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## REGULATION OF MEMORY CD8+T CELL DIFFERENTIATION DURING ACUTE VIRAL INFECTIONS

VARUN N KAPOOR

Department of Cancer Immunology, Genentech, CA, USA.

### Editorial

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#### \*For Correspondence

Varun N. Kapoor, Department of Cancer Immunology, Genentech Inc, South San Francisco, USA, Tel:7749227786

E-mail: varunkapoor81@gmail.com

In response to a virus infection, CD8+T cells proliferate and differentiate into effector cells that eradicate the pathogen. The population of effector CD8+T cells generated during an immune response is heterogeneous; upon clearance of the viral antigen the majority of effector cells die, leaving behind a small [5-10% of the peak response] but stable population of memory CD8+T cells to provide protection to secondary challenge. The precise mechanisms, which govern effector-memory CD8+T differentiation, are beginning to be elucidated.

IL-2, IL-7 and IL-15 belong to the common  $\gamma$  chain family of cytokines and are required at various stages for an optimal T cell immune response. IL-7 and IL-15 are known to mediate survival and self-renewal of memory CD8+T cell population<sup>[1, 2]</sup>. CD8+T cells expressing IL-7R $\alpha$  preferentially give rise to memory CD8+T cells<sup>[3]</sup>. Surface expression of IL-7R $\alpha$  along with KLRG-1 [inhibitory receptor found on T and NK cells] has been used to identify cells which will preferentially make it into memory [Memory Precursor effector cells: IL-7Rhi KLRG-1lo] or die during contraction of the immune response [Short-Lived effector cells: IL-7Rlo KLRG-1hi]<sup>[4]</sup>. IL-2 is a T cell growth factor and plays an important role in regulating CD8+ T cell responses during the different stages of viral infection<sup>[5]</sup>. In vivo IL-2 therapy during the contraction and memory stages of the immune response promotes CD8+T cell survival<sup>[6]</sup>. Moreover, IL-2-producing CD8+T cells are more likely to become memory cells than those that do not make IL-2<sup>[7]</sup>.

Apart from cytokine receptors, various co-stimulatory and chemokine receptors have been shown to be important in generation of memory CD8+T cells. CD27 is a co-stimulatory receptor of the TNFR family and has also been used as a marker to identify memory precursor CD8+T cells<sup>[8]</sup>. Expression of CD27 on virus-specific CD8+T cells promotes survival, induces IL-7R expression, and protects against Fas-dependent apoptosis<sup>[9-12]</sup>. Activated T cells may express CXCR3, a chemokine receptor required for T cell chemotaxis to the site of antigen<sup>[13, 14]</sup>. Moreover, expression of IL-7R, CD27 and CXCR3 has been used to identify memory CD8+T cell populations with an efficient recall response<sup>[15]</sup>.

Transcriptional regulation of effector and memory CD8+T cell differentiation is beginning to be elucidated. Blimp-1 [B lymphocyte induced maturation protein-1, encoded by Prdm1] is a transcription factor important for regulating differentiation of various cell types<sup>[16]</sup>. Blimp-1 suppresses memory generation and Blimp-1-deficient CD8+T cells are better at producing IL-2 and develop into memory precursor CD8+T cells<sup>[17, 18]</sup>. We have recently shown that Blimp-1 suppresses CD25 [IL-2Ra] and CD27 expression by inducing histone modifications to negatively regulate CD8+T cell differentiation<sup>[19]</sup>. Bcl-6 is a transcription factor expressed in memory T cells and is an antagonist of Blimp-1 activity<sup>[17, 20]</sup>. Bcl-6 has been shown to be important for generation and maintenance of memory CD8+T cells<sup>[21, 22]</sup>. T cell factor-1 [TCF-1, encoded by Tcf7] is a transcription factors acting downstream in the Wnt signaling pathway<sup>[23]</sup>. TCF-1 was shown to be important for generation and maintenance of memory CD8+T cells<sup>[24, 25]</sup>, and TCF-1 deficient CD8+T cells had impaired expansion after a secondary antigen challenge<sup>[24-26]</sup>. T-bet and EOMES are T-box transcription factors, and co-operate to induce CD122 [IL-2R $\beta$ ] expression and IL-15 responsiveness in CD8+T cells<sup>[27]</sup>. However, T-bet promotes the generation of terminally differentiated effector cells<sup>[27, 28]</sup>, whereas EOMES expression promotes generation of memory precursor effector CD8+T cells<sup>[29]</sup>. The forkhead box (Fox) family of transcription factors have been show to play a role regulating T cell homeostasis and tolerance<sup>[30]</sup>. FoxO1 has been shown to be important for generation of competent memory T cells and in it's absence memory T cells were lost over time primarily due to decreased TCF-1 and CCR7 expression<sup>[31, 32]</sup>. FoxO3a

also belongs to the Fox family of transcription factors and was shown to negatively impact CD8+T cell memory formation by promoting contraction of CD8+T cells during resolution of immune response to *Listeria* infection [33].

Transcription factors of the JAK [Janus kinases] - STAT [Signal transducers and activators of transcription] family of transcription factors transmit signals from cell surface receptors to in response to a large number of growth factors and cytokines [34]. STAT proteins are known to play a key role in CD8+T cell differentiation in response to extracellular cytokine signals [35]. STAT5 can be induced downstream of  $\gamma$  chain family of cytokines such as IL-2, IL-7 and IL-15 [34]. STAT5 was shown to promote effector and memory T cell survival via up regulation of Bcl-2 during acute LCMV infection [36, 37]. STAT3 can be induced downstream of IL-10 and IL-21 and STAT-3 deficient CD8+T cells were defective in generating a memory cell pool [20]. In the same study STAT-3 was shown to be important for maintenance of EOMES and Bcl-6 expression, which are transcription factors associated with memory development. Overall these studies show that signals induced by cytokines can provide cues to the cells to regulate the generation of effector and memory CD8+T cells.

Recent studies have identified that strength of TCR signals can in script a transcriptional program in effector CD8+T cells governing their fate. In this regard IRF4 [Interferon regulatory factor 4] has been shown to play a critical role in orchestrating expansion and effector differentiation of CD8+T cells in response to TCR signals [38-40].

The studies mentioned above show that strength and duration of TCR signals, exposure to inflammatory cytokines and co-stimulatory molecules instruct a transcriptional program within the T cells governing their fate conversion to memory. With the advent of technologies for high throughput screening of transcriptional profiles and the availability of vast array of gene expression data it has now become possible to define transcriptional networks which regulate T cell differentiation during various stages of the immune response. Knowledge of this will help us better understand T cell immunity after infections and will eventually help develop better vaccines.

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