

Contribution of the cleavage of serum response factor to viral cardiomyopathy

Honglin Luo and Jerry Wong
University of British Columbia, Canada

Viral myocarditis can lead to reduced cardiac function and the progression to dilated cardiomyopathy (DCM), which accounts for 10~20% of heart failure and sudden death in children and youth. Viral proteases have been recognized as important pathogenic mechanisms through the cleavage of important host proteins. However, the precise mechanisms underlying the development of DCM remain unclear. Serum response factor (SRF) is a cardiac-enriched transcription factors regulating the expression of a variety of target genes, including cardiac contractile/regulatory genes and microRNAs. SRF has been shown to play a central role in cardiac development and function. We recently demonstrated that SRF is cleaved during enteroviral infection through the action of viral protease 2A. This cleavage is accompanied by impaired cardiac function and downregulation of cardiac specific contractile/regulatory genes. We further identified the cleavage site (before G327) and showed that cleavage of SRF dissociates its DNA-binding domain from the transactivation domain, resulting in the loss of functional SRF and the generation of a dominant-negative truncate of SRF which competes for DNA binding. Finally, based on the identified cleavage site of SRF, we designed a modified SRF-based tetrapeptide (z-LKST-fmk) using a strategy similar to that used to inhibit caspases with the peptide substrate analogue z-VAD-fmk. Our preliminary *in vitro* results demonstrated that this peptide inhibitor inhibits SRF cleavage and reduces viral replication in cardiomyocytes. Novel therapeutic approaches are expected to be developed to ameliorate myocardial damage and progression to DCM *in vivo*.

Biography

Dr. Honglin Luo is an Associate Professor in the Department of Pathology and Laboratory Medicine/James Hogg Research Center at the University of British Columbia, Canada. Dr. Luo completed her MSc and MD training in China. She then pursued her postdoctoral training at the University of Washington. Dr. Luo has published over 60 refereed papers and served as an editorial board member of several journals.

Honglin.Luo@hli.ubc.ca