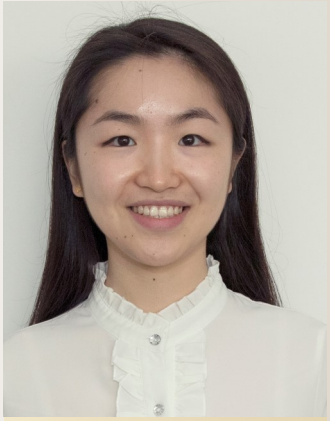
THESIS DEFENSE – PUBLIC SEMINAR

THE *BIM* DELETION POLYMORPHISM ENHANCES THE FITNESS OF CHRONIC MYELOID LEUKAEMIA STEM CELLS

YU, MENGGE
IBM PHD PROGRAM (INTAKE 2016)

ABSTRACT:

An intronic deletion polymorphism in *BIM* gene, resulting in impaired production of pro-apoptotic *BIM* isoforms, is associated with resistance to tyrosine kinase inhibitors (TKI) and higher relapse rates upon TKI cessation in patients with chronic myeloid leukaemia (CML), suggesting the *BIM* deletion could protect leukaemic stem cells (LSC) from TKIs. To study the role of the *BIM* deletion in the rare stem cell population, we created a mouse model phenocopying the effects of the human *BIM* deletion. We found that the *Bim* deletion has little effect on normal haematopoiesis. To study the effects on CML LSCs, we crossed the humanized *Bim* mouse into the *ScltTA; BCR-ABL1* CML mouse. CML faithfully developed in $hBim^{i2+/+}$, $hBim^{i2+/-}$, and $hBim^{i2-/-}$ mice after BCR-ABL1 induction, with more aggressive disease observed in $hBim^{i2-/-}$ compared to $hBim^{i2+/+}$ mice. Strikingly, when transplanted into irradiated recipients, *Bim* deletion-harboring BM cells greatly accelerated CML onset. The $hBim^{i2-/-}$ LSCs are less apoptotic and more competitive in reconstituting capacity compared to $hBim^{i2+/+}$ LSCs. In addition, the $hBim^{i2-/-}$ LSCs were significantly less apoptotic compared to $hBim^{i2+/+}$ cells with TKI treatment. Together, our data demonstrates that the effects of the *Bim* deletion reach into the LSC compartment of CML, and may serve as a useful model to identify novel strategies to enhance LSC eradication and cures in CML.



Date :
11 Oct 2021 (Monday)

Time :
8.30 - 9.30am

Thesis Advisor :
A/Prof. Ong Sin Tiong

Venue :
Amphitheatre, Level 2, Duke-NUS

This Seminar is part of the fulfillment of her PhD requirements

GRADUATE STUDIES DEPARTMENT