

## CD127 and virus infection

with

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### What is currently known about CD127?

**Allan J. Zajac:** CD127 is the ligand binding  $\alpha$ -chain of the IL-7 receptor. It associates with CD132, also known as the common  $\gamma$ -chain, which is utilized by several other cytokine receptors including those for IL-2, IL-4, IL-9, IL-15, and IL-21. In addition to forming the IL-7 receptor, CD127 is also a component of the thymic stromal lympho-

poietin receptor, which does not include CD132.

T cells which express the heterodimeric CD127-CD132 receptor complex are able to perceive IL-7 derived signals which are critical for the maintenance of naïve T cells and for the survival and basal homeostasis of antigen-experienced memory T cells (reviewed in 1).

### How does the expression of CD127 change on T cells during the course of viral infections?

**Allan J. Zajac:** Naïve T cells present in the periphery are CD127<sup>hi</sup>. As they encounter their cognate antigen, and become activated, the levels of CD127 mRNA are downregulated leading to a decrease in cell surface expression. At the peak of the immune response to acute infections the majority of the pathogen-specific effector T cells are CD127<sup>lo</sup> and only a fraction CD127<sup>hi</sup> (2-5). Ideally, as a result of the mobilization of the immune response, the pathogen is cleared and the expanded pool of antigen-specific T cells is downsized. The T cells which survive this contraction phase form a pool of CD127<sup>hi</sup> memory T cells, which are maintained overtime and help to confer long-lived

protective immunity. Expression of CD127 has been described as a critical factor that distinguishes effector T cells that either succumb to apoptosis (CD127<sup>lo</sup>), or represent precursors that survive and go on to establish the memory T cell pool (CD127<sup>hi</sup>); (2-5). CD127<sup>hi</sup> T cells are able to “sense” IL-7 and have a survival advantage; they have been shown to express somewhat higher levels of the anti-apoptotic proteins Bcl-2 and Bcl-xL, as well as preferentially persist following adoptive transfer. Nevertheless, in biological systems there are few absolutes and the concept that CD127 expression exclusively marks memory T cell precursors has been questioned (6).

### After infections, what are the main differences between CD127high and CD127low T cells?

**Allan J. Zajac:** As expected CD127<sup>lo</sup> effector cells display an activated phenotype (CD27<sup>lo</sup>, CD43<sup>hi</sup>, CD44<sup>hi</sup>, CD62L<sup>lo</sup>, CCR7<sup>lo</sup>), and can kill target cells as well as produce cyto-

kines including IFN- $\gamma$ , although the production of TNF- $\alpha$  may be somewhat less vigorous. The capacity of effector T cells to proliferate is, however, depressed as these cells lack the “self-renewal”

properties of memory T cells. By contrast, CD127<sup>hi</sup> memory cells usually display a resting antigen-experienced phenotype (CD27<sup>hi</sup>, CD43<sup>lo</sup>, CD44<sup>hi</sup>, CD122<sup>hi</sup>), undergo homeostatic turnover, and have the capacity to rapidly elaborate effector functions (2-5, 7-9). CD127<sup>hi</sup> memory CD8

T cells are also more potent than CD127<sup>lo</sup> effector T cells at producing IL-2 (3,4,8,9). Although memory T cells are CD127<sup>hi</sup>, reductions in the levels of CD127 occur if secondary responses are elicited by re-exposure to the inducing antigen.

### Do CD127high memory T cells always develop?

**Allan J. Zajac:** Antigen-specific CD8 T cells which expand without CD4 T cell help tend to remain CD127<sup>lo</sup>, exhibit reduced effector functions and fail to proliferate vigorously (reviewed in 10). Persistent infections are also associated with the failure to develop and maintain functionally robust memory T cell responses. Under these conditions virus-specific CD127<sup>lo</sup> CD8 T cells are often initially detectable but the subsequent emergence of functionally robust memory CD127<sup>hi</sup> T cells is compromised. Instead, the CD127<sup>lo</sup> CD8 T cells adopt a pseudo-effector phenotype as they display a diminished capacity to elaborate effector functions,

which is most marked for IL-2 production, do not proliferate robustly in response to antigenic stimulation, but typically retain an activated (CD27<sup>lo</sup>, CD43<sup>hi</sup>, CD62L<sup>lo</sup>, CCR7<sup>lo</sup>) phenotype, especially if the antigen persists at high levels (9,11,12). The maintenance of CD127<sup>lo</sup> CD8 T cells may require TCR-derived antigen-dependent signals (12). Nevertheless, exhausted CD127<sup>lo</sup> T cells cannot receive “pro-survival” IL-7 signals and may become deleted from the host overtime, although the rate of attrition can differ depending upon the precise epitope-specificity of the responding cells and whether CD4 T cell help is present (9).

### Do you believe that it is possible to manipulate CD127low T cells to improve viral control?

**Allan J. Zajac:** As mentioned above, regulators of CD127<sup>hi</sup> memory CD8 T cell development include the longevity and magnitude of antigenic exposure as well as the provision of CD4 T cell help. In persistently infected hosts, lowering viral loads, within a sufficient timeframe, may facilitate the emergence of more functionally competent CD127<sup>hi</sup> CD8 T cells. There are good indications from both studies of LCMV infected mice and from

HIV-1 infected humans that this can occur if the conditions are optimal (9,13,14). Also, prosurvival cytokines including IL-2, IL-4, IL-6, and IL-15, have been shown to negatively regulate the expression of CD127 (15). So one strategy may be to manipulate the cytokine milieu during persistent infections; however, it is important to be cautious here as more potent responses could result in exacerbated immunopathology.

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