A Novel Therapeutic Approach for Targeting CML Stem Cells

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Chronic myeloid leukemia (CML) is caused by a defined genetic abnormality that generates *BCR-ABL*, a constitutively active tyrosine kinase. Although the discovery of the tyrosine kinase inhibitor (TKI) Imatinib mesylate/Gleevec/STI-571 is a great milestone for the therapy of CML patients, it is the next challenge to eradicate a rare population of CML stem cells known to be resistant to TKI therapy.

We have previously reported that FOXO transcription factors are key regulator for the self-renewing normal hematopoietic stem cells (HSCs). Given that CML stem cells originates from HSC level, it is of great interest to determine whether FOXO would be involved in the maintenance of CML stem cells. In fact, the transplantation experiments for mouse CML stem cells indicated that the *Foxo3a*-deficient CML stem cells became exhausted in their transplanted mice after administration of Imatinib mesylate in comparison with the wild-type CML stem cells. Importantly, inhibition of TGF-β signaling that could regulate Foxo3a activity reduced the self-renewal ability of the CML stem cells *in vivo*. These results indicated that TGF-β-FOXO axis plays an essential role for the maintenance of TKI-resistant CML stem cells.

The purpose of our current research is to clarify the molecular mechanisms for regulating TKI-resistance in CML stem cells via TGF-β-FOXO signaling. The long-term outcome of our investigation will hopefully be the development of agents that can specifically suppress the TGF-β-FOXO signaling, and thereby open up a novel avenue for curative CML patient therapy.

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EDUCATIONS/TRAINING

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RECENT PUBLICATIONS

1. Naka K, Hoshii T, Muraguchi T, Tadokoro Y, Ooshio T, Kondo Y, Nakao S, Motoyama N and Hirao A. TGF- β -FOXO signalling maintains leukaemia-initiating cells in chronic myeloid leukaemia. ***Nature*** 463: 676-680, 2010.
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