NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Seminar Announcement

Novel pro-tumorigenic functions for redox regulators in NSCLC

Date: 01 September 2015 Tuesday

Time: 3:00pm to 4:00pm

Venue: SBS Classroom 4 (SBS-01n-24)

Host: Asst/Prof Melissa Jane Fullwood

Speaker: Dr. Gina DeNicola
Meyer Cancer Center,
Weill Cornell Medical College, USA



Abstract

Mutations in NRF2 and its negative regulator KEAP1 are common in NSCLC. These mutations result in constitutive NRF2 activation and enhanced transcription of NRF2 target genes, which include antioxidant defense genes and genes that promote biosynthesis of the antioxidant glutathione. However, the precise mechanisms by which NRF2 promotes tumorigenesis are unclear. NRF2 regulates multiple metabolic pathways including the pentose phosphate pathway, the tricarboxylic acid cycle, and fatty acid synthesis. By integrating metabolic tracing and transcriptional profiling in a large panel of 80 NSCLC cell lines Dr. DeNicola found that NRF2 regulates the activity of the serine/glycine biosynthesis pathway to support nucleotide and glutathione biosynthesis for cellular proliferation. In an effort to identify other redox regulators that are altered in NSCLC, Dr. DeNicola found that nicotinamide nucleotide transhydrogenase (NNT) is amplified in 11% of NSCLC cases. NNT is a mitochondrial enzyme that catalyzes the transhydrogenation of NADH to NADPH to promote mitochondrial redox homeostasis. Thus, multiple redox regulatory mechanisms support lung tumorigenesis. In this presentation, Dr. DeNicola will discuss how genetic alteration in the redox regulators NNT and NRF2 promote tumor cell proliferation through both redox-dependent and -independent mechanisms.

Gina DeNicola is a postdoctoral fellow in the laboratory of Dr. Lewis Cantley at Weill Cornell Medical College. Dr. DeNicola obtained a bachelor's degree in Biochemistry and Molecular Biology at the Pennsylvania State University and a doctoral degree in Cell and Molecular Biology at the University of Pennsylvania. During her graduate years in the lab of Dr. David Tuveson, Dr. DeNicola identified and characterized the regulation of the NRF2 transcription factor by the oncogene K-RAS in mouse models of lung and pancreatic cancer and human tumor samples. Although it was widely believed that production of ROS by cancer cells drives cancer progression and promotes many tumorigenic processes, Dr. DeNicola's work demonstrated that active suppression of ROS contributed to tumorigenesis. This groundbreaking discovery established NRF2 as a cancer-promoting transcription factor. Dr. DeNicola then joined the lab of Dr. Lewis Cantley to study the regulation of cellular metabolism by NRF2 and the therapeutic implications of inhibition of NRF2-regulated metabolism for the treatment of cancers with high NRF2 activity. She identified that NRF2 regulates the activity of the serine/glycine biosynthesis pathway in lung cancer and was awarded the Pancreatic Cancer Action Network – AACR Pathway to Leadership grant to extend these findings to pancreatic cancer.