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The Wnt-TCF1 pathway is necessary and sufficient for modulation of mature CD8$^+$ T cell responses

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The canonical Wnt signaling pathway stabilizes β-catenin, which translocates into nucleus and complexes with the TCF1 transcription factor to modulate gene expression. This signaling cascade is known to critically regulate normal T cell development; however, its physiological roles in mature CD8$^+$ T cell responses are less known. Using a Listeria monocytogenes infection model, we found that ectopic expression of TCF1 and stabilized β-catenin limited effector CD8$^+$ T cell expansion but augmented the pool of antigen-specific memory CD8$^+$ T cells. These memory CD8$^+$ T cells expanded to a larger number of secondary effectors and cleared bacteria faster when the immunized mice were rechallenged with virulent L. monocytogenes. On the other hand, TCF1 deficiency compromised production of memory CD8$^+$ T cells and impaired their differentiation towards a central memory phenotype. Moreover, TCF1-deficient memory CD8$^+$ T cells were progressively lost over time, exhibiting reduced expression of the anti-apoptotic molecule Bcl-2, interleukin-2 receptor β chain and diminished IL-15-driven proliferation. Mechanistically, TCF1 was directly associated with the Eomes allele, and Eomes expression was modulated by the Wnt signaling pathway in naïve and memory CD8$^+$ T cells. Importantly, forced expression of Eomes partly protected TCF1-deficient memory CD8$^+$ T cells from time-dependent attrition. Our studies thus indicate that the Wnt-TCF pathway is both necessary and sufficient to promote differentiation and longevity of memory CD8$^+$ T cells. The Wnt-TCF1 pathway can thus be explored to improve vaccine/adjuvant design, aiming for enhanced protective immunity.

Biography

Xue completed his Ph.D with Dr. Arata Ichiyama in 2000 (Hamamatsu University College of Medicine, Japan) and postdoctoral fellowship with Dr. Warren Leonard in 2006 (National Heart, Lung, and Blood Institute, NIH). He is currently an associate professor at Department of Microbiology, the University of Iowa. His primary research interest focuses on transcriptional regulation of T cell development and mature T cell responses.

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