Niche cells essential for hematopoietic stem cell maintenance and hematopoiesis and adipo-osteogenesis in bone marrow

Graduate School of Frontier Biosciences/Graduate School of Medicine/Immunology Frontier Research Center

Distinguished Professor Takashi Nagasawa Researchmap https://researchmap.jp/read0094728?lang=en

Associated Professor Yoshiki Omatsu Researchmap https://researchmap.jp/yskomt?lang=en

Abstract

Special microenvironments known as niches are essential for the maintenance of hematopoietic stem cells (HSCs) and lympho-hematopoiesis within bone marrow. We found that CAR cells are the major producer of CXCL12 and SCF and the major cellular components of niches for HSCs and immune cells, that CAR cells are mesenchymal stem cells, which give rise to adipocytes and osteoblasts, and that the transcription factors, Foxc1 and Ebf3 are preferentially expressed in CAR cells and play a critical role in the formation and maintenance of niches for HSCs and immune cells, inhibiting differentiation of CAR cells into adipocytes and osteoblasts, respectively. Furthermore, we found that CAR cells require the transcription factors Runx1 or Runx2 to prevent their fibrotic conversion and maintain HSCs and hematopoiesis in adults. Recently, we identified the human counterpart of CAR cells, enabling the evaluation of their alterations in various hematological disorders by flow cytometric and histological analyses.

Background & Results

Special microenvironments known as niches are essential for the maintenance of hematopoietic stem cells (HSCs), which give rise to all blood cells, within bone marrow. We identified a population of fibroblastic reticular cells expressing CXCL12 at high levels, termed CXCL12-abundant reticular (CAR) cells within murine bone marrow and found that CAR cells are the major producer of CXCL12 and SCF, and the major cellular components of niches for HSCs and immune cells. In addition, we determined the nature of CAR cells, showing that CAR cells are mesenchymal stem cells, which give rise to adipocytes and osteoblasts and that transcription factors, Foxc1 and Ebf3 are preferentially expressed in CAR cells and play a critical role in the formation and maintenance of niches for HSCs and immune cells, inhibiting differentiation of CAR cells into adipocytes and osteoblasts, respectively. Recently, we found that CAR cells require the transcription factors Runx1 or Runx2 to prevent their fibrotic conversion and maintain HSCs and hematopoiesis in adults. Here, we showed the presence of cells expressing much higher CXCL12 than other cells in human adult bone marrow. CXCL12^{hi} cells express the receptor of leptin (LepR) and most CXCL12^{hi} cells or LepR^{+} cells expressed high levels of SCF, FOXC1, and EBF3 and contained cells, which had the potential to differentiate into adipocytes and osteoblasts. Histologically, the nuclei of CXCL12^{hi} cells were identified and quantified by EBF3 expression in fixed marrow sections. CXCL12^{hi} cells sorted from residual bone marrow aspirates of chronic myeloid leukemia patients expressed reduced levels of CXCL12, SCF, FOXC1, and EBF3 in correlation with increased leukemic burden. Together, the human counterpart of CAR cells are major components of non-hematopoietic and **non**-endothelial cells in the bone marrow in humans.

Significance of the research and Future perspective

We identified the human counterpart of CAR cells, enabling the evaluation of their alterations in various hematological disorders by flow cytometric and histological analyses. For clinical application, our results raise the possibility that activators and/or inhibitors of CAR cell functions might be applied to novel non-cell-autonomous therapies targeting the niches for HSCs and immune cells in hematological disorders and infection.

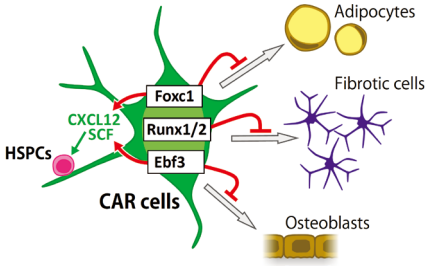

Figure 1. CAR cells are the major cellular component of HSC niches.
Foxc1 and Ebf3 are preferentially expressed in CAR cells and play a critical role in the formation and maintenance of niches for HSCs, inhibiting differentiation of CAR cells into adipocytes and osteoblasts, respectively. CAR cells require the transcription factors Runx1 or Runx2 to prevent their fibrotic conversion and maintain HSCs and hematopoiesis in adults.

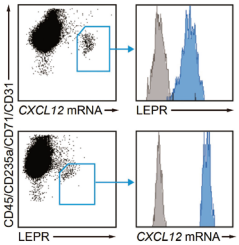

Figure 2. CAR cells are present in human bone marrow.
The human counterpart of CAR cells express LepR and are major components of non-hematopoietic and non-endothelial cells in the bone marrow in humans.

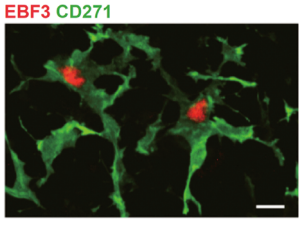

Figure 3. Human CAR cells can be observed in fixed marrow sections.
Histologically, the nuclei of CXCL12hi cells were identified and quantified by EBF3 expression in fixed marrow sections. CAR cells expressing CD271 (green) and EBF3 (red) have long processes.

Patent

Treatise

Omatsu, Yoshiki; Aiba, Shota; Nagasawa, Takashi et al. Runx1 and Runx2 inhibit fibrotic conversion of cellular niches for hematopoietic stem cells. Nat Commun. 2022;13(1), 2654. doi: 10.1038/s41467-022-30266-y
Aoki, Kazunari, Kurashige, Masako; Nagasawa, Takashi et al. Identification of CXCL12-abundant reticular cells in human adult bone marrow. Br. J. Haematol. 2021 May;193(3), 659-668. doi: 10.1111/bjh.17396
Seike, Masanari; Omatsu, Yoshiki; Nagasawa, Takashi et al. Stem cell niche-specific Ebf3 maintains the bone marrow cavity. Genes Dev. 2018, 32(5-6), 359-372. doi: 10.1101/gad.311068.117
Omatsu, Yoshiki; Seike, Masanari; Nagasawa, Takashi et al. Foxc1 is a critical regulator of haematopoietic stem/progenitor cell niche formation. Nature 2014, 508, 536-540. doi: 10.1038/nature13071
Omatsu, Yoshiki; Sugiyama, Tatsuki; Nagasawa, Takashi et al. The essential functions of adipo-osteogenic progenitors as the hematopoietic stem and progenitor cell niche. Immunity 2010, 33, 387-399. doi: 10.1016/j.immuni.2010.08.017
Sugiyama, Tatsuki; Kohara, Hiroshi; Nagasawa, Takashi et al. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity 2006, 25, 977-988. doi: 10.1016/j.immuni.2006.10.016

URL

Keyword hematopoietic stm cell, niche, bone marrow