How bone marrow regenerates after chemotherapy

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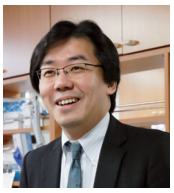

Abstract

Chemotherapy has a damaging effect on hematopoietic stem and progenitor cells (HSPCs) in bone marrow. However, once chemotherapy ends, HSPCs regenerate, a process that has remained unknown. In this study, we show that BM-resident group 2 innate lymphoid cells (ILC2s) support the recovery of HSPCs from chemotherapy-induced stress by secreting granulocyte-macrophage colony-stimulating factor (GM-CSF). Mechanistically, IL-33 released from chemo-sensitive B cell progenitors activates MyD88-mediated secretion of GM-CSF in ILC2. GM-CSF knockout mice showed severe loss of myeloid lineage cells following chemotherapy, causing lethality, which was rescued by transferring BM ILC2s from wild-type mice. Further, the adoptive transfer of ILC2s accelerates hematopoietic recovery. ILC2s may function by "sensing" the damaged BM spaces and subsequently support hematopoietic recovery under stress conditions. Thus, we clarify the essential mechanism of hematopoietic recovery after bone marrow injury.

Background & Results

The cell-cycle status of hematopoietic stem and progenitor cells (HSPCs) becomes activated following chemotherapy-induced stress, promoting bone marrow (BM) regeneration; however, the underlying molecular mechanism remains elusive. Our goal is to elucidate the key signals transmitted from stressed BM environments. To achieve this, we conducted a comprehensive RNA-seq analysis of transplanted HSPCs that had homed into recipient BM treated with or without an anti-cancer drug 5-fluorouracil (5-FU). Upstream analysis revealed that signals from colony-stimulating factor 2 (GM-CSF) were activated in HSPCs transplanted into 5-FU-treated mice. GM-CSF-deficient mice treated with 5-FU showed severe loss of myeloid lineage cells, suggested that GM-CSF is crucial for BM recovery. Single cell RNA-seq analysis of BM cells from 5-FU-treated mice revealed that group 2 innate lymphoid cells (ILC2s) expressed high level of GM-CSF. Nevertheless, the expression level was dramatically suppressed in BM ILC2s obtained from 5-FU-treated MyD88- or IL-33-deficient mice compared to those from wild-type mice. These results suggested that IL-33 activates MyD88-mediated secretion of GM-CSF in ILC2. Further, the adoptive transfer of ILC2s to 5-FU-treated mice accelerated hematopoietic recovery. These results indicated that BM-resident ILC2s support the recovery of HSPCs from 5-FU-induced stress by secreting GM-CSF.

Significance of the research and Future perspective

In this study, we address a fundamental question regarding the trigger of hematopoietic recovery at an early time point in bone marrow injury. Our findings show that the adoptive transfer of ILC2s resulted in faster recovery during the process of myeloid differentiation, meaning that it might have therapeutic potential in myelosuppressive conditions. An improved understanding of how GM-CSF and other growth factors modulate the balance between self-renewal and differentiation of HSPCs in stressed microenvironment will provide clues for better adjunct therapy aimed at early hematopoietic recovery and for the development of ex vivo expansion of hematopoietic stem cells.

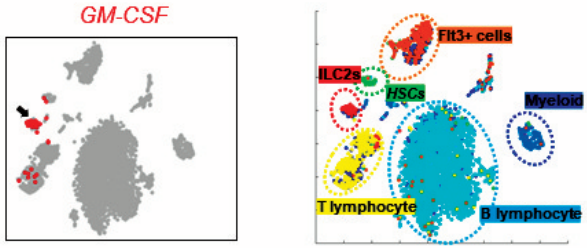

Figure1
Single-cell RNA-seq analysis of bone marrow showing that GM-CSF-positive cluster is composed of ILC2s.

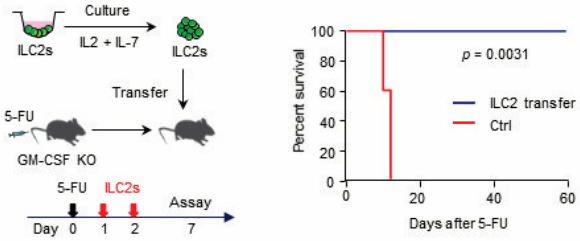

Figure2
Adoptive transfer of ILC2s resulted in the improved survival of GM-CSF-KO mice after treatment with 5-FU.

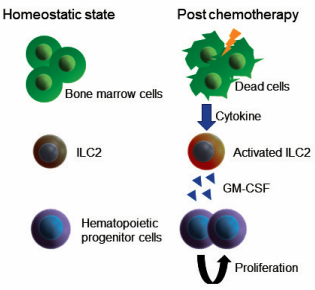

Figure3
After chemotherapy, bone marrow-resident ILC2s receive cytokine signals from dying cells and support hematopoietic recovery through secretion of GM-CSF.

Patent
Treatise Sudo, T; Ishii, M et al. Group 2 innate lymphoid cells support hematopoietic recovery under stress conditions. J Exp Med. 2021; 218(5): e20200817. doi: 10.1084/jem.20200817.
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Keyword GM-CSF, group 2 innate lymphoid cell, in vivo imaging