UNIVERSITY of GUELPH

gairdner
LES PRIX CANADA GAIRDNER AWARDS

MOLECULAR and Cellular Biology

2017 Gairdner Lecture

Lynne E. Maquat, PhD

Professor, Department of Biochemistry & Biophysics, and Oncology, School of Medicine and Dentistry, and Director, Center for RNA Biology, University of Rochester

"Nonsense-mediated mRNA Decay and Human Disease: Genome Guardian and Executor"

(Faculty Host: Dr. Steven Rothstein)

Wed. May 17th, 2017
PAHL 1800 @ 10:30 am

Much progress has been made on how nonsense-mediated mRNA decay (NMD), which we first described for humans in 1981, controls the quality of gene expression by detecting and rapidly degrading aberrant mRNAs that contain a premature termination codon (PTC)1. Our studies of NMD have led to the discovery of the pioneer round of translation, the post-splicing "mark" on newly synthesized mRNAs – later named the exon-junction complex (EJC) in a collaboration with Melissa Moore – and the mechanistically related Staufen-mediated mRNA decay pathway. More recently, we tracked individual cellular transcripts in collaboration with Tatjana Trcek and Rob Singer to confirm our results from the mid-1990's indicating that NMD for a number of mRNAs occurs on the cytoplasmic side of the nuclear envelop2. Our data provide explicit evidence that proteins acquired by newly synthesized mRNAs in the nucleus, including the cap-binding protein CBP80 and constituents of the EJC, are critical for mRNA quality control via translation in the cytoplasm. We have also described the molecular mechanism for how NMD targets are discriminated from other transcripts: the central NMD factor – the ATP-dependent RNA helicase UPF1 – preferentially associates with mRNA 3'- untranslated regions (3' UTRs) in a way that correlates with 3' UTR length and the presence of a 3' UTR EJC3,4. Importantly, NMD also targets ~10% physiologic mRNAs that are key to maintaining cellular homeostasis in a changing environmental milieu. In this regard, we have found that a sufficient level of DNA damage induced by commonly used frontline chemotherapeutics inhibits NMD by triggering the caspase-mediated cleavage of sub-stochiometric amounts of UPF1, thereby upregulating the half-lives of mRNAs that include those encoding proteins promoting apoptosis5. Notably, the modest inhibition of NMD promotes but is not sufficient for programmed cell death. These and other results6 will be discussed.

1. Popp MW, Maquat LE. (2013) Organizing principles of mammalian nonsense-mediated mRNA decay. Annu Rev Genet. 47:139-165.
2. Trcek T, Sato H, Singer RH, Maquat LE. (2013) Temporal and spatial characterization of nonsense-mediated mRNA decay. Genes Dev. 27:541-551.
3. Kurosaki T, Maquat LE. (2013) Rules that govern UPF1 binding to mRNA 3' UTRs. Proc Natl Acad Sci U S A. 110:3357-3362.
4. Kurosaki T, Li W, Hoque M, Popp MW, Ermolenko DN, Tian B, Maquat LE. (2014) A post-translational regulatory switch on UPF1 controls targeted mRNA degradation. Genes Dev. 28:1900-1916.
5. Popp MW, Maquat LE. (2015) Attenuation of nonsense-mediated mRNA decay facilitates the response to chemotherapeutics. Nat Communications, 6632.
6. Kurosaki T, Maquat LE. (2016) Nonsense-mediated mRNA decay in humans at a glance. J. Cell Sci. 129:461-467.

*** ALL WELCOME TO ATTEND ***

*** COFFEE, TEA AND TIMBITS ***

For more information, please visit MCB`s website http://www.uoguelph.ca/mcb