Memory T cells: a matter of life and death

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Abstract

Central memory T cells constitute the major correlate of protection in chronic viral diseases including HIV infection. They are essential for the development of protective immune responses in vaccines to viruses. Central memory T cells are endowed with a capacity to persist for up to twenty to thirty years in vivo in an infected or vaccinated individual. The mechanisms that lead to this persistence remain unknown. We have used multiparametric flow cytometry including Phosflow analysis to identify signal transduction pathways involved in central memory T-cell persistence and to validate gene array data. The latter had identified the FOXO3A transcription factor as a critical integrator of survival pathways leading to TCM persistence. FOXO3A is a member of the forkhead box protein family of genes which are essential in regulating survival and differentiation processes. FOXO3A regulates the transcription of several proapoptotic genes such as Bim, Puma and Fas-L and anti-proliferative genes such as Gadd 45 and p130. Upon dephosphorylation of FOXO3A this factor translocates to the nucleus and initiates the transcription of these genes leading to cell cycle arrest and apoptosis. Our results clearly demonstrate that the inhibition of phosphorylation of FOXO3A using several inhibitors leads specifically to TCM cell death. We further show that patients who naturally control HIV infection (Elite Controllers) have significantly higher levels of phosphorylated FOXO3A while HAART treated aviremic patients show mostly non phosphorylated, transcriptionally active FOXO3A; inhibition of FOXO3A using specific siRNAs or dominant negative mutants rescues the cell death of Cell sorted homogenous population of Central memory T cells from ECs allows them to persist in culture for up to 45 days. Our data clearly demonstrate the importance of FOXO3A in long term survival of central memory T cells and have allowed us to correct a major defect which occurs during HIV infection.