CANCER SCIENCE INSTITUTE OF SINGAPORE

NUS National University of Singapore

CSI SINGAPORE



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PhD Candidate

(Supervisor: Prof Lorenz Poellinger)

CSI Graduate Programme

PH.D ORAL DEFENSE

#01-02 Learning Room

Centre for Translational Medicine
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No registration required. All are welcome.

Wed, 08 April 2015
2:30 – 3:30PM

Hypoxia mediates tumourigenesis via the H3K9 epigenetic regulators G9A and JMJD1A

Hypoxia regulated epigenetic mechanisms play essential roles in tumourigenesis and drive adaptive changes to low oxygen conditions in cancer cells. To determine how some of these mechanisms occur, we examine the opposing functions of the hypoxia-regulated H3K9 methyltransferase G9A and H3K9 demethylase JMJD1A in concerted transcriptional/epigenetic gene regulation of hypoxic solids tumours. Loss of *G9a* in mouse ES-derived teratomas led to smaller tumours with decreased angiogenesis, cell proliferation and stem cell-like populations, and increased cell death. Conversely, *Jmjd1a* KO cells produced larger tumours with an opposing phenotype, suggesting that *G9a* has oncogenic properties and *Jmjd1a* is tumour suppressive. In human breast cancer cells, a group of *de novo* derepressed genes were responsive to chronic hypoxia only with G9A inhibition. G9A inhibition was found to decrease global H3K9 methylation, a mark of transcriptional repression, suggesting a synergistic effect between hypoxia and G9A inhibition on gene expression. Functional assays indicate that G9A inhibition limits colony formation, induces cell cycle arrest and decreases cell proliferation. Finally, breast and lung cancer patients with lower G9A expression had better prognosis, indicating that the inhibition of G9A may provide a novel therapeutic approach in the treatment of cancer in the context of hypoxic solid tumours.