JEM Journal of Experimental Medicine

INSIGHTS

UBE2F impedes CD8 T cell memory

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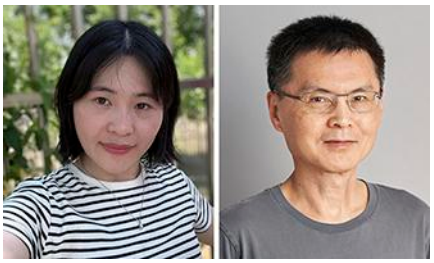
Long-term maintenance of immune memory is critical for the control of recurring virus infections and cancer. In this issue of *JEM*, Ma et al. (https://doi.org/10.1084/jem.20252687) report that the E2 ubiquitin–conjugating enzyme UBE2F restrains long-term CD8 T cell memory.

Immunological memory is critical for maintaining a durable immune control over repeated pathogen infections and cancer growth. Orchestrated by multiple lineages of adaptive and innate immune cells, this process relies heavily on CD8 memory T (T_M) cells, which generating cytotoxic T cells to directly eradicate pathogen-infected or malignant cells (Turner et al., 2021; Zhang and Bevan, 2011). CD8 T cell development constitutes a broad spectrum of differentiation states, with cytotoxic effector T (T_{EF}) cells and T_M cells residing at the two extreme ends (Obar and Lefrancois, 2010). CD8 T_{EF} cells are terminally differentiated cells with a short lifespan of only a few weeks; in contrast, CD8 T_M cells are long-lived cells and are responsible for the sustained replenishment of T_{EF} cells (Joshi et al., 2007). Impaired CD8 T cell memory has been linked to failures in viral clearance and cancer immune surveillance (Luxenburger et al., 2026). In this regard, understanding the mechanisms underlying the maintenance of CD8 T_M cells is crucial to harnessing the power of CD8 T cell–mediated immunity for efficient vaccination and cancer immunotherapy.

CD8 T_M cells comprise several distinct subtypes, encompassing conventional T_M, exhausted T (T_{EX}) memory, tissue-resident memory T (T_{RM}), and virtual memory T (T_{VM}) cells, whose developmental trajectory depends on the mode and duration of antigen stimulation and environmental signals (Pokhrel et al., 2025; Rausch and Kallies, 2025). Our current knowledge about T_M cells mainly comes from studies on conventional T_M and T_{EX} cells. During acute virus infections or strong antigenic stimulations, naïve CD8 T cells undergo vigorous proliferation, generating large numbers of short-lived T_{EF} cells to combat immediate antigenic threats. After clearance of the threats, while most T_{EF} cells die by apoptosis, a small proportion of IL-7Rα$^+$KLRG1$^-$ T_{EF} cells, termed memory precursor effector cells, adopt a developmental trajectory to become long-lived conventional T_M cells (Joshi et al., 2007). T_M cells can be further divided into central memory T (T_{CM}) cells, which are stem cell–like cells equipped with self-renewal capacity and differentiation plasticity, and effector memory T (T_{EM}) cells, which generate a continuum of differentiated T_{EF} cells upon re-exposure to the same antigens. In contrast, during chronic viral infections or in tumors, persistent and weak antigen exposure prevents conventional T_M cell formation and instead drives CD8 T cell differentiation along a different trajectory known as CD8 T cell exhaustion (Collier et al., 2021; Gebhardt et al., 2023). While most T_{EX} cells also have a short lifespan, they are distinct from short-lived T_{FE} cells in their characteristic expression of multiple inhibitory receptors (Gebhardt et al., 2023). T_{EX} cells are also comprised of heterogeneous subsets, including precursor/progenitor exhausted T (T_{PEX}), effector-like exhausted T (T_{EEX}), and terminally differentiated exhausted T (T_{TEX}) cells. T_{PEX} cells are T_{CM}-like cells, which can both self-renew and differentiate to populate downstream T_{EX} cell subsets. In contrast, unlike



Li Zhong and Hua Gu.

T_{EM} and T_{EF} cells, T_{EEX} and T_{TEX} cells are characterized by their reduced capabilities to proliferate and produce cytokines such as IL-2, IFN-γ, and TNF. However, despite lower responsiveness to antigen stimulation, T_{EX} cells play a critical role in immune protection against viral infections and tumors, as the loss of T_{EX} cells impairs the control of chronic virus infections and the efficacy of tumor immunotherapy (Gebhardt et al., 2023).

Given the importance of CD8 T_M cells in sustained immunity, strategies that mitigate T_M cell contraction could significantly enhance post-infection immune protection, vaccination, and tumor immunotherapy. Previous studies have identified several positive regulators, such as transcription factors TCF-1, MYB, and FOXO1, etc., and cytokines IL-7 and IL-15, that control the generation, growth, and survival of CD8 T_M cells (Rausch and Kallies, 2025). However, while the ectopic expression of TCF-1, MYB, or IL-7 boosts the early generation and expansion of T_M cells, such modulations cannot

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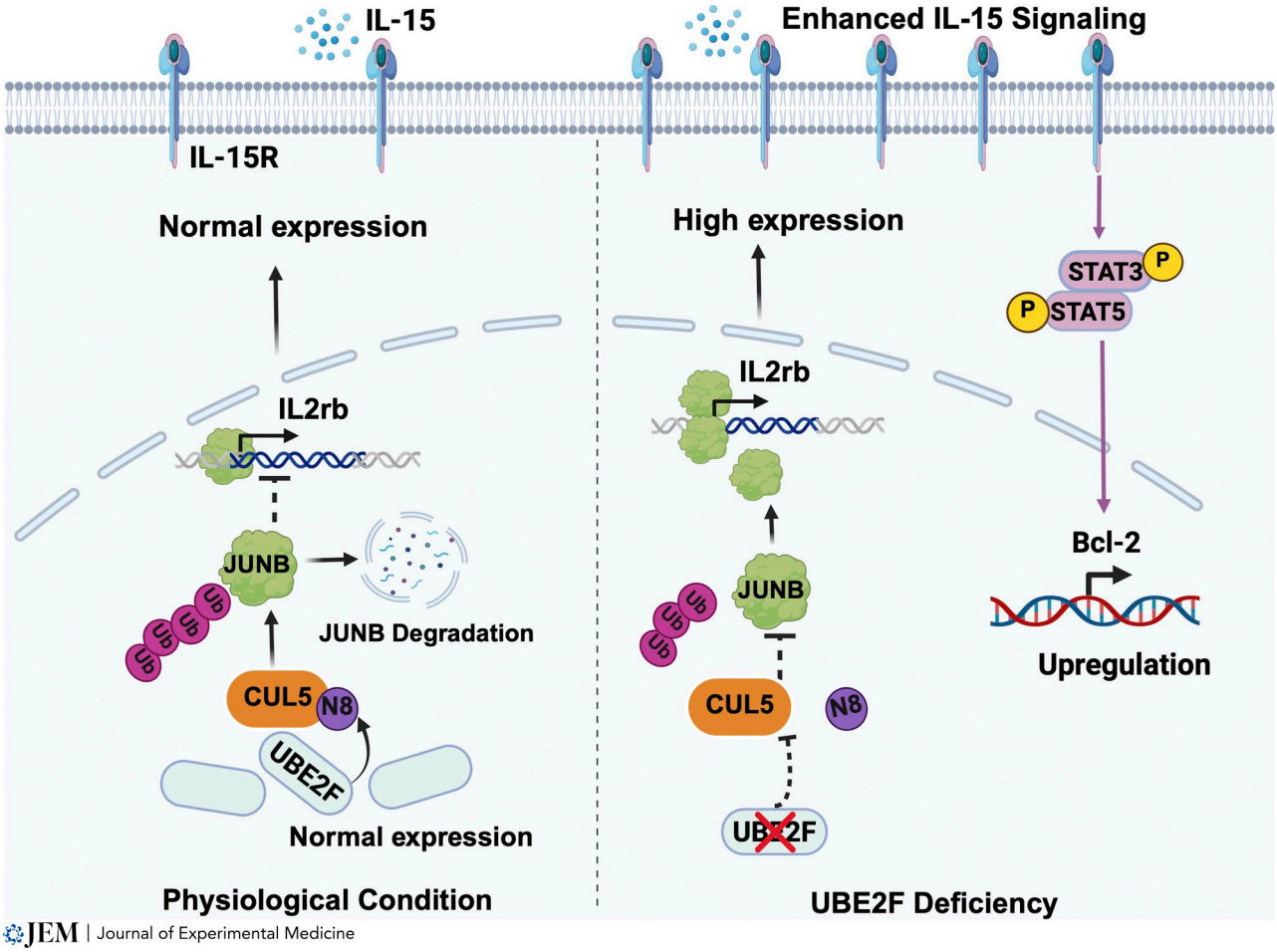

UBE2F deficiency enhances T_M cell survival. Left: In wild-type CD8 T_M cells, UBE2F promotes neddylation of CUL5, which activates the CRL5 ubiquitin ligase, leading to JUNB ubiquitination (Ub) and degradation in the proteasome. This regulation restrains *IL2b* gene expression and IL-15R signaling, thereby limiting the lifespan of CD8 T_{CM} and T_{PEX} cells under physiological conditions. Right: However, in UBE2F-deficient CD8 T_M cells, the lack of CUL5 neddylation impairs JUNB ubiquitination and degradation, leading to the accumulation of JUNB. Increased JUNB drives higher *IL2rb* expression, which enhances IL-15R signaling and consequently promotes the survival of CD8 T_{CM} and T_{PEX} cells, because stronger IL-15R signaling induces greater *Bcl-2* gene expression under physiological conditions.

prevent the long-term contraction of T_M cell pools (Gautam et al., 2019; Shan et al., 2021). To date, little is known about the negative regulators that impede sustained T_M homeostasis. In this issue of *JEM*, Ma et al. (2026) report that the ubiquitin-conjugating enzyme E2F (UBE2F) is a critical negative regulator of the homeostasis of T_M and T_{EX} cells. UBE2F is a neddylation enzyme responsible for transferring the ubiquitin-like protein NEDD8 to cullin 5 (CUL5), a component of the CUL5–RING E3 ligase complex (CRL5), which then mediates target protein ubiquitination (Zhou et al., 2017). Combining the genome-wide CRISPR screening approach with *in vivo* acute and chronic LCMV viral infection models, these authors demonstrate that UBE2F ablation in CD8 T cells significantly boosts anti-viral responses and suppresses tumor growth, driven by the long-term persistence of T_M and T_{EX} cell pools. The UBE2F mutation does not affect the developmental trajectory of CD8 T cells at different stages. Instead, it significantly attenuates the contraction of T_{CM} and T_{PEX} cell populations over time. Flow cytometric and single-cell RNA sequencing analyses reveal that mutant T cells express normal levels of transcription factors related to T_M cell development and differentiation. However, they significantly upregulate BCL-2 and Ki67 expression, indicating that these cells have acquired enhanced survival and self-renewal capacities. Mechanistically, the authors find that UBE2F promotes CUL5 neddylation and is required for JUNB degradation in the proteasome, although it is not yet clear whether CUL5 neddylation directly mediates JUNB ubiquitination. UBE2F-deficient CD8 T cells express more JUNB, which in turn promotes the transcription of IL2rb and enhances IL-15R signaling, consequently improving the fitness of both T_{CM} and T_{PEX} cells to survive at physiological concentrations of IL-15. The significance of this work is twofold: First, it identifies, for the first time, that the UBE2F–CUL5–JUNB–IL2RB axis is a critical negative regulator that controls the homeostasis of T_{CM} and T_{PEX} cells. Second, it suggests that targeting UBE2F-mediated neddylation could be an effective strategy to enhance T_{CM} and T_{PEX} cell survival for the better outcome of vaccination and cancer immunotherapy. It should be mentioned that the pharmacological inhibition of UBE2F–CRL5 neddylation has been shown to induce tumor apoptosis (Xu et al., 2022). Thus,

targeting UBE2F may offer the dual benefit of simultaneously boosting anti-tumor immunity and inhibiting cancer growth in cancer treatment.

To avoid "population contraction" of T_M and T_{EX} cells over time, it requires that the death of T_M and T_{EX} cells must be matched with an almost equal rate of T_M and T_{EX} cell proliferation and self-renewal. Since both IL-7 and IL-15 are involved in the regulation of CD8 T_M homeostasis, it is important to elucidate their precise roles in the self-renewal and survival of these cells. Previous experiments have shown that IL-7Rα$^{-/-}$ CD8 T cells fail to generate normal T_M cells during viral infection (Schluns et al., 2000). However, overexpression of IL-7Rα chain or IL-7 treatment only leads to transient, rather than persistent, expansion of T_M cells (Nanjappa et al., 2008). In contrast, lack of IL-15 does not impact the initial generation but instead impairs the later maintenance of T_M cells (Becker et al., 2002). The latter observation is consistent with the finding by Ma et al. that IL-15 supports the long-term survival of T_{CM} and T_{PEX} cells. Thus, it is plausible to propose that IL-7 and IL-15 control different stages and aspects of T_M cell homeostasis, with IL-7 regulating early commitment and expansion and IL-15 controlling later survival of T_{CM} and T_{PEX} cells.

At present, it remains unclear whether UBE2F also regulates the homeostasis of T_{VM} and T_{RM} cells. CD8 T_{VM} cells are the largest subset of memory-phenotype CD8 T cells, composing >90% of total CD44$^+$CD62L$^+$ CD8 T_{CM} cells in peripheral lymphoid organs and blood at steady state (Pokhrel et al., 2025). These cells develop through mechanisms of homeostatic expansion rather than activation by specific antigens and function as innate-like cells to control pathogen infections by secreting inflammatory cytokines and NKG2D-dependent bystander cytotoxicity (White et al., 2016). Development of T_{VM} cells has been shown to depend on IL-15 signaling (White et al., 2016). However, it is surprising to note that the UBE2F mutation does not seem to affect the development of peripheral CD44$^+$CD62L$^+$ CD8 T_{VM} cells, suggesting that UBE2F is dispensable for the maintenance of T_{VM} cell homeostasis. If confirmed, it will be interesting to determine whether T_{VM} cells use other E2-conjugating enzymes to regulate their homeostasis. Further work is also needed to elucidate whether UBE2F controls the homeostasis of T_{RM} cells. Finally, given the critical role of UBE2F in the homeostasis of CD8 T_{CM} and T_{PEX} cells, it is important to validate that this regulation also controls the homeostasis of human CD8 T_{CM} and T_{PEX} cells.

Acknowledgments

Li Zhong: visualization and writing—original draft. Hua Gu: conceptualization, formal analysis, funding acquisition, project administration, resources, supervision, validation, visualization, and writing—original draft, review, and editing.

Disclosures: The authors declare no competing interests exist.

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