University of Cyprus
Department of Biological Sciences

Ph.D. Thesis Defense

Student Presentation

Friday, 15 September 2023 at 11:30
Building FST01, Room 023, Panepistimioupoli Campus

https://ucy.zoom.us/j/61112860449?pwd=UzZxd2RTMUhnbUZYcjAweDlRb0kwUT09
Meeting ID: 611 1286 0449
Passcode: 067169

This seminar is open to the public

Savvas Teloni

Thesis Supervisor: Assoc. Prof. Yiorgos Apidianakis

"Genetic, region-specific and environmental factors induce DNA Damage Response and dysplasia in the aging *Drosophila* midgut"

Mammalian and insect intestines are continuously exposed to pathogens and stress factors making them susceptible to damage, inflammation and tumorigenesis. Spontaneous colonic dysplasia precedes and may be causal to tumorigenesis, however, it is only detectable upon histopathological analysis in old individuals. Using a *Drosophila* model of spontaneous intestinal dysplasia and tumorigenesis, I show that dysplasia starts early in adult life and progresses rapidly in both sexes. Progressive dysplasia is positively corelated in female and male flies with mitotic activity. This is in full agreement with the well-established correlation between stem cell divisions and cancer in humans. However, the mechanisms that drive high mitosis into dysplasia and tumorigenesis remain elusive. My work unravels a fundamental flaw in the *Drosophila* midgut cell differentiation leading to dysplasia and tumorigenesis. I identify dysplastic cells in the young *Drosophila* midgut which are found in a miss-differentiation state and various degrees of ploidy. Moreover, dysplastic cells form clusters throughout the midgut, but posterior midgut regions serve as hotspots for dysplasia and spontaneous tumor formation. Performing transcriptomics comparing the cold spot anterior midgut region, A1, with the hotspot posterior midgut regions, P1 and P4, in 4-day and 30-day old flies, I identified genes and pathways controlling ISC mitosis and dysplasia, including JNK, Insulin and Target of Rapamycin (TOR) signaling pathways genes.
Moreover, using the chemotherapy drugs rapamycin and floxuridine and yeast calorie restriction I managed to lower the progression of dysplasia and tumorigenesis during aging. Furthermore, JNK, a pathway involved in the intestinal stem cell (ISC) proliferation

and dysplasia formation during aging, is activated in the hotspot midgut regions of female and male flies. Downregulation of the JNK pathway genes, including the ligand, *eiger*, and its receptors *grinderwald* and *wengen* reduces ISC mitosis and dysplasia. Another key factor contributing to dysplasia is Notch signaling. I find that strong Notch signaling safeguards midgut enteroblast differentiation into enterocyte, reducing dysplasia. Finally, I find that DNA damage response is not only active in old age tumors but is also a key attribute of progressive dysplasia.