PhD DEFENCE Monday, February 5th, 2018

Student: Haoyu (Eric) Deng

Title: THE DEVELOPMENT OF COXSACKIEVIRUS TYPE B3 AS A NOVEL ONCOLYTIC VIRUS AGAINST KRAS-MUTANT NON-SMALL-CELL LUNG CANCER

Time and location: 10:30am PST; Room 4007/8 Providence, Level 4, St. Paul's Hospital, 1081 Burrard Street, Vancouver

Supervisor: Dr. Honglin Luo

ABSTRACT

Lung cancer is the leading cause of cancer-related deaths worldwide. Despite a better understanding of the molecular mechanisms of lung cancer and the subsequent emergence of targeted therapies, treatment responses are typically shortlived. Oncolytic virotherapy provides a possible alternative direction for controlling this incurable disease. Coxsackievirus type B3 (CVB3) is a common human pathogen associated with viral myocarditis in young adults. Due to its highly lytic nature and ability to selectively replicate within cancerous cells, I hypothesize that CVB3 can be developed as an oncolytic virus. Here we demonstrated that *in vitro,* CVB3 specifically targets *KRAS*-mutant (*KRAS*mut) non-small-cell lung cancer (NSCLC), a subtype of NSCLC with limited treatment options. Furthermore, we showed *in vivo* that intratumoral injection of CVB3 significantly reduces tumor volumes in patient-derived *KRAS*mut NSCLC xenograft models. Mechanistically, we found that aberrant activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling and elevated expression of the coxsackievirus and adenovirus receptor (CAR), the primary receptor for CVB3 internalization, are associated with preferential replication of CVB3 within *KRAS*mut NSCLC. However, despite a satisfactory tumor regression rate, CVB3 treatment leads to the onset of viral myocarditis in immunocompromised mouse models, indicating that potential safety issues need to be addressed prior to its potential application in lung cancer therapy. It is known that CVB3 subverts host machinery to gain survival advantages, and this process is highly associated with a spectrum of human disorders. We reported that Grb2-associated binding protein 1 (GAB1), a scaffolding adaptor protein responsible for intracellular signaling assembly and transduction, plays a crucial role in regulating compensatory cardiac response to aging and hemodynamic stress. Furthermore, we demonstrated that both GAB1 and Grb2-associated binding protein 2 (GAB2, a functional homologue of GAB1), are proteolytically cleaved after CVB3 infection by virus-encoded protease 2Apro, independent of caspase activation. We showed that virus-induced cleavage of GAB1 is beneficial for viral growth as the resulting cleavage fragment (GAB1-N1-174) further enhances ERK1/2 activation and promotes viral replication. Taken together, our findings suggest that CVB3 is a potent oncolytic agent against *KRAS*mut NSCLC, and that elimination of CVB3-induced cardiotoxicity would significantly enhance the safety of this virotherapy.