Menin-Bach2 pathway controls senescence-associated secretory phenotype (SASP) in CD4 T cells

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Abstract

Although the senescence-associated secretory phenotype (SASP) is thought to induce low-level chronic inflammation status, and be associated with the onset of inflammatory disorders, the molecular mechanisms of the SASP remain unclear. Menin is a tumor suppressor encoded by the *MEN1* gene that is mutated in patients with multiple endocrine neoplasia type 1. We assessed the role of Menin in T cell functions and found that Menin controls senescence of CD4 T cells. *Menin*-deficient (Men KO) effector CD4 T (Th) cells normally proliferated after antigenic stimulation during the initial activation phase. However, Men KO Th cells showed a markedly reduced proliferation rate in comparison to the control wild-type (WT) Th cells from day 5 after the initial antigenic stimulation, even in the presence of exogenous IL-2. Menin KO Th cells also showed a senescence-like phenotype more rapidly than WT Th cells, based on the expression of senescence-associated β-galactosidase activity and cell cycle regulators. Therefore, Menin KO CD4 T cells underwent premature senescence after antigenic stimulation.

In addition, Menin KO Th cells expressed large amounts of pro-inflammatory cytokines, chemokines, enzymes, and angiogenic factors including *Il6*, *Opn*, *Ccl3*, *Ccl4*, *Ccl5*, *Cxcl2*, *Gzms*, *S100a4*, *Pdgfα*, and *Vegfc*. A prolonged activation of RelA/p65 was also detected in Menin KO Th cells. These findings suggest that Menin KO Th cells exhibited a SASP. A DNA microarray analysis was performed to identify the gene(s) that contribute to a SASP observed in Men KO Th cells. The decreased expression of Bach2, a member of the CNC transcription factor family, was detected in Men KO Th cells. The SASP in Men KO Th cells was restored by retrovirus vector-mediated transduction of *Bach2*. Furthermore, the binding of Menin at the *Bach2* gene locus was detected by a ChIP-sequencing analysis, and the level of binding was reduced in senescent Th cells. These results indicate that the Menin-Bach2 pathway plays an important role in the inhibition of SASP in CD4 T cells.