Department of Biomedical Sciences

& School of Veterinary Medicine

present Seminar

"Retinoic Acid-Induced Leukemic Stem Cell Differentiation: Nuclear translocation of Raf Kinase"

By

Prof. Andrew Yen

Professor
Department of Biomedical Sciences
Cornell University

Date: 25 March 2015 (Wednesday)

Time: 10:30 am – 12:00 noon

Venue: CSE Conference Room
Room B6605 *(near Lift 3)*
Level 6, Blue Zone, Academic 1
City University of Hong Kong
Tat Chee Avenue, Kowloon Tong

For abstract, please refer to the attachment.

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~ All are Welcome ~

" Retinoic Acid-Induced Leukemic Stem Cell Differentiation:Nuclear translocation of Raf Kinase "

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About the speaker

Dr. Andrew Yen, a professor in the Department of Biomedical Sciences, is a member of several graduate fields. His undergraduate and graduate training at Haverford College (BA, physics/mathematics 1969), University of Washington (MS, physics 1970) and Cornell University (PhD, biophysics 1976) led to postdoctoral work at Harvard with A.B. Pardee and subsequent faculty appointments at the Sloan-Kettering Institute for Cancer Research, the University of Iowa, and now Cornell University. Dr. Yen's research has focused on the cellular/molecular control mechanisms regulating cell growth and differentiation which may be pathologically aberrant in cancer. His work has been supported by the National Institutes of Health, The American Institute for Cancer Research, The Council for Tobacco Research, The Children's Leukemia Research Foundation, The United States Department of Agriculture, and the March of Dimes Foundation. Dr. Yen is Director of Graduate Studies in Environmental Toxicology, Director of the Biomedical Sciences Flow Cytometry Core Laboratory.

Summary

Retinoic acid (RA) is an embryonic morphogen that directs development, a necessary dietary factor governing proper development in juveniles and maintenance of adult tissues, a toxicological teratogen, and a cancer chemotherapeutic agent used in differentiation therapy of leukemia. RA is thus a fundamental biological regulator of cell differentiation and proliferation. The traditional mechanism of action of retinoic acid and its retinoid metabolites is ligand activation of RAR and RXR ligand activated receptors that bind retinoic acid response elements (RARE) in the promoters of target genes to control transcription. Using a model patient derived cell line that is a leukemic stem-like cell that undergoes differentiation and G0 arrest when treated with RA, we show that there is another hitherto unknown mechanism. This mechanism uses a novel cytosolic MAPK signaling machine that discharges the c-Raf kinase to the nucleus to control transcription.

In particular we find that when retinoic acid causes differentiation and G0 cell cycle arrest of HL-60 leukemic lineage bipotent stem cells, the mechanism depends on a surprising nuclear translocation of Raf from the cytoplasm:

1. RA induces expression of the CD38 trans-membrane protein, an ectoenzyme receptor

2. CD38 anchors assembly of a signaling complex in which the Raf/Mek/Erk axis is imbedded, generating long lasting MAPK signaling activation

3. Activated Raf, phosphorylated at S621, is discharged to the nucleus

4. pS621 Raf in the nucleus complexes with the NFATc3 transcription factor on the promoter of the CXCR5 gene, which encodes a membrane receptor, causing NFATc3 serine phosphorylation and allowing CXCR5 transcription

5. CXCR5 expression drives retinoic acid-induced differentiation and G0 cell cycle arrest

This demonstrates a novel pathway where RA causes assembly of a hyperactive MAPK signaling machine resulting in nuclear translocation of activated Raf to phosphorylate transcription factors needed to drive RA-induced differentiation. It demonstrates that the Raf kinase, traditionally perceived as a membrane signaling molecule, has a novel role in the nucleus to effect RA-induced cell differentiation.