Name of Student: Shahram Khosravi

Research Supervisor: Dr. Christopher Ong

Title of Presentation: eIF4E, an adverse prognostic marker of melanoma patient survival, increases melanoma cell invasion

Abstract

Human cutaneous melanoma is a life-threatening skin cancer due to its invasive nature and high metastatic potential, leading to poor prognosis for melanoma patients. However, the mechanisms for melanoma invasion and metastasis are poorly understood. Human eukaryotic translation initiation factor 4E (eIF4E) has been shown to be associated with tumor progression in multiple cancer types but the role of eIF4E in melanoma progression is not very well known. We examined eIF4E expression in 448 melanocytic lesions at different stages using tissue microarray and found that moderate-strong eIF4E staining was significantly increased in primary melanomas compared to dysplastic nevi, and further increased in metastatic melanomas compared to primary melanomas. eIF4E expression was correlated with melanoma thickness and was inversely correlated with overall and disease-specific 5-year survival of all and primary melanoma patients especially those with tumours ≥1mm thick. Furthermore, moderate-strong eIF4E expression was significantly higher in AJCC stage III-IV melanomas compared to stage I-II melanomas. Multivariate Cox regression analysis also revealed that eIF4E is an independent prognostic marker. FACS analysis and sulforhodamine B (SRB) cell proliferation assay showed that eIF4E knockdown in melanoma cells resulted in a significant increase and decrease in apoptosis and cell proliferation, respectively. eIF4E knockdown in melanoma cells also resulted in a down regulation of mesenchymal markers such as vimentin, N-cadherin, α-smooth muscle actin (α-SMA) and the EMT inducing transcription factor, Twist. Additionally, eIF4E knockdown in melanoma cells led to a decrease in the expression of Bcl2 and an increase in the expression of cleaved PARP and active Caspase-3. Moreover, down regulation of eIF4E resulted in a decrease in both melanoma cell invasion and MMP-2 activity. Taken together our data suggests the eIF4E may promote melanoma cell invasion and metastasis by inducing EMT and preventing apoptosis and also by increasing MMP-2 activity. eIF4E may also serve as a promising prognostic marker and a potential therapeutic target for melanoma.