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

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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. 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.

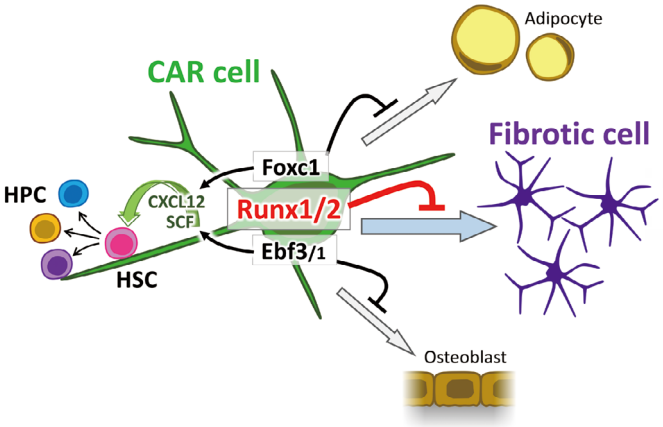
Background & Results

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.

Runx2, which is essential for generation of osteoblasts, is highly expressed in CAR cells. Recently, we showed that Runx1, which is known to be essential for the establishment of HSCs during ontogeny, is predominantly expressed in CAR cells. CAR cells are normally formed and maintained in mice lacking Runx1 or Runx2 in CAR cells. However, mice lacking both Runx1 and Runx2 in CAR cells (Ebf3-CreERT2;Runx1$^{f/f}$Runx2$^{f/f}$ mice) displayed an increase in fibrosis and bone formation with markedly reduced HSCs and hematopoietic progenitor cells in bone marrow. Consistent with this, CAR cells from the mutants displayed markedly increased expression of fibrotic genes, including Col1a1, Col3a1, and Col6a3. Thus, CAR cells require Runx1 or Runx2 to prevent their fibrotic conversion and maintain HSCs and hematopoiesis in adults.

Significance of the research and Future perspective

We found that CAR cells are the bone marrow specific fibroblastic reticular cells, which express specific and critical transcription factors, including Foxc1, Ebf 1/3, and Runx1/2, providing HSC niches and bone. 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.



Patent

Treatise

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URL

Keyword hematopoietic stm cell, niche, bone marrow