A Role of TGF-β-FOXO Signaling in 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 inhibitors (TKIs) has significantly improved the prognosis of CML patients, a complete cure is not possible due to the existence of a rare population of CML stem cells known to be resistant to TKI therapy. To date, therapeutics that can eradicate CML stem cells, however, have remained under investigation.

To overcome the clinical problems, we studied the molecular mechanisms regulating maintenance of TKI-resistant CML stem cells by Forkhead O transcription factor FOXO that is a key regulator for the self-renewing normal hematopoietic stem cells (HSCs). Transplantation experiments for mouse CML stem cells indicated that the *Foxo3a*-deficient CML stem cells became exhausted in their transplanted mice after administration of a TKI, 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 signaling 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 regulating maintenance of TKI-resistant CML stem cells via TGF-β-FOXO signaling.

REFERENCE:

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EDUCATIONS AND POSITIONS

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