UNIVERSITY OF CYPRUS
DEPARTMENT OF BIOLOGICAL SCIENCES

The Department of Biological Sciences cordially invites you to the thesis defense of the PhD candidate

Charis Achilleos
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entitled

"Mouse Models for Papillomavirus-Mediated Phenotypes"

Abstract

HPVs have been associated with the development of the majority of cervical cancers, a subset of head and neck cancers, skin cancer and other anogenital cancers. Our goal was to use mouse models of papillomavirus gene expression to study the mechanisms through which these viruses contribute to cancer.

HPV-mediated carcinogenesis is thought to be driven by the continuous expression of the viral oncogenes E6 and E7. These oncogenes have no known enzymatic activity and promote carcinogenesis by impinging on cellular processes, including telomere homeostasis Deregulation of telomere homeostasis has been observed in carcinogenesis as a mechanism of overcoming the telomere-shortening problem of the continuously proliferating cancer cells. Telomere maintenance has also been proposed to play an important role in HPV-driven cancers, as both E6 and E7 have been implicated in regulating telomere length by means of telomerase activation and alternative lengthening of telomeres (ALT) respectively. Even though several lines of evidence from *in vitro* studies show that E6 and E7 oncogenes are involved in telomeric regulation, the involvement of these oncogenes in telomere homeostasis has never been demonstrated *in vivo*. Thus, to probe potential in vivo roles of the viral oncogenes in telomere homeostasis we utilized animals transgenic for HPV16 E6 and E7 in order to study the interaction of the E6 and E7 viral oncogenes with telomere homeostasis. Specifically, we examined whether the short-term effects of HPV16 E6 and E7 on stratified epithelia and their stem cell populations are mediated through telomere homeostasis. Terc is the RNA subunit of telomerase and it is necessary for telomere elongation by telomerase. We showed that Terc is dispensable for most of the short-term HPV16 oncogene-mediated phenotypes in mice. Terc deficiency did not affect the E6 and E7-induced proliferation in basal and suprabasal layers of the epithelium, and the increase in keratin 15 (K15) expression in the

hair follicle compared with the non-transgenic mice. Also, E6-mediated reduction of slowly cycling bulge cells (LRCs) was unaffected despite the absence of Terc. Surprisingly, E7-mediated reduction of LRCs was dependent on the presence of Terc, but the mechanism underlying this phenotype is not well understood. Further examination is needed in order to examine the role of Terc in longer-term phenotypes or during natural infection.

While transgenic models have been useful in teasing out the role of individual gene products, research geared toward understanding the interaction of the virus with its host tissue and stem cells was hindered by the lack of animal models that can recapitulate the course of natural infection. This is mostly because papilloma virus infection is species-specific, and as a result, human papillomaviruses do not productively infect rodents. Recently, a papilloma virus strain that infects mice (MmuPV1) and can cause papillomas *in vivo* has been isolated and characterized. MmuPV1 was shown to have many similarities with cutaneus HPVs. To better understand the effects of viral infection on stratified epithelia, we used MmuPV1 genome to infect mice and obtained tissue from the papillomas that were developed. We also obtained tissues from papillomas developed after MmuPV1 infection on mice. We examined the acute effects of papillomavirus on epidermal stem cell markers and on the morphology of the epithelium within the course of natural infection. We showed that stem cell markers K15, K14, CD34, p63, and Lrig1 were upregulated in MmuPV1 infected tissues. These phenotypes mimic at least in part those previously observed in transgenic mice. This upregulation was accompanied with hyperplasia of the epithelium indicated by H&E staining. Additional recent evidence consistent with our findings indicates that this model can serve as a biologically relevant animal model for cutaneous HPVs. We plan to use this model as a tool to examine the interaction of papillomavirus infection with telomere homeostasis. Furthermore, we will use it to interrogate the interaction of papillomavirus infection with the stem cell compartment and cellular plasticity in the epithelium during infection and tumorigenesis.

Wednesday, July 4, 2018 at 11:00
Building ΘΕΕ02, Room B127 (Panepistimioupoli Campus)

The presentation is open to the public.