CANCER SCIENCE INSTITUTE OF SINGAPORE

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TAY Lavina Sierra

PhD Candidate

(Supervisor: Prof Yoshiaki Ito)

CSI Graduate Programme

PH.D ORAL DEFENSE

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Centre for Translational Medicine MD6 Level 1
14 Medical Drive, Singapore 117599

No registration required. All are welcome.

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2:30 – 3:30 PM

A non-canonical role for RUNX proteins in the Fanconi Anemia pathway of DNA repair

RUNX proteins are evolutionarily conserved transcription factors containing the highly homologous Runt domain, which possesses DNA binding ability. RUNX proteins heterodimerize with a β subunit, CBFβ and bind to RUNX consensus sites to mediate transcription. This study seeks to elucidate the role of RUNX in tumorigenesis as RUNX dysregulation is frequently found in human malignancies. Proteomic analysis to identify novel interacting partners of RUNX, found a striking enrichment for DNA repair proteins, including FANCI. FANCI belongs to one of the 17 identified proteins of the Fanconi anemia (FA) pathway. The FA pathway is involved in repairing DNA interstrand crosslinks through the monoubiquitination and recruitment of FANCI and FANCD2 heterodimer to DNA damage sites. Co-immunoprecipitation assay validated RUNX interaction with FANCI and FANCD2 and interstrand crosslinking drug (mitomycin C) further stimulates the association. Importantly, RUNX/FANCI/FANCD2 complex formation is independent of the canonical transcription RUNX/CBFβ complex.

In a human disease model, leukemogenic RUNX1-ETO disrupted the FA pathway, contributing to genomic instability. Further analyses of leukemic RUNX mutations that abolish DNA binding function or result in a C-terminus truncation revealed that such mutants were incapable of mediating FANCD2 recruitment. Together, these results indicate that the conserved Runt domain is required for mediating interstrand crosslink repair through the FA pathway.

Given that the RUNX family of proteins have been studied mainly in the context of transcription and development, this study reveals an unexpected role in DNA repair. By controlling DNA repair, we propose that RUNX deregulation is responsible for fuelling the process of genomic instability during cancer progression.