

Research Theme: Cancer epigenetic and novel epigenetic drug development
Research Project Title: Hypoxia-sensitive epigenetic regulators (HYSERs) as novel targets for the treatment of solid tumors
Principal Investigator/Supervisor: A/Prof Newman Siu-kwan Sze
Co-supervisor/ Collaborator(s) (if any): NA
Project Description
<p>a) Background</p> <p>Tumor progression is driven by selective pressure on cancer cells exerted by the hostile microenvironment, leading to the clonal evolution of many different cancer cell phenotypes that are increasingly difficult to kill using conventional therapies. In solid tumors, lack of oxygen (hypoxia) is a major environmental stress that drives changes in the composition of the chromatin-associated proteome (chromatome), thereby modifying the epigenome and modulating gene expression to promote clonal evolution. We therefore hypothesize that targeting hypoxia-responsive chromatin-associated proteins represents a novel and potentially powerful approach to the treatment of common solid tumors.</p> <p>By profiling the chromatome in cancer cell lines, we have identified several hypoxia-sensitive epigenetic regulators (HYSERs) that change their chromatin binding pattern during hypoxia. Using a combination of in vitro and in vivo assays we have already shown that HP1BP3 protein induces tumor cell pluripotency, enhances cancer cell survival, and causes resistant to chemo- and radio-therapy to promote tumor progression. Our recent paper reporting this findings has been highlighted in ASBMB Today (Nov 2014 issue) under the title 'A new epigenetic target for treating all cancers', indicating this protein is a promising target for developing novel cancer therapeutics.</p>
<p>b) Proposed work</p> <p>In this project, we will investigate the roles of the HYSER proteins by assessing their functions, defining their molecular mechanisms of action (via analysis of their post-translational modifications), and identifying their protein complex partners. We will then determine the effects of these HYSERs on genome-binding using ChIP-seq, assess their influence on the epigenome using DNA-methylation profiling, evaluate modulation of the cellular transcriptome using RNA-seq, and finally investigate changes in the cellular proteome using iTRAQ-LC-MS/MS. Using a systems biology approach, we will then integrate and analyze these data to uncover the molecular mechanisms that underpin hypoxia-driven cancer development. Finally, having already demonstrated a role for the hypoxia-induced regulator HP1BP3 in tumor progression, we will conduct new experiments in a HP1BP3-knockout transgenic mouse model, screen for HP1BP3 inhibitor, and determine the 3D structure of the protein to enable the future design of specific inhibitors for potential therapeutic use in cancer patients.</p>

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Please apply at the following: [http://admissions.ntu.edu.sg/graduate/R-Programs/R-](http://admissions.ntu.edu.sg/graduate/R-Programs/R-WhenYouApply/Pages/R-ApplyOnline.aspx)

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