Higher miR-126 levels are associated with human and mouse CML LSCs with self-renewal of chronic myelogenous leukemia.

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Introduction

Chronic Myelogenous Leukemia (CML) stem cells (LSCs) are responsible for initiating and maintaining clonal haematopoiesis. These cells persist in the Bone Marrow (BM) despite effective inhibition of BCR-ABL kinase activity by Tyrosine Kinase Inhibitors (TKIs). Here, we show that although miR-126 supports the quiescence, self-renewal and engraftment capacity of CML LSCs, miR-126 levels are lower in CML LSCs as compared to normal Long Term Hematopoietic Stem Cells (LT-HSCs). Down regulation of miR-126 levels in CML LSCs is due to phosphorylation of SPRED1 by *BCR-ABL,* leading to inhibition of the RAN/EXP-5/RCC1 complex that mediates miRNA maturation. Endothelial Cells (ECs) in the BM supply miR-126 to CML LSCs to support quiescence and leukemia growth, as shown using CML mouse models with conditional miR-126 Knock Out (KO) in ECs and/or LSCs [1].

Description

Chronic Myelogenous Leukemia (CML) is a clonal myeloproliferative disorder characterized at the cytogenetic level by the translocation of chromosomes 9q34 and 22q11. This translocation creates a fusion gene, *BCR-ABL*, which encodes a constitutively activated tyrosine kinase responsible for transforming normal Hematopoietic Stem Cells (HSCs) into Leukemia Stem Cells (LSCs). LSCs are characterized by growth factor independent proliferation and enhanced survival, resulting in uncontrolled myeloproliferation that eventually evolves into fatal blast crisis if left untreated. CML LSCs are at the apex of malignant clonal haematopoiesis and initiate and maintain leukemia growth. In CML, LSC activity is restricted to the LT-HSC enriched Lin-CD34+CD38−CD90+ cell population in humans and the Lin-Sca-1+c-Kit+Flt3-CD150+CD48 cell population in mice. CML LSCs are thought to reside in a leukemia niche that may be anatomically and functionally different from that of normal HSCs [2].

Currently, oral Tyrosine Kinase Inhibitors (TKI) is used as the first line treatment to induce long term disease remission in CML patients. Although most patients treated with TKI monotherapy achieve major clinical and molecular responses, cells from the original *BCR-ABL* clone frequently persist, likely due to the failure of these agents to eliminate CML LSC and treatment discontinuation frequently results in disease relapse [3].

miR-126-3p (miR-126) is microRNA (miRNA) that is highly expressed in normal HSCs and Hematopoietic Progenitor Cells (HPCs) and restrains cell cycle progression during haematopoiesis. Our group and others have shown that increased miR-126 levels are associated with an increased frequency of quiescent LSCs and a worse outcome in Acute Myeloid Leukemia (AML). Here we show that miR-126 biogenesis in CML LSCs is down regulated through a BCR-ABL dependent mechanism, a finding which is seemingly inconsistent with a proleukemic role for miR-126. However, miR-126 is also highly expressed in Endothelial Cells (ECs). Anatomical and functional connections between the endothelium and normal HSCs regulate normal haematopoiesis. We hypothesized that miR-126 may mediate a functional interplay between ECs and LSCs in the leukemia BM niche that regulates CML progression. Consistent with this hypothesis, we found that ECs supply miR-126 to CML LSCs to modulate their quiescence and self-renewal [4].

miR-126 has been shown to contribute to leukemogenesis in acute leukemia. To determine miR-126 expression in CML cell subpopulations, we sorted immunophenotypically defined subsets of HPCs (Lin-CD34+(CD34+) and Lin-CD34+CD38+ (CD38+)), HSCs (Lin-CD34+CD38−(CD38-) and Lin-CD34+CD38-CD90-(CD90-)) and LT-HSCs (Lin-CD34+CD38−CD90+(CD90+)) from Peripheral Blood (PB) and BM samples of normal donors (n=12) and newly diagnosed Chronic Phase (CP) CML patients (n=12). LT-HSCs in both normal and CML samples showed the highest expression of miR-126. Similar results were obtained in Wild Type (WT) B_6 and inducible SCLtTA/BCR-ABL transgenic B_6 mice, a well-established CML mouse model 13. We isolated Lin-Sca-1-c-Kit- (L-S-K-), Lin-Sca-1-c-Kit+(L-S-K+) (including Common Myeloid Progenitors (CMP), Granulocyte Macrophage Progenitors (GMP) and Megakaryocyte Erythrocyte Progenitors (MEP)), Lin-Sca-1+c-Kit+ (LSK) and LSK Flt3-CD150+CD48- (LT-HSC) cells from the BM of WT mice and CML mice after *BCR-ABL* induction by tetracycline withdrawal. As in the human samples, mouse normal and CML LT-HSCs showed the highest expression of miR-126 [5].

Conclusion

Thus, the identification of mechanisms that support CMLLSC persistence is clinically relevant as it may enable the design of new targeting strategies aimed at complete disease elimination, allowing for discontinuation of life long TKI therapy.

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