and regulate downstream transcriptional programs, including the key exhaustion-associated transcription factor TOX (Scott et al., 2019; Khan et al., 2019; Alfei et al., 2019). Together, these findings suggest that Mettl8 coordinates both posttranscriptional and chromatin-level mechanisms to maintain the Tpex program.

Beyond its mechanistic insights, this study may have key therapeutic implications. The authors demonstrate that pharmacological inhibition of Mettl8 using the compound ginkgolic acid enhances CD8⁺

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T cell effector function and suppresses tumor growth in mouse models. Mettl8 inhibition by the sumoylation inhibitor ginkgolic acid also synergizes with PD-1 blockade, leading to improved tumor control compared with either treatment alone. This synergistic antitumor effect is associated with increased expansion of effector-like exhausted T cells and elevated production of cytotoxic molecules.

These findings offer the Mettl8-Tcf1 axis as a potential new target for improving cancer immunotherapy. Although immune checkpoint inhibitors have transformed cancer treatment, many patients fail to achieve durable responses due to T cell exhaustion. Novel therapeutic approaches that reshape the exhausted T cell landscape, either by preserving the progenitor pool or promoting productive effector differentiation, represent an active area of investigation (Hashimoto et al., 2018). Therefore, the current study suggests that modulation of RNA methylation may provide a novel strategy for tuning these differentiation dynamics.

The work by Song et al. (2026) raises several important questions for the field. First, the interaction between Mettl8 and the Tcf1 transcriptional network raises the possibility that RNA modification enzymes may coordinate multiple layers of gene regulation, linking transcript stability, chromatin architecture, and cellular differentiation state. While transcriptional and epigenetic programs governing exhausted T cells have been intensively studied, the roles of chemical modifications of RNA that influence transcript fate in T cell exhaustion have not been fully understood. Do similar mechanisms operate in human tumor-infiltrating lymphocytes? If so, pharmacological targeting of RNA methylation pathways could represent a new class of immunotherapeutic intervention.

Second, how broadly do RNA modifications regulate T cell fate decisions in other disease contexts? While modifications such as m^6A have been implicated in immune regulation (Li et al., 2017), the role of m^3C methylation in T cells has remained largely unexplored. The discovery that Mettl8 influences exhausted T cell differentiation suggests that additional RNA-modifying enzymes may participate in shaping immune responses.

Third, what could be the long-term impact of altering exhausted T cell subset formation by targeting Mettl8? Enhancing effector differentiation may boost immediate antitumor responses, but excessive differentiation could also deplete the progenitor pool required for sustained therapy responses to checkpoint blockade therapies and long-term memory formation. Achieving an optimal balance between stem-like maintenance and effector function should be an important consideration for future therapeutic strategies.

By uncovering a role for Mettl8 in regulating the Tcf1 network and exhausted T cell differentiation, Song et al. (2026) discovers an unexpected link between RNA methylation and antitumor immunity. As the field continues to explore strategies for improving checkpoint blockade therapy, targeting RNA modification pathways may provide a promising new direction.

Acknowledgments

Author contributions: Cansu Yerinde: conceptualization and writing—original draft, review, and editing. Debattama Rai Sen: conceptualization and writing—review and editing.

Disclosures: The authors declare no competing interests exist.

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