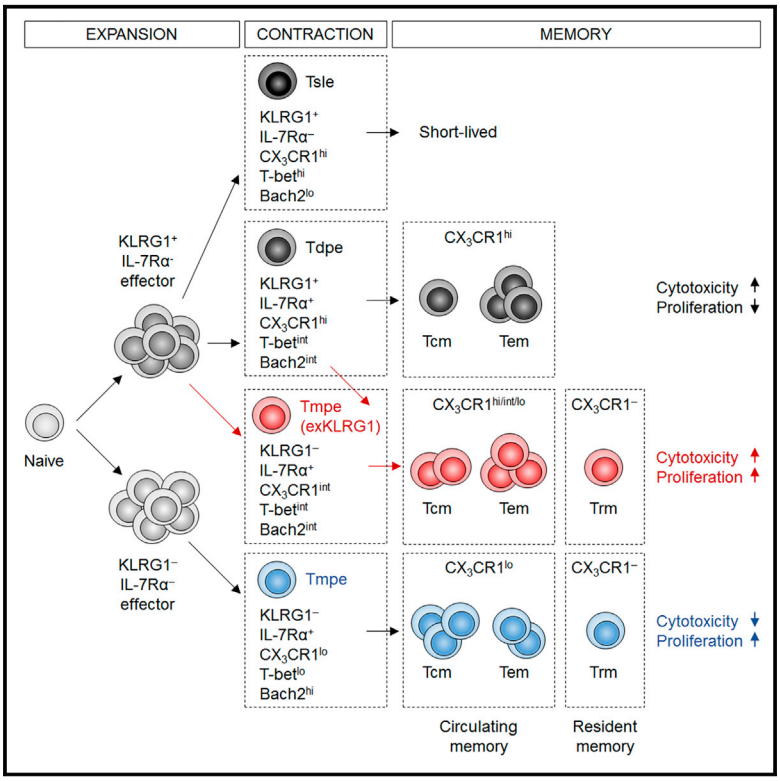
Article

Immunity

KLRG1$^+$ Effector CD8$^+$ T Cells Lose KLRG1, Differentiate into All Memory T Cell Lineages, and Convey Enhanced Protective Immunity

Graphical Abstract



Highlights

- KLRG1$^+$IL-7Rα$^+$ effector cells lose KLRG1 and differentiate into exKLRG1 memory cells
- ExKLRG1 memory cells comprise CX$_3$CR1$^+$ circulating and CX$_3$CR1$^-$ tissue-resident cells
- ExKLRG1 memory cells mount highly effective anti-viral and anti-tumor responses
- *Bach2* promotes exKLRG1 memory CD8$^+$ T cell development

Authors

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In Brief

Herndler-Brandstetter et al. demonstrate that KLRG1$^+$IL-7Rα$^+$ effector CD8$^+$ T cells downregulate KLRG1 in a *Bach2*-dependent manner and differentiate into long-lived circulating and tissue-resident "exKLRG1" memory cells. Developmental plasticity of KLRG1$^+$ effector cells therefore drives functional diversity within memory T cell lineages and promotes enhanced anti-influenza and anti-tumor immunity.

Herndler-Brandstetter et al., 2018, Immunity *48*, 1–14
April 17, 2018
https://doi.org/10.1016/j.immuni.2018.03.015

CellPress

Please cite this article in press as: Herndler-Brandstetter et al., KLRG1+ Effector CD8+ T Cells Lose KLRG1, Differentiate into All Memory T Cell Lineages, and Convey Enhanced Protective Immunity, Immunity (2018), https://doi.org/10.1016/j.immuni.2018.03.015

KLRG1$^+$ Effector CD8$^+$ T Cells Lose KLRG1, Differentiate into All Memory T Cell Lineages, and Convey Enhanced Protective Immunity

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https://doi.org/10.1016/j.immuni.2018.03.015

SUMMARY

Protective immunity against pathogens depends on the efficient generation of functionally diverse effector and memory T lymphocytes. However, whether plasticity during effector-to-memory CD8$^+$ T cell differentiation affects memory lineage specification and functional versatility remains unclear. Using genetic fate mapping analysis of highly cytotoxic KLRG1$^+$ effector CD8$^+$ T cells, we demonstrated that KLRG1$^+$ cells receiving intermediate amounts of activating and inflammatory signals downregulated KLRG1 during the contraction phase in a *Bach2*-dependent manner and differentiated into all memory T cell linages, including CX_3CR1^{int} peripheral memory cells and tissue-resident memory cells. "ExKLRG1" memory cells retained high cytotoxic and proliferative capacity distinct from other populations, which contributed to effective anti-influenza and anti-tumor immunity. Our work demonstrates that developmental plasticity of KLRG1$^+$ effector CD8$^+$ T cells is important in promoting functionally versatile memory cells and long-term protective immunity.

INTRODUCTION

CD8$^+$ T cells are important in host protection from infectious and malignant diseases, and memory CD8$^+$ T cell heterogeneity is a core feature of protective immune responses. Following a primary infection, naive CD8$^+$ T cells are activated by antigen-presenting cells, clonally expand, and differentiate into short-lived effector and long-lived memory cell subsets (Jameson and Masopust, 2009; Mueller et al., 2013; Williams and Bevan, 2007). Two subsets of circulating memory CD8$^+$ T cells with distinct migratory and effector properties have been described: central-memory T (Tcm) and effector-memory T (Tem) cells. Tcm cells express the lymph node (LN) homing receptors CCR7 and CD62L and have a high proliferative capacity but exhibit low cytotoxicity. In contrast, Tem cells lack CCR7 and CD62L, home to non-lymphoid tissues, and have a lower proliferative capacity but display high cytotoxicity. In addition, tissue-resident memory T (Trm) cells constitute a recently identified memory cell lineage that does not recirculate but resides in barrier and non-barrier tissues (Mueller et al., 2013; Steinert et al., 2015). Trm cells are phenotypically distinct from recirculating Tcm and Tem cells and represent the first line of defense upon reinfection at barrier sites, such as the skin and mucosal surfaces. However, considerable heterogeneity within each memory cell lineage has been reported (Kaech and Wherry, 2007; Mackay and Kallies, 2017). For example, a recently identified peripheral memory T (Tpm) cell population, which expresses intermediate levels of CX_3CR1, shares features of both Tcm and Tem cells and is chiefly responsible for the global surveillance of non-lymphoid tissues (Gerlach et al., 2016). So far, it remains unclear whether such heterogeneity originates from different effector cell precursors or differential states of activation.

Killer cell lectin-like receptor subfamily G, member 1 (KLRG1) is induced in highly cytotoxic and proliferative effector CD8$^+$