University of Cyprus
Department of Biological Sciences

Postgraduate Seminars

Seminar Series 2018-2019

Ms. Evangelia G. Loizou

Ph.D. Student

Weill Cornell Medicine, Memorial Sloan-Kettering Cancer Center (MSKCC), USA

&

Howard Hughes Medical Institute (HHMI), USA

"A p53 mutant oncogene mediates aberrant self-renewal in Acute Myeloid Leukemia"

Wednesday, 10 October 2018, at 17:00

Building CTF 01, Room 108, Panepistimioupoli Campus

This seminar is open to the public

TP53 is the most highly mutated gene across all tumor types. Although *TP53* mutations in acute myeloid leukemia (AML) are not as common as they are in solid tumors, they occur in ~70% of an aggressive and chemoresistant AML subtype known as complex karyotype-AML (CK-AML). Here, we demonstrate that the most common *TP53* mutation in patients with CK-AML does not simply inactivate the gene but instead endows it with oncogenic potential. We identify mouse Trp53R172H (in humans TP53R175H) as a gain-of-function (GOF) Trp53 mutation that accelerates CK-AML initiation beyond that produced by p53 loss and is required for the maintenance of the disease. Mutant p53 exerts its GOF effect by promoting aberrant and continuous self-renewal that is present prior to transformation in otherwise normal hematopoietic stem and progenitor cells (HSPCs). We further identify Foxh1, the Forkhead box H1 transcription factor, as an important mediator of mutant p53 GOF activity. Foxh1 binds and regulates leukemic and stem cell genes and is necessary and sufficient to drive the enhanced self-renewal phenotype observed in p53 GOF mutant cells. All other studies on mutant p53 action have been in the context of tumorigenesis, our findings support that the GOF effect of mutant p53 pre-exists in the cells that harbor the mutation even before the onset of the disease."