Abstract

Type I interferon (IFN) production is a pivotal step in establishing antiviral immunity and eliminating viral pathogens. However, a sustained type I IFN response elicits hyperinflammation, tissue damage and/or autoimmunity. Consequently, a delicate balance in maintaining optimal type I IFN expression is critical without compromising effective host antiviral immunity. Negative post-transcriptional control of IFN-β production involves ARE-mediated decay of IFN-β mRNA and miRNAs-induced silencing. However, the molecular mechanism of the latter is poorly understood.

Using *in vitro* assays and *in vivo* mouse models, we demonstrate that *Ifnb1* mRNA translation is strongly repressed by miRNAs, which is dependent on a eukaryotic initiation factor 4E homologous protein (4EHP) without induction of mRNA decay. Recent work has demonstrated that 4EHP, a mRNA cap-binding protein, acts as a vital component of the translational silencing machinery via its interaction with the miRNA-Induced Silencing Complex (miRISC) and the carbon catabolite repression 4-negative on TATA-less (CCR4-NOT) complexes. Here, we show that translational repression of IFN-β by 4EHP is mediated by miR-34a, whose expression, in turn, is induced by type I IFN, thereby triggering a negative feedback loop in response to viral infection. Our data unveil a novel and potent regulatory function of the miRNAs via translation in host intrinsic regulation of IFN expression and highlights its essential role in dampening virally induced sustained innate immune response to maintain host homeostasis.

Based on this original research, we further explored the molecular mechanism of how the SARS-CoV-2 Non-Structural Protein 2 (NSP2) outmaneuvers the human innate immune response by co-opting a unique cellular translational control mechanism to suppress IFN-β production. In detail, we show that the SARS-CoV-2 NSP2 protein binds to the 4EHP-interacting protein, GRB10 interacting GYF protein 2 (GIGYF2), to enhance translational repression of IFN-β mRNA through 4EHP. NSP2 thereby impedes the host innate antiviral immune response and enhances of SARS-CoV-2 replication. This mechanistic insight of NSP2-mediated repression of IFN-β production *via* the GIGYF2/4EHP complex is of considerable value for devising drugs to combat SARS-CoV-2, and of other known and yet-to-emerge novel coronaviruses.

McGill University

Graduate and Postdoctoral Studies

Final Oral Examination
for the Degree of
Doctor of Philosophy
of **Xu ZHANG**

of the Department of Biochemistry**, on Friday, Februray 24, 2023 @ 1:00 PM In-person/Hybrid**: **Room B530, Bellini Life Sciences Building**.

COMMITTEE:

Professor Massimo Avoli,	(Pro Dean)
Neuroscience Integrated Program	
Professor Bhushan Nagar	(Deputy Chair)
Professor Nahum Sonenberg	(Thesis Supervisor)
Professor Michel Tremblay	(Internal Examiner)
Professor Rongtuan Lin	(Internal Member)
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Dr. Josephine Nalbantoglu
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Members of Faculty and Graduate
Students are invited to be present

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