THE CHINESE UNIVERSITY OF HONG KONG
FACULTY OF MEDICINE
SCHOOL OF BIOMEDICAL SCIENCES

SBS PI Seminar Series 2023-2024

Prof. Wai-yee CHAN

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School of Biomedical Sciences
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will present a seminar entitled

"Developmental and metabolic impacts of the WRN mutation in Werner Syndrome"

Abstract: Werner Syndrome (WS) is an autosomal recessive disorder caused by mutations of the *WRN* gene. Classical symptoms in WS patients include short stature and metabolic dysfunction. The underlying mechanisms of these changes are not well understood. A zebrafish model lacking *wrn* exhibited impairment of bone growth and shorter body stature. With RNA-seq and ChIP-seq, the *SHOX* (short-stature homeobox) gene was shown to be a direct target of WRN in bone homeostasis. The promoter of *SHOX* is rich in guanine. WRN regulated SHOX expression through unwinding G4-quadruplexes and facilitating transcription. Consistent with this, *shox*$^{-/-}$ zebrafish exhibited impaired bone growth, while genetic overexpression of SHOX or shox rescued the bone developmental deficiency induced in *WRN/wrn* null mutants both *in vitro* and *in vivo*. Another consequence of the loss of WRN was adipocyte prematurity at an early stage. RNA-seq and ATAC-seq analyses of WRN knockout adipocytes showed that chromatin accessibility and chromatin remodeling were significantly altered with accelerated expression of late-stage adipocyte-specific markers. WRN deficiency also caused aberrant upregulation of SMARCA5. Suppression of SMARCA5 expression in WRN knockout adipocytes rescued late-stage adipocyte-associated gene expression. Furthermore, NAD+ precursor, nicotinamide riboside (NR), supplementation corrected adipocyte metabolism dysfunction in both stem cells and zebrafish models by decreasing SMARCA5 expression. Our results provided a possible treatment for metabolic dysfunction in WS.

11 July 2024, Thursday, 4:00 pm– 5:00 pm

Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building,
Area 39, The Chinese University of Hong Kong