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ICAM-1 on cDC1 promotes the survival ofstem-like memory CD8 T cells generated in tumor draining lymph nodes

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Abstract

Dendritic cells (DCs) cross-present tumor antigens to cognate T cells in tumor-draining lymph nodes (TdLNs). ICAM-1 is a key adhesion molecule involved in the formation of diverse cell-cell contacts between immune cells as well as blood vessels and stromal cells. We have recently found that ICAM-1 expressed by lymph node DCs can stabilize antigen-dependent contacts with naïve CD8 T cells but is dispensable for CD8 T cell differentiation and proliferation into effector and memory lymphocytes generated in various models of vaccination and virus infections. To follow the role of DC ICAM-1 in CD8 proliferation and differentiation triggered by tumor expressed neoantigens, we orthotopically implanted breast cancer E0771 cells expressing the model OVA neoantigen in immunocompetent mice conditionally deleted of ICAM-1 expression in all CD11c expressing -conventional DCs (cDCs), monocyte derived DCs (mDCs) and pDCs. Strikingly, in contrast to viral challenges, the tumor challenge drove naïve tumor-antigen specific CD8 differentiation almost exclusively into T-stem-like central memory T cells (T_{SL}) with high expression of L-selectin (CD62L), PD-1, and the transcription factor TCF-1 implicated in T cell stemness and proliferative potential. Early CD8 activation and differentiation into these central memory T cells remained normal in these mice. This indicated that tumor antigen transfer by migratory DCs to lymph node DCs and its initial cross presentation to naïve T cells do not require ICAM-1 expression by all types of DCs. Furthermore, deletion of ICAM-1 selectively in XCR1 conventional type 1 dendritic cells (cDC1), specialized in tumor antigen uptake and cross priming of tumor specific T cells in tumor draining lymph nodes, did not impair early tumor specific CD8 activation and differentiation. Nevertheless, the maintenance of resident self-renewing stem-like tumor specific CD8 memory cells in the tumor draining lymph nodes was diminished in the absence of ICAM-1 expression by cDC1. We currently explore the possibility that ICAM-1 deficiency in these DCs impairs the stability of survival niches generated by Ag-specific CD8 T_{SL} and cDC1. Our results highlight a specialized instructive role of cDC1 ICAM-1 in antigen dependent maintenance of a pool of lymph node stem-like tumor-specific lymphocytes. This pool is a main source of tumor specific CD8 T cells which egress the draining lymph nodes and home into primary tumors, where they differentiate into short-lived terminally differentiated effector T cells (CTLs) critical for tumor eradication.
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