Spermidine rescues ER stress-mediated dysfunction in tumor-infiltrating CD8+ T cells by promoting BiP chaperone activity in aged mice

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Abstract

T cells become dysfunctional with aging partly because of loss of proteostasis. However, the underlying mechanisms and its impact on anti-tumor immunity remain largely unidentified. In this study, we investigated the effect of the unfolded protein response of endoplasmic reticulum (UPR^{ER}), which is involved in the maintenance and quality control of proteostasis, on the function of tumor-infiltrating lymphocytes (TILs) in aged mice. The expression of spliced X-box binding protein 1 (XBP1s), a classic marker of UPR^{ER}, was upregulated in dysfunctional aged $CD8^+$ TILs, suggesting high ER stress in these T cells. Comprehensive metabolite analysis by mass spectrometry revealed spermidine (SPD) levels were decreased in aged tumor-bearing mice. SPD supplementation could reduce Xbp1s expression and restore the dysfunctional status of aged $CD8^+$ TILs. We then found that binding immunoglobulin protein (BiP), a key chaperone responsible for protein folding in the ER, could be a direct binding protein of SPD and that less SPD bound to BiP in aged $CD8^+$ TILs. Mechanistically, SPD could directly enhance the folding activity, substrate binding affinity and anti-aggregation capacity of BiP. When combined with SPD, PD-1 blockade therapy showed improved efficacy in aged tumor-bearing mice. These findings illustrate that spermidine could increase the activity of $CD8^+$ TILs by promoting BiP function in aged mice and may provide a new strategy for the treatment of aged cancer patients.