Cd8+ effector and memory t cells differentiation

What controls CD8+ effector and memory T cells differentiation?

Introduction:

The capability of initiating and cultivating a population of memory T cells is the key component of an effective adaptive immune response and the fundamental foundation for a productive vaccine since memory cells can trigger an aggressive response upon reinfection. Throughout an infection, T cells can differentiate into a multitude of effector and memory cells, which help resolve pathogenic invasion and promote protective immunity. Effector and memory CD8+ T cells are one group of T cells that help cells maintain homeostasis by maintaining the proper proportion of heterogeneous cells in the immune system. Technical advances and progressive research has made it possible to unravel some of the mechanisms necessary in generating effector and memory CD8+ T cells. Here, we discuss some regulatory molecules, transcriptional factors, and signaling pathways that contribute to current models of how heterogeneous populations of CD8+ T cell arise after infection.

Separate-Precursor and Decreasing-potential model:

There are currently several models put forth to explain the rise of different differentiated states of CD8+ T cells. Historically, one of the earliest models put forth is the separate-precursor model. In this model, naïve T cells are primed and pre-programmed in the thymus to evolve into the specific effector states. Thus, when the cells reach their peripheral locations, they can readily differentiate into their predetermined states. But, research

revolving around cellular barcoding has shown that naïve T cells are actually multi-potent – thus this model seems unlikely,

The decreasing-potential model, on the other hand, suggests that the degree of differentiation is dependent on the duration of exposure to signaling molecules that the T cell encounters. Cumulative signaling will drive the naïve T cell into a differentiated state. This is seen when repetitive exposure of IL-2 drives T cells to proliferate and become terminally differentiated. However, once a cell becomes terminally differentiated, the cell looses other functional aspects – such as longevity and proliferative capabilities – an integral component of becoming a memory cell. However, the exact mechanism of how this process occurs is unclear.

Signaling strength model:

The signaling strength model states that formation of heterogeneous CD8+ T cells is contingent on the overall strength of three signals (signal 1, 2, and 3) that are stimulated during early T cell priming. The strength and duration of signal 1 is mediated by antigens, signal 2 by co-stimulatory molecules, and signal 3 by inflammatory cytokines – each influencing later T cell development and differentiation. The aggregation of these signals results in clonal expansion and development into memory CD8+ T cells, while superfluous signaling results in differentiation into effector CD8+ T cells. Thus, CD8+ T cell populations are delicately modulated by homeostatic mechanisms that are tightly coordinated with environmental cues and concentration gradients of signaling molecules.

But, how does CD8+ T cells sense the intensity and duration of signals 1, 2, and 3 and then properly respond to these signals and differentiate into distinctive states? This model suggests that the stromal microenvironment that the T cell migrates to early in their development influences later cell commitments. The delicate balance between cytokines and signaling molecules directs the degree of differentiation – resulting in a continuum of cells that are essential for mediating a proper immune response. On one end of the continuum are naïve T cells that are highly proliferative, young, and can become memory cells while on the other end are cells that are terminally differentiated. In the middle are an array of cells with variability in these three characteristics.

To try and differentiate between this heterogeneous populations of CD8+ T cells, scientists are trying to determine which phenotypic surface markers, individually or in combination, severe as an indicator of a particular cell lineage and differentiate those markers from markers that arise simply due to response from an infection. Simply put, can we determine which diverse set of expression surface molecules are necessary for cell lineages from markers due to environmental cues? In some ways, this seems like a likely avenue. In an acute infection, it has been shown that CD8+ T cells with KLRG1 ^{low} IL-7R ^{high} are more likely to survive after an infection than KLRG1 ^{high} IL-7R ^{low} cells. This indicates that IL-7R ^{high} cell induces T cells into a memory states, while KLRG1 ^{high} populations stimulates the cells to become terminally differentiated. While these markers are useful, they have yet to capture the degree of heterogeneity seen in these CD8+ T cells since other phenotypic or functional characteristics have been seen in these cells.

Another area of research of great interest is the role of transcriptional factors that are potentially linked to CD8+ T cell differentiation and evolution into memory cells. From these researches, an important theme has emerged – the idea that pairs of transcriptional factors operate in an antagonistic fashion to mediate effector vs. memory cell fates. For example, high concentrations of T-bet foment CD8+ T cells to become terminally differentiated, while high concentration of Eomes foster the development of memory cells. Thus, concentration gradients of these transcriptional pairs are key regulators in the differentiation of terminal effector cells and memory cells. Other transcriptional factor pairs include Bcl-6 and BLIMP1, ID3 and ID2, and STAT3 and STAT4.

The asymmetric cell fate model:

One of the last models mentioned is the asymmetric cell fate model. This model states different T cell populations arise from a single T cell precursor due to asymmetric cell division. During APC-T cell interaction, the proximal side of the T cell will adopt an effector cell fate, while the distal side of the T cell will adopt a memory cell fate. Evidence for this type of cell division and differentiation has been shown, however it does not explain all mechanisms associated with CD8+ T cell differentiation. Overall, these models show the progression in our understanding of potential pathways that could explain how CD8+ T cells can either become an effector or memory cell.

Signaling pathways:

As mentioned above, consolidated signaling via TCR, co-stimulatory receptors, and inflammatory cytokine receptors can shift the expression

level of paired transcriptional factors, thus changing the differentiation states of CD8+ T cells. Thus, it would be apparent to assume that this structural organization is also influenced by other signals such as signals from the PI3K/AKT signal transduction pathway. In particular, researchers have shown that molecules within this pathway can influence and regulate cell growth and protein synthesis thus directing CD8+ differentiation. For example, mTOR stimulation results in terminal differentiation of effector T cells but lack differentiation of memory T cells. It has been suggested that mTOR regulates differentiation by regulating the concentration gradients of T-bet: Eomes since mTOR promotes T-bet expression while suppressing Eomes. Thus, increases in T-bet promotes effector T cell differentiation. Additionally, PI3K/AKT has been suggested to regulate T cell metabolism via FOXO1 by stimulating crosstalking with other signaling pathways such as Wnt/β-catenin. However, many specific roles and key players in these interactions are still unclear; but, understanding these players might lead to drug delivery system that could modulate the T cell repertoire.

Conclusion:

Concentration gradients of signaling molecules and transcriptional factors control the differentiation and functional maturation of T cells into effector or memory CD8+ T cells. Though many advances have been made in understanding these mechanisms, there are still many unanswered questions about the physiological characteristics of these cells. By uncovering how T cells are able to diversify from a naïve T cell to its heterogenous population have important implications for future vaccines, drug therapies, and the fight against cancer and autoimmune diseases.