Department of Biochemistry and Molecular Biology

2017 Seminar Series – PhD Oration

Wednesday 13th of September
12-1pm
Bio21 Institute Auditorium
30 Flemington Road, Parkville

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A biochemical and regulatory study of the tumour suppressor: Csk homologous kinase.

C-terminal Src kinase (Csk) and Csk-homologous kinase (Chk) are the major endogenous inhibitors of Src-family kinases (SFKs). They phosphorylate the C-terminal tail tyrosine (Y_T) of SFKs which stabilizes them in a closed inactive conformation. They are also able to employ a non-catalytic inhibitory mechanism to directly bind to the active forms of SFKs. My PhD project focuses on determining the contributions of these two mechanisms to inhibit SFKs by Csk and Chk *in vitro* using biochemical and biophysical approaches. Our results revealed that Csk is a more robust enzyme catalysing phosphorylation of SFKs as compared to Chk. However, Chk binds SFKs with much higher affinity as compared to Csk and efficiently inhibits them via the non-catalytic inhibitory mechanism. We mapped some determinants governing the non-catalytic inhibitory mechanism to the Chk kinase domain. Much is known about the regulation of Csk by its upstream regulators, in contrast, little is known about Chk. Chk is reported to be a potential tumour suppressor and is downregulated in colorectal cancer (CRC) possibly causing aberrant activation of SFKs. My PhD project also focused on delineating the regulation of Chk in CRC. Microarray analysis and MS-PCR indicated the epigenetic silencing of the *Chk* promoter by hyper-methylation. Reintroduction of Chk in CRC cell lines reduced anchorage independent growth and SFK activity confirming its tumour suppressor action. Moreover, we suspected involvement of Chk in signalling pathways independent of SFKs in CRC. We used Chk-GFP expressing CRC cell lines and an unbiased proteomics approach to determine binding and phosphorylation substrates of Chk. Understanding the mechanism of action of Chk and its signalling pathway may help develop targeted therapeutics for CRC.

ALL WELCOME. Please join us for Pizza to celebrate this PhD Oration!
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