NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

BIOLOGY COLLOQUIUM

Friday, 25 August 2017 | 4pm | DBS Conference Room 1

Hosted by A/P Ganesh Anand

Hepatitis C virus: From research on translation to translational research

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Hepatitis C Virus (HCV) infection is a serious health problem that leads to liver cirrhosis and hepatocellular carcinoma. It is a positive-sense, single stranded RNA virus that injects its genomic content into the host cytoplasm upon infection. Following this first step of infection, translation of the viral-encoded proteins is an essential prerequisite for viral replication. The viral RNA hijacks the host translation machinery for this purpose in a unique way. Since the HCV RNA is naturally uncapped, its translation is guided by an 'internal ribosome entry site' (IRES) element present in the 5'-untranslated region. Ribosomes binding to the HCV-IRES element are also unique and fundamentally different from the cellular mRNA, and are influenced by a number of trans-acting host proteins and cis-elements on the HCV RNA.

We have identified several sequence and structural features of the HCV RNA important for viral translation and replication. We have also identified several of the host factors, among which the human La protein plays a pivotal role in this regulation. La interacts with a conserved GCAC-element at the 5'-region of the HCV RNA and promotes ribosome assembly at the HCV-IRES leading to viral translation. Interestingly, La also interacts with 3'UTR of the viral RNA, mediating a translation-replication switch and helping in circularization of the viral genome for efficient replication. The other cellular factors that directly or indirectly assist La in these processes include the HuR protein and the microRNA miR-125b. Successful establishment of viral infection can eventually modulate cellular gene expression leading to hepatocellular carcinoma.

Our findings provided important leads for rational designing of synthetic peptides and small RNAs that inhibit viral translation. In parallel, we have identified several, plant-based natural products that inhibit different steps of HCV infection for therapeutic intervention.

We aim to continue our basic research on HCV infection that would eventually help us design more effective vaccine as well as therapeutic molecules towards better management of HCV infection.