Interplay amongst chronic immune activation, apoptosis, cross-presentation, immune-regulation, and autoimmunity

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In previous studies, we found that the proteome of apoptotic T cells includes prominent caspase-cleaved cellular proteins and that a high proportion of distinct epitopes in these fragments (apoptotic epitopes) can be cross-presented by DCs to autoreactive CD8+ T cells (Moroni-Rawson et al., Nat Med 2007). In chronic HIV infection, these autoreactive CD8+ T cells correlate with the proportion of apoptotic CD4+ T cells in vivo and are involved in establishing polyclonal T cell activation that in the long run results in generalized T cell dysfunction/depletion. In addition, our previous report showed that apoptotic cells derived from activated T cells (in contrast to those derived from resting T cells or from non-lymphoid cells) retain the expression of CD40 ligand (L) and can then condition CD40+ DCs to acquire high capacities to prime or cross-prime autoreactive T cells (Propato et al., Nat Med 2001). This mechanism is consistent with the evidence that the signals provided by CD40L+ apoptotic cells and not those provided by conventional apoptotic cells facilitate the emergence of autoreactive T cell responses to apoptotic self-antigens.

Here we used the hepatitis C virus (HCV) infection as a human model of acute infection that generally undergoes chronic progression to verify whether CD8+ T cells that are specific for apoptotic self-epitopes have a distinct effector type-1, -2, or -17 phenotype, to distinguish which of them may participate in determining the fate of a viral infection (recovery versus chronicity), and to ascertain the mechanisms whereby these responses are induced and maintained. We demonstrated for the first time that the emergence of mixed polyfunctional (type-1, -2, -17) CD8+ T EM cell responses to apoptotic self-epitopes is related to the chronic evolution of acute HCV infection. The responses were directly correlated with the plasma viral load or the serum ALT levels, and were then sustained over time in relation to the viral persistence. These results suggest that, in conditions in which HCV has been able to evade the virus-specific immunity, strong CD8+ T cell responses against apoptotic self-epitopes are maintained and may contribute to the liver immunopathology through the production of high levels of inflammatory cytokines. This hypothesis is further emphasized by our parallel study indicating that similar autoreactive CD8+ T cell responses in chronically infected patients are recruited in the inflamed livers, are related with the signs of hepatic damage, and decrease in relation with the decline or the disappearance of the viral load upon antiviral therapy (interferon plus ribavirin®).

We also demonstrated that cross-presentation of apoptotic T cells by DCs promptly activates CD8+ T EM cells specific for caspase-cleaved apoptotic self-epitopes ex vivo indicating that this mechanism might be operative in the induction of the resulting
polyfunctional autoreactive responses in patients with acute HCV infection who are experiencing chronic progression. The strong production of IFN-γ and IL-17 may favor the triggering of recruitment of inflammatory cells to the liver, which contribute to liver pathology.

An important facet of our findings is that they demonstrate a link between the TCR avidity of autoreactive CD8+ T cells and the difference in the responsiveness of apoptotic epitope-specific CD8+ T cells exhibited by patients experiencing chronic infection and those undergoing infection resolution. Our results suggest that autoreactive CD8+ T cells with higher avidity for apoptotic self-epitopes are sustained over time and correlate with the progression toward chronic infection. The selection of the autoreactive CD8+ T cells with higher avidity likely occurs because of a sustained stimulation by apoptotic antigens. By contrast, lower avidity CD8+ T cells in the presence of weaker stimuli would undergo rapid contraction, as seen in the peripheral blood of patients with self-limited HCV infection.

Publications


Research Group

Daniele Accapezzato, Silvia Piconese, researcher; Alessandra Citro, Helen Martini, Valeria Schinzari, post-doc fellows; Carmela Martire, Alessandra Proia, Eleonora Timperi, PhD students.