

Coregulation of CD8⁺ T cell exhaustion during chronic viral infection by multiple inhibitory receptors

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T cell exhaustion often occurs during chronic infections and prevents optimal viral control. The molecular pathways involved in T cell exhaustion, however, remain poorly understood. We demonstrate that exhausted CD8⁺ T cells are subject to complex layers of negative regulation due to co-expression of multiple inhibitory receptors. Exhausted CD8⁺ T cells expressed up to 7 inhibitory receptors. Co-expression of multiple distinct inhibitory receptors correlated with greater T cell exhaustion and more severe infection. Regulation of T cell exhaustion by diverse inhibitory pathways was non-redundant since blockade of PD-1 and LAG-3 simultaneously *in vivo* synergistically improved T cell responses and reduced viral load. Thus, CD8⁺ T cell responses during chronic viral infections are regulated by complex patterns of co-expressed inhibitory receptors.