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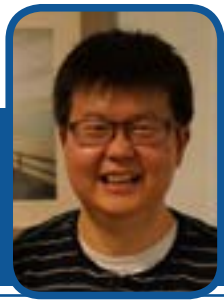

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Luminal progenitors in prostate regeneration and tumour initiation

Master regulators of tissue specification are important in the regulation of stem cell/progenitor activity and often play a key role during cancer initiation and progression. In the prostate, androgen receptor (AR) remains as a crucial master regulator for tissue development, homeostasis and tumourigenesis, but its specific functions in prostate stem/progenitor cells remain unclear. We have investigated AR function in CARNs (CAstration-Resistant Nkx3.1-expressing cells), the first luminal stem/progenitor population that has been identified in the prostate. Using genetically-engineered mouse models and novel adherent progenitor cell lines in combination with lineage-tracing approach, we discover that progenitor properties of CARNs are largely unaffected by AR deletion, apart from decreased proliferation in vivo. Furthermore, loss of AR suppresses tumour initiation after deletion of the *Pten* tumour suppressor in CARNs. In comparison, combined *Pten* deletion and activation of oncogenic *Kras* results in aggressive AR-negative tumours with focal neuroendocrine differentiation. These results suggest that oncogenic *Kras* overrides the requirement of AR for CARNs to serve as cell of origin for *Pten*-deleted prostate tumors. Taken together, our findings demonstrate that AR is not crucial for the survival and progenitor properties of CARNs. Consequently, targeting tumor-initiating luminal progenitors may serve as a novel treatment strategy for advanced prostate cancer.

Biography

Chee Wai Chua grew up in Kuala Lumpur, Malaysia and studied at the National University of Malaysia, where he received a Bachelor of Biomedical Science in 2002. In 2005, Dr. Chua started his graduate work at the Department of Anatomy, LKS Faculty of Medicine, The University of Hong Kong under the mentorship of Professor Y. C. Wong. During his graduate studies, he had become interested in prostate cancer biology, particularly on the ability of prostate tumors to preferentially metastasize to bone. Dr. Chua's studies were the first to confirm prognostic significance of the master regulator of bone formation, Runx2 in the formation of bone metastasis in prostate cancer patients. In addition, he demonstrated anticancer properties of the fungal compound FTY720 in castration-resistant prostate cancer xenografts. Dr. Chua was awarded a Ph.D. in Cancer Biology in 2009 and then joined Professor Michael Shen's group at the Columbia University Medical Center as a Postdoctoral Research Scientist and was later promoted to an Associate Research Scientist position at the Department of Urology and Medicine at Columbia University in October 2014. In the Shen Lab, Dr. Chua has pursued studies of genetically engineered mouse models of prostate cancer and prostate stem cell biology, focusing on the role of androgen receptor in prostate epithelial stem cells and organogenesis. In 2011, Dr. Chua received the Department of Defense (DOD) Prostate Cancer Research Program (PCRP) Postdoctoral Training Award to functionally analyze the role of androgen receptor in a prostate luminal progenitor population. This work was recently accepted for publication in the prestigious eLife journal. More importantly, Dr. Chua has developed a novel organoid culture method for maintaining prostate luminal progenitors as well as prostate and bladder cancers and metastases. The works were published in Nature Cell Biology and Cell, and has earned him two international patents. In the first ever 2-week organoid workshop held at the Cold Spring Harbor Laboratory, Dr. Chua was invited to serve as a Laboratory Instructor to teach trainees from all over the world on the prostate organoid methodology.

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