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COLLOQUIUM

LFA-1 Signals for Leukocyte Differentiation & Effector Functions: Facts & Puzzles

Speaker:

Ronen Alon, Ph.D., Department of Immunology and Regenerative Biology, Weizmann Institute of Science, Rehovot, Israel.

Time:

Wednesday, August 24, 2022, 4:30 pm

Venue:

ISAS Campus, Lecture Hall
Otto-Hahn-Straße 6b
44227 Dortmund

&

Webex: https://bit.ly/3PeiQjm
Meeting-ID: 2733 895 6850
Password: 3srF6W4GTMm

Abstract

Intercellular adhesion molecule 1 (ICAM-1) is a ubiquitously expressed Ig superfamily high-affinity ligand of the lymphocyte integrin LFA-1. Lymphocyte priming in lymph nodes (LNs) depends on the formation of functional TCR specific immune synapses (ISs) with antigen (Ag) presenting dendritic cells. The importance of LFA-1-ICAM-1 interactions for the formation of functional ISs has been demonstrated in many *in vitro* experimental settings, but rarely corroborated *in vivo*. The in vivo roles of DC ICAM-1 in Ag stimulated T cell differentiation have been unclear. In newly generated DC conditional ICAM-1 knockout mice, we report that under strong Th1 polarizing conditions, ICAM-1 deficient DCs could not engage in stable conjugates with CD8 T blasts. In vitro, ICAM-1 deficient DCs triggered poor CD8 T cell proliferation and differentiation.

Nevertheless, in vivo, ICAM-1 deficient DCs triggered normal CD8 lymphocyte priming, proliferation and differentiation into functional cytotoxic T cells (CTLs) in the draining lymph nodes of both vaccinated and MVA virus infected skin. Single cell RNAseq analysis confirmed that naïve and Tcm normally expanded in these mice and gave rise to normal T effectors during a recall skin response. DC-ICAM-1 was also dispensable for CD4 and CD8 activation and differentiation in mediastinal lymph nodes of mice infected with influenza. Breast tumors also express ICAM-1 and elevated ICAM-1 expression results in a favorable outcome and prolonged survival of breast cancer patients. Addressing the role of ICAM-1 in the C57BL/6 derived luminal B breast cancer cell line E0771, we found that ICAM-1 is dispensable for breast tumor growth and Ag directed killing by cytotoxic T cells. Furthermore, elimination of endogenous Tregs led to rapid killing of primary breast tumors independently of tumor ICAM-1 expression.

Interestingly, whole lung imaging of these cells by light sheet microscopy revealed that ICAM-1 deficient breast cancer cells developed much larger metastatic lesions than their control counterparts. Strikingly, the majority of these cells grew inside pulmonary vessels both in spontaneous and experimental metastasis models. In the latter model, ICAM-1 expressing E0771 but not their ICAM-1 deficient counterparts were highly susceptible to elimination by tumor-entrained neutrophils. These results are a first indication that ICAM-1 expressed by metastatic breast cancer cells is involved in innate rather than in adaptive cancer cell killing. Collectively, our DC and tumor results suggest the role of ICAM-1 on distinct APCs and its major integrin receptor LFA-1 on different adaptive and innate leukocytes are far more restricted and specialized than previously anticipated.

Future studies on additional vaccination and infection models and other types of T cell differentiation processes should reveal the outcomes of ICAM-1-mediated strengthening of T-DC synapses on T cell differentiation and exhaustion. Such insights should help in the future design of genetically modified DCs for improved vaccines.