



Early interferon therapy for hepatitis C virus infection rescues polyfunctional, long-lived CD8⁺ memory T cells.

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Abstract:

The majority of acute hepatitis C virus (HCV) infections progress to chronicity and progressive liver damage. Alpha interferon (IFN-alpha) antiviral therapy achieves the highest rate of success when IFN-alpha is administered early during the acute phase, but the underlying mechanisms are unknown. We used a panel of major histocompatibility complex class I tetramers to monitor the phenotypic and functional signatures of HCV-specific T cells during acute HCV infection with different infection outcomes and during early IFN therapy. We demonstrate that spontaneous resolution correlates with the early development of polyfunctional (IFN-gamma- and IL-2-producing and CD107a(+)) virus-specific CD8(+) T cells. These polyfunctional T cells are distinguished by the expression of CD127 and Bcl-2 and represent a transitional memory T-cell subset that exhibits the phenotypic and functional signatures of both central and effector memory T cells. In contrast, HCV-specific CD8(+) T cells in acute infections evolving to chronicity expressed low levels of CD127 and Bcl-2, exhibited diminished proliferation and cytokine production, and eventually disappeared from the periphery. Early therapeutic intervention with pegylated IFN-alpha rescued polyfunctional memory T cells expressing high levels of CD127 and Bcl-2. These cells were detectable for up to 1 year following discontinuation of therapy. Our results suggest that the polyfunctionality of HCV-specific T cells can be predictive of the outcome of acute HCV infection and that early therapeutic intervention can reconstitute the pool of long-lived polyfunctional memory T cells.

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