THESIS DEFENSE – PUBLIC SEMINAR

SRSF1-MEDIATED TYROSINE KINASE INHIBITOR RESISTANCE IN CHRONIC MYELOID LEUKAEMIA

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IBM PHD PROGRAM (INTAKE 2013)

ABSTRACT:

Tyrosine kinase inhibitors (TKIs) control but do not cure chronic myeloid leukaemia (CML), suggesting the existence of BCR-ABL1-independent factors such as cytokines that preserve CML-leukaemic stem cells (LSCs).

Using RNA-sequencing, we identified differentially expressed splicing factors in $CD34^+$ CML stem and progenitor cells compared to healthy controls. Among them, we found SRSF1 to be consistently increased at both transcript and protein levels.

Using a variety of mouse and human cells, increased SRSF1 expression was found to be a result of both BCR-ABL1- and cytokine-mediated signalling. Functionally, SRSF1 overexpression led to partial TKI-resistance and cytokine-independence in cell lines. Conversely, depleting SRSF1 impaired colony formation and cell proliferation in CML cell lines and $CD34^+$ CP CML cells. Mechanistically, we find that elevated SRSF1 levels antagonise genes involved in signal transduction, hence, implying the activation of several signal transduction pathways for survival. Additionally, we observe that the SRSF1 RS domain and non-nuclear functions are required for survival in CML.

In summary, we find SRSF1 to be upregulated in CD34+ CP CML progenitors in a BCR-ABL1- and cytokine-dependent manner, and that elevated levels promote TKI-resistance. Together, our data suggest that SRSF1 acts a downstream effector of cytokine-mediated TKI-resistance in CP CML-LSCs.



Date :
27 April 2018 (Friday)

Time :
3.00 - 4.00pm

Thesis Advisor :
A/Prof. Ong Sin Tiong

Venue :
Meeting Room 7C, Level 7, Duke-NUS

This Seminar is part of the fulfillment of her PhD requirements

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