442-H IL-21 ON/OFF SWITCH CAR-T ENHANCE ANTI-TUMOR EFFECTS BY EPIGENETIC AND TRANSCRIPTIONAL REGULATION

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Background The orchestration of T cell responses, particularly CD8+ T cells, through complex epigenetic and transcriptional mechanisms, plays a crucial role in boosting anti-tumor immunity.[1–3] The interplay between TET enzymes as essential epigenetic modulators and BATF, a central transcription factor for T cell functionality, stands out as a key regulatory mechanism.[4 5]

Methods This study draws upon our previous findings, where we identified the effects of TET deficiency on BATF expression, and its pivotal role in countering T cell exhaustion through the inhibition of TOX and NR4A. Additionally, we found that TOX and NR4a repressed IL-21 secretion in CAR-T cells. Based on these insights, we developed a novel approach by pairing TET knockout (KO) with IL-21-mediated BATF upregulation, integrating an IL-21 on/off switch using a destabilization domain, thus enabling controlled IL-21 secretion via a small molecule. The resulting impact on tumor-infiltrating CD8+ T cell survival, expansion, effector functionality, and exhaustion was systematically assessed.

Results Our dual intervention significantly amplified the anti-tumor responses of CD8+ T cells. The data showcased a marked enhancement in the survival, expansion, and effector functionality of these cells within tumors, accompanied by a substantial reduction in exhaustion. These changes were reflected in the decreased expression of inhibitory receptors and exhaustion-linked transcription factors. Notably, our on/off switch system successfully controlled IL-21 secretion using a small molecule.

Conclusions This research pioneers a promising therapeutic strategy that melds both epigenetic and transcriptional manipulation, specifically through TET inhibition and IL-21-driven BATF overexpression, enhanced by TOX and NR4a downregulation. The integrated approach, including the innovative on/off switch for IL-21 secretion, has the potential to significantly amplify CD8+ T cell anti-tumor responses. This multifaceted strategy opens new paths for refining and augmenting the effectiveness of cancer immunotherapy.

Acknowledgements This work was supported by the New Faculty Startup Fund and Creative-Pioneering Researchers Program from Seoul National University, and the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT)(No. RS-2023-00242443, RS-2023-00210035).

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http://dx.doi.org/10.1136/jitc-2023-SITC2023.0442-H