

CD4 T cell protection against influenza

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Our studies over the last decade have indicated that the progression from CD4 effector to memory T cell is achieved by a default mechanism independent of and induced by the absence of antigen and inflammation. The phenotypic and functional profiles of effector cells are largely retained as they progress to memory cells. Memory cells, like the effectors that gave rise to them, immediately release cytokines and chemokines upon restimulation despite their resting stage and they quickly become “memory effectors” with the ability to migrate to non-lymphoid sites and carry out effector functions. Thus we have transferred homogeneous, in vitro generated, flu-specific CD4 effectors derived from a TcR Tg mouse, to intact recipient mice to explore the possibility that primed CD4 T cells may effectively mediate protection to otherwise lethal influenza (flu) infections in mice. Since T cell responses to flu can be induced against internal proteins of the virus, T cell priming may provide protection from emerging new flu strains that could lead to pandemics.

We found that Th1 effectors, introduced at day 0, were able to reverse weight loss and death in mice challenged with a lethal dose of flu. This protection was also achieved in T cell-deficient nude mice, indicating that host T cells were not needed for the protection. The protection in this model was not dependent on the induction of IFN γ by the donor T cells. The primed CD4 T cells exhibited perforin-dependent cytotoxicity and perforin-deficient Th1 cells were less protective. The protection was also dependent on host B cells, but could be restored in B cell deficient mice by introduction of a small quantity of immune serum at day 6. The kinetics of weight loss and survival in the different situations, suggested that the primed CD4 T cells initially reduced viral replication, and that they induced a larger, more rapid, Ab response that acted to mediate the final protection. This indicates that CD4 T cells can use multiple mechanisms to counter flu infection and suggests that vaccines inducing T cell priming against conserved flu epitopes could provide a measure heterotypic protection against new flu strains. They also suggest that passive Ab, administered post infection, might augment the cellular immunity to give more impressive protection.

Extensions of these studies indicate in vivo generated effectors also can provide protection using similar mechanisms to the in vivo generated populations. Memory CD4 T cells specific for influenza can also provide protection but in this case the dynamics of response are markedly different.

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