Science 2017 Blog

Speaker: Lynne Maquat Ph.D.

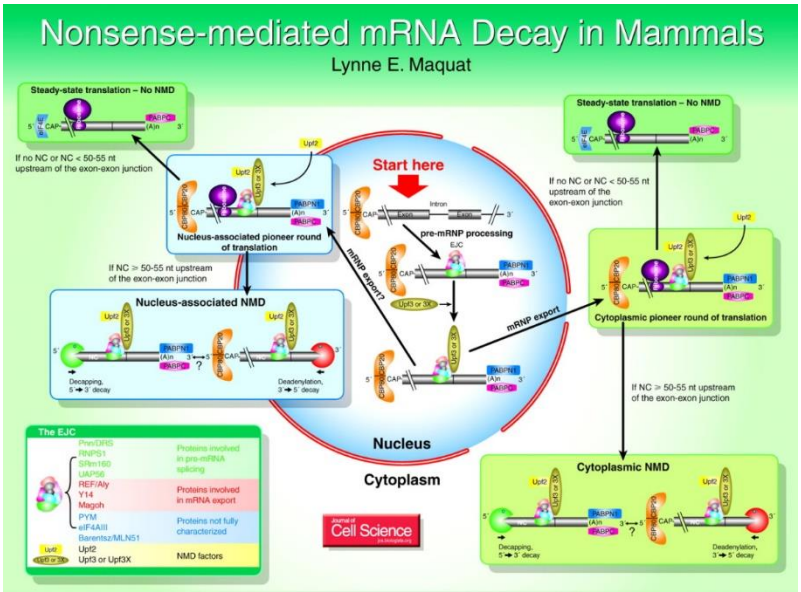
Title: Nonsense-Mediated mRNA decay and human disease: Genome guardian and executor

By David A. Macar

Fixing Mistakes and Regulating Change: Modulating mRNA Translation through Decay

We are not perfect, we all make mistakes! It makes sense that the building blocks of humans, and cells, also make mistakes and have the capacity to correct them. Dr. Lynne Maquat, Ph.D. spoke on mRNA decay and how it can protect heterozygous carriers from disease states or regulate gene expression during development at Science 2017 at the University of Pittsburgh. Dr. Maquat discussed two competing mechanisms of mRNA decay: Nonsense mediated mRNA decay and Staufen mediated mRNA decay, each acting to degrade mRNA which could potentially encode harmful peptides or regulate protein expression during cellular differentiation.

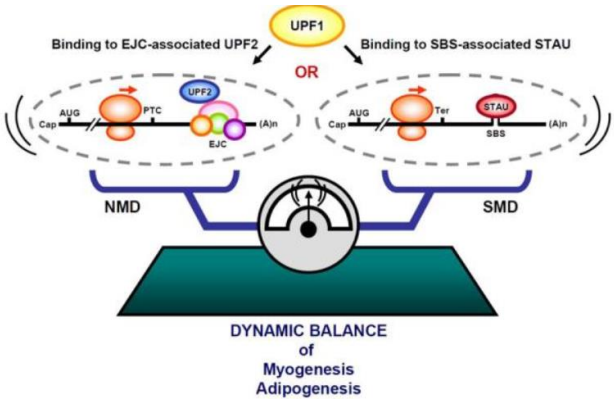
Nonsense-mediated mRNA decay(NMD) and Staufin-mediated mRNA decay(SMD) evolved to eliminate mistakes and through their competition, to regulate gene expression. Approximately one-third of spliced mRNA are mistakes due to exon skipping, splicing downstream or upstream of splice sites, and inclusion of spliced segments in mature mRNA. To guard against the production of toxic peptide fragments, NMD and SMD serve as mRNA quality control mechanisms. Prior to steady state translation, a pioneer round of translation occurs to identify premature termination codons. Dr. Maquat showed NMD is promoted by an exon junction complex(EJC), specifically UPF1 and UPF2, and a mRNA cap-binding protein(CBP80). If NMD occurs, it is the consequence of nonsense codon recognition during the pioneer round of translation. Dr. Maquat's group showed that if a nonsense codon is located greater than 55 base pairs upstream of the 3' most exon-exon junction, NMD is likely to occur. Conversely, if there is no early nonsense codon or it is located less than 55 base pairs upstream of the 3' most exon-exon junction then NMD will not occur and the ribosome will remove the exon junction complex during the pioneer round of translation, allowing for reorganization of the translation machinery and steady state



Marquet, Lynne E. "Nonsense-Mediated mRNA decay in mammals." Journal of Cell Science, vol. 118, no. 9, 1 May 2005, pp. 1773–1776., doi: 10.1242/jcs.01701.

translation. They then used electron microscopy to show that NMD most often occurs while the 3' mRNA end is still dissociating from the nuclear pore complex.

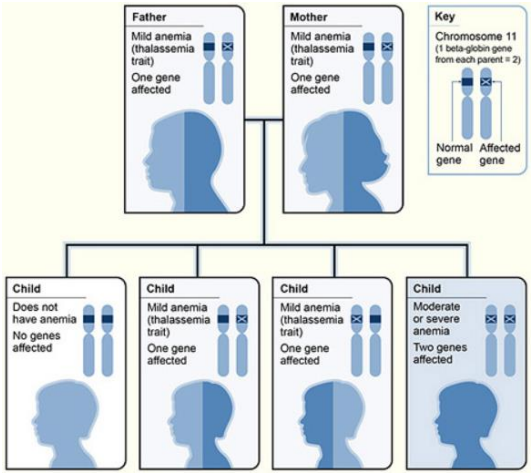
SMD occurs when UPF1 binds Staufen binding site associated Staufen instead of EJC associated UPF2. The Maquat group used doxorubicin, a chemotherapeutic drug, to induce DNA damage to study NMD and SMD response.



Park, Eonyoung, and Lynne E. Maquat. "Staufen-Mediated mRNA Decay." Wiley interdisciplinary reviews. RNA 4.4 (2013): 423–435.

They showed that UPF1 phosphorylation triggers translational repression and inhibition of UPF1 cleavage decreased doxorubicin mediated toxicity. DNA damage from doxorubicin attenuated NMD and the efficiency of NMD was shown to be less than the efficiency of SMD. The same was shown during myogenesis and adipogenesis. Dr. Maquat found that during myogenesis and adipogenesis if the concentration of Staufen was less than the concentration of UPF2 the efficiency of SMD increased and the efficiency of NMD decreased. Therefore, NMD target degradation and SMD target degradation can be controlled, effectively regulating gene expression and developmental differentiation.

Last, Dr. Maquat described a disease where NMD allows for heterozygotes to be relatively healthy individuals. Beta-thalassemia's are hemolytic anemias due to defects in the human beta globin gene. A premature termination codon in the beta globin mRNA creates a stable truncated form of the protein and causes the disease. In heterozygous carriers who have one copy of the disease-causing gene and one copy of the healthy gene, NMD destroys the disease-causing mRNA, protecting the individual. She compared beta-plus and beta-zero thalassemia where low levels and no beta globin protein is produced respectively. In beta-zero thalassemia, mRNA was shown to be deficient due to NMD because the mRNA contained a premature termination codon in the first exon. NMD eliminated the mistake and protected carriers, allowing them to have 50% normal protein levels and eliminating toxic truncated proteins.



Dr. Maquats' Science 2017 talk at the University of Pittsburgh was fascinating and highlighted how an understanding of cellular mechanisms directly translates into an understanding of human disease and development. Dr. Maquat ended with her future goals of applying her mechanistic findings to designing and developing therapies to inhibit or promote NMD to lessen the severity of nonsense-generated diseases. A remarkable one-third of inherited or acquired diseases are nonsense-generated.

References

Marquet, Lynne E. “Nonsense-Mediated mRNA decay in mammals.” Journal of Cell Science, vol. 118, no. 9, 1 May 2005, pp. 1773–1776., doi: 10.1242/jcs.01701.

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