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EZH2: an epigenetic governor of T-cell Ca^{2+} homeostasis

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Cellular & Molecular Immunology; https://doi.org/10.1038/s41423-026-01429-4

In modern immunology, Ca^{2+} first emerged as a key determinant of T cell activation in the early 1980s. In 1984, Weiss et al. first reported that T-cell receptor (TCR) stimulation leads to a rapid increase in the cytoplasmic Ca^{2+} concentration [1]. In 1991, Flanagan et al. first identified the nuclear factor of activated T cells (NFAT) pathway, firmly establishing Ca^{2+} as a key component of T cell function [2]. However, despite this importance, the epigenetic mechanisms that precisely control the balanced Ca^{2+} response in activated T cells have long remained largely unknown. This has become a critical limitation that prevents the fundamental resolution of clinical challenges, such as the pathological hyperactivation of graft-versus-host disease (GVHD) or the premature death and exhaustion of chimeric antigen receptor (CAR) T cells. Recently, Wang et al. identified EZH2, a representative epigenetic regulator, as a homeostatic governor that directly controls Ca^{2+} homeostasis, presenting a new therapeutic paradigm that encompasses the conflicting domains of immunosuppression and enhancement [3].

Since T cells are chronically exposed to antigens in a variable immune environment, epigenetic plasticity is essential for fine-tuning the intensity and timing of Ca^{2+} signaling. On the basis of previous reports [4] that T cell homeostasis decreases upon EZH2 deficiency, the authors hypothesized that EZH2 is a key switch for Ca^{2+} regulation. Indeed, reanalysis of prior RNA sequencing data revealed that the expression of Ca^{2+} signaling regulators was abnormally high in EKO (*Ezh2* KO) T cells. They reported that EZH2 deficiency leads to the derepression of *Itpr2* (encoding $InsP_3R2$), resulting in excessive Ca^{2+} leakage from the endoplasmic reticulum (ER) into the cytosol. This chronic depletion of ER Ca^{2+} stores triggers the constitutive activation of STIM1, the ER Ca^{2+} sensor, which subsequently forces the opening of ORAI1 channels on the plasma membrane [5]. This sequential cascade culminates in a pathological overload of store-operated calcium entry (SOCE). These findings demonstrate that EZH2 serves as a master homeostatic regulator, safeguarding T cells from lethal Ca^{2+} toxicity by maintaining the integrity of ER Ca^{2+} storage (Fig. 1A) [3, 6]. This defect in Ca^{2+} regulation manifested as a lethal phenotype in a GVHD model. In an allogeneic hematopoietic stem cell transplantation (allo-HSCT) model, severe GVHD was induced in mice infused with WT T cells, whereas in the EKO T cell recipient group, premature cell death was induced because of excessive Ca^{2+} influx and failure to induce GVHD. To determine whether excessive STIM1-mediated Ca^{2+} signaling is a direct cause of the loss of viability in EKO effector T cells, the authors attempted to verify the mechanism using an ESKO (*Ezh2/Stim1* dKO) model in which STIM1 was also removed [3]. Notably, the ability to produce interferon-gamma (IFN-γ) and interleukin-2 (IL-2), which were lost upon deletion of only STIM1, was dramatically restored when EZH2 was removed along with STIM1 (ESKO). These findings suggest that EZH2- and STIM1- are key axes that interdependently coordinate T cell function. To identify the top switch controlling STIM1-mediated Ca^{2+} signaling by EZH2, researchers focused on candidates that exhibited the most dramatic expression differences in previous RNA sequencing data. As a result, they selected *Itpr2* (encoding $InsP_3R2$), the gatekeeper that opens the door to intracellular Ca^{2+} stores, as a key target. In particular, through ChIP-seq analysis, they demonstrated that EZH2 directly regulates the trimethylation of histone H3 at lysine 27 (H3K27me3) modification of the *Itpr2* promoter region and maintains epigenetic sealing, thereby clearly establishing a direct causal relationship between EZH2 and Ca^{2+} leakage [3]. The final constructed EI2KO (*Ezh2/Itpr2* dKO) model highlights the logical conclusions of this paper. When *Itpr2* expression was defective, the proliferative capacity of dying EKO T cells not only recovered to WT levels but also revived as powerful effector cells that released IFN-γ and IL-2 in the spleen and liver. By infiltrating the host's major organs and inducing lethal GVHD, these functionally restored EI2KO cells demonstrated that EZH2 acts as a molecular safeguard, balancing the aggressiveness and survival of T cells by repressing *Itpr2* (Fig. 1B).

On the basis of the genetic principles identified in the GVHD model, researchers constructed an hCD19 CAR-T cell system and verified its efficacy in anticancer immunity [3]. As previously reported, EZH2-deficient CAR-T cells undergo premature death because of excessive Ca^{2+} influx upon tumor antigen stimulation and fail to eliminate cancer cells. However, at the WT level, EI2KO CAR-T cells were free from the shackles of premature death and recovered robust numerical maintenance and expansion capabilities, which led to significant anticancer efficacy that increased the survival rate of leukemia model mice to more than 60% [3]. The most critical insight of this study was derived from tracking the fate of EI2KO cells with extended survival. Compared with WT cells, EI2KO CAR-T cells that avoided premature death entered a terminal exhaustion state ($PD\text{-}1^{+}CD39^{+}$) much faster [3]. These findings suggest that EZH2 is not limited to preventing death through *Itpr2* inhibition but is essential for maintaining T cell persistence under conditions of chronic antigen exposure. In other words, EZH2 acts as a dual protective shield, safeguarding T cells from self-destruction when they first encounter antigens and managing them to prevent exhaustion during prolonged battles (Fig. 1B).

The EZH2-$InsP_3R2$ axis identified by Wang et al. is a key mechanism determining the fate of T cells, but the challenge of sophisticated decoupling between preventing death and maintaining persistence in clinical applications remains [3]. Notably, the

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Received: 28 April 2026 Accepted: 7 May 2026
Published online: 25 June 2026

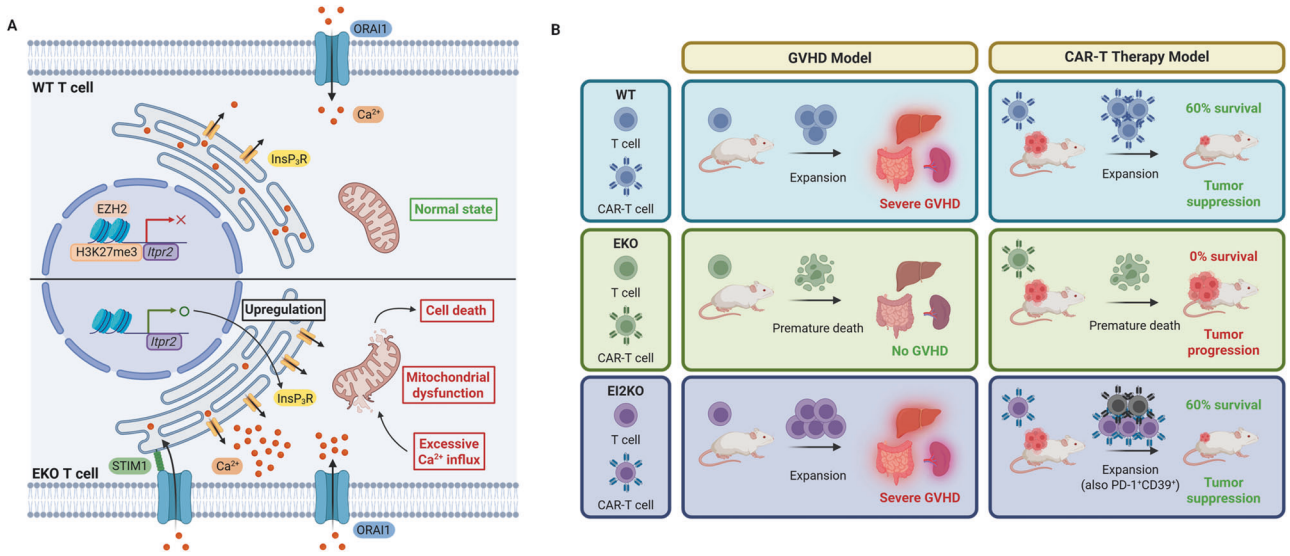

Fig. 1 EZH2-mediated *Itpr2* silencing regulates T cell Ca^{2+} homeostasis. **A** In WT T cells, EZH2 maintains Ca^{2+} homeostasis by catalyzing the trimethylation of histone H3 at lysine 27 (H3K27me3) at the *Itpr2* (encoding $InsP_3R2$) promoter, which silences its expression and effectively limits Ca^{2+} efflux from the endoplasmic reticulum (ER). Conversely, EZH2 deficiency in EKO (*Ezh2* KO) T cells leads to the derepression of *Itpr2*, triggering pathological Ca^{2+} overload that ultimately results in mitochondrial dysfunction and premature cell death. **B** In a graft-versus-host disease (GVHD) model, while WT T cells induce potent systemic inflammation, EKO T cells fail to elicit disease pathogenesis because of premature cell death; however, genetic loss of *Itpr2* in EZH2-deficient cells causes severe GVHD. Similarly, in a chimeric antigen receptor (CAR) T cell therapy model, WT CAR-T cells facilitated tumor regression, with a 60% survival rate despite gradual progression toward an exhausted state characterized by $PD\text{-}1^{+}CD39^{+}$ expression. In contrast, EKO CAR-T cells exhibit complete therapeutic failure, with 0% survival due to premature death. Notably, although EI2KO (*Ezh2/Stim1* dKO) CAR-T cells reconstitute the effector pool to levels comparable to those of WT cells and achieve a 60% survival rate, they undergo accelerated terminal exhaustion in the absence of EZH2-mediated homeostatic control

cell death mechanism, which has previously been reported primarily in innate immune cells, is latent as a powerful self-destructive program within T cells, the central hub of adaptive immunity [7]. PANoptosis is a broad inflammatory cell death mechanism in which the pathways of pyroptosis, apoptosis, and necroptosis are integrated and executed by the PANoptosome complex [8, 9]. Notably, excessive Ca^{2+} influx not only induces metabolic arrest but also transforms T cell mitochondria into a danger signaling platform for innate immune signaling. The mtDNA and ROS released from these Ca^{2+}-overloaded mitochondria force T cells to transcend their identity as adaptive responders and instead function as innate-like sensors that trigger self-destruction under extreme stress [10]. Therefore, the uncontrolled Ca^{2+} influx observed in EKO T cells transforms the intracellular microenvironment into one that is extremely vulnerable to PANoptosis, and EZH2 can be redefined as an epigenetic threshold that controls T cells from entering this innate immune self-destruct program upon antigen exposure. Ultimately, the key to subsequent research lies in selectively blocking only the execution pathway through which Ca^{2+} overload translates into cell death while preserving the epigenetic state of EZH2. Strategies such as incorporating innate immune-derived endogenous inhibitory mechanisms into T cells or fine-tuning the key nodes of PANoptosis will serve as a strong rationale for simultaneously ensuring T cell survival and sustained anticancer efficacy even in harsh tumor microenvironments. This is expected to become a new milestone in an integrated immunological model that resolves the limitations of adaptive immunity through the principles of innate immunity.

In summary, Wang et al. have successfully completed a conceptual reconfiguration of the functional role of EZH2 in T cell immunology. By defining EZH2 as a molecular rheostat that precisely controls Ca^{2+} homeostasis, this study has clearly resolved the academic challenges that obstruct the causal relationship between T cell antigen recognition and the execution of abnormal death. The EZH2-$InsP_3R2$ axis model proposed by researchers not only highlights the multifaceted nature of T cell function but also provides an essential mechanistic foundation for a decoupled understanding of death signaling and maintenance mechanisms. In the future, technology designed to control these ion regulatory circuits at lower levels will become essential for achieving a sophisticated equilibrium between maximizing tumor-killing efficacy and preserving immune homeostasis.

REFERENCES

1. Weiss A, Imboden J, Shoback D, Stobo J. Role of T3 surface molecules in human T-cell activation: T3-dependent activation results in an increase in cytoplasmic free calcium. Proc Natl Acad Sci USA. 1984;81:4169–73.
2. Flanagan WM, Corthesy B, Bram RJ, Crabtree GR. Nuclear association of a T-cell transcription factor blocked by FK-506 and cyclosporin A. Nature. 1991;352:803–7.
3. Wang Y, Huang Q, Zhou Y, Hooper R, Sanders-Braggs R, Chen M, et al. EZH2 and intracellular Ca2+ signals interdependently coordinate alloreactive and CAR T-cell responses. Cell Mol Immunol. 2026;23:840–54.
4. He S, Liu Y, Meng L, Sun H, Wang Y, Ji Y, et al. Ezh2 phosphorylation state determines its capacity to maintain CD8(+) T memory precursors for antitumor immunity. Nat Commun. 2017;8:2125.
5. Pauken KE, Sammons MA, Odorizzi PM, Manne S, Godec J, Khan O, et al. Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. Science. 2016;354:1160–5.
6. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, et al. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. Nature. 2006;441:179–85.
7. Doitsh G, Galloway NL, Geng X, Yang Z, Monroe KM, Zepeda O, et al. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. Nature. 2014;505:509–14.
8. Lee S, Karki R, Wang Y, Nguyen LN, Kalathur RC, Kanneganti TD. AIM2 forms a complex with pyrin and ZBP1 to drive PANoptosis and host defense. Nature. 2021;597:415–9.
9. Jang Y, Bae H, Oh S, Yu G, Bae H, Nguyen MQ, et al. Innate immune sensing of dietary alcohol ignites inflammation to drive alcohol-related disease. Sci Adv. 2026;12:eaea3979.

10. Spetz J, Presser AG, Sarosiek KA. T cells and regulated cell death: kill or be killed. Int Rev Cell Mol Biol. 2019;342:27–71.

ACKNOWLEDGEMENTS

We thank all the members of the Lee laboratory for their comments and suggestions during the development of this manuscript. This research was supported by the Korea Drug Development Fund, funded by the Ministry of Science and ICT, Ministry of Trade, Industry and Energy, and the Ministry of Health and Welfare, Republic of Korea (RS-2025-02222987 to SL). This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (MSIT) (2022R1C1C1007544, 2024M3A9H5043152 to SL), a grant from the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea under the Korea Health Technology R&D Project (RS-2025-25459955 to SL), a Research and Development (R&D) project on the animal and plant quarantine technology of the Animal and Plant Quarantine Agency in the Republic of Korea (Z-1543083-2026-29-0101 to SL), a Korean ARPA-H Project grant from the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (RS-2025-2542273 to SL), the Institute for Basic Science (IBS), Republic of Korea (IBS-R801-D9-A09, IBS-R801-D1-2025-A02, IBS-R801-D1-2026-a Additionally, research funds were granted from the Republic of Korea's National Institute of Health (Project Nos. #2025ER160200 and #2025ER240100 to SL).

AUTHOR CONTRIBUTIONS

SK and SL conceived this study, prepared the manuscript, and critically revised and approved the final submitted version of the manuscript. All the authors contributed to the manuscript and approved the submitted version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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