The amazing web of post-transcriptional gene control: The sum of small changes can make for significant consequences

LYNNE E. MAQUAT^{1,2}

¹Department of Biochemistry and Biophysics, School of Medicine and Dentistry, University of Rochester, Rochester, New York 14642, USA

²Center for RNA Biology, University of Rochester, Rochester, New York 14642, USA

It is now well established that eukaryotic cells respond to their changing milieu through coordinate transcriptional and post-transcriptional mechanisms. Post-transcriptional mechanisms include those that tune the expression of a battery of genes encoding proteins of diverse function, if not mRNAs of diverse structure, via targeted mRNA decay. As recently as 10 years ago, a change in mRNA abundance that was less than five- to 10-fold was deemed by many to be physiologically insignificant. However, an appreciation for the importance of small changes has grown as a consequence of new methodologies that are sufficiently sensitive and sophisticated to quantitate small and concomitant changes to the abundance of groups of mRNAs.

Only relatively recently—since the inception of technological advances in transcriptome deep-sequencing and RT-coupled to real-time PCR that enable scientists to reliably measure changes in RNA abundance that are less than 1.5-fold and that typify groups of RNAs—has the existence of a truly remarkable and previously inconceivable network of post-transcriptional processes been uncovered. While this network is far from completely established, it has become clear that it consists of responses that individually do not necessarily promote an appropriate cellular response but together, and in conjunction with transcriptional and other regulated pathways, most certainly do.

The idea that the sum of small changes can have significant consequences is epigenomic to a broad range of cellular processes, including epigenomic modifications to DNA. Nevertheless, evidence presented here will be limited to mRNA decay. Furthermore, while the focus will be on nonsense-mediated mRNA decay (NMD), small changes in the half-lives of groups of mRNAs as part of a cellular response to changes in cellular environment also characterize other mRNA decay pathways, as exemplified by many in studies of microRNA-

mediated mRNA decay and my lab and the lab of Yoon Ki Kim on Staufen-mediated mRNA decay.

NMD: Easy does it

NMD is largely a quality-control pathway that degrades mRNAs that prematurely terminate translation so as to obviate the production of truncated proteins that are potentially toxic to cells. These mRNAs are often the result of mistakes made during gene expression, and in humans they include an estimated one-third of alternatively spliced mRNAs as well as an estimated two-thirds of mRNAs that derive from genes that undergo somatic-cell rearrangement and hypermutation. Furthermore, NMD targets are responsible for approximately one-third of inherited diseases because they harbor a frameshift or nonsense mutation that generates a premature termination codon and precludes the production of functional protein. Pertinent to this piece, NMD additionally degrades ~10% of normal mRNAs. These mRNAs, which derive from splicing (since unspliced mRNAs are generally not NMD targets), are heterogenous in structure, encode proteins of diverse functions, and are NMD targets for one of a variety of reasons: for example, they harbor an upstream open translational reading frame, an 3'-untranslated region (3'UTR) intron, or an abnormally long 3'UTR, each of which may be the consequence of alternative pre-mRNA splicing or 3'-end formation.

Relatively recently, data indicate that NMD is used by cells to fine-tune gene expression in response to environmental stimuli. For example, my lab has shown that during muscle-cell differentiation in not only humans but also rodents, the efficiency of NMD is downregulated approximately two-fold (as determined using β -globin-based NMD reporters to compare the efficiency of NMD in undifferentiated

Corresponding author: lynne_maquat@urmc.rochester.edu

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myoblasts vs. differentiated myotubes) while the efficiency of a competing pathway, Staufen-mediated mRNA decay (SMD), is upregulated approximately twofold (as determined using luciferase-based SMD reporters to compare the efficiency of SMD in undifferentiated myoblasts vs. differentiated myotubes). These small and opposing changes to the efficiencies of SMD and NMD during myogenesis offer means to downregulate a pool of mRNAs that includes some whose protein products maintain myoblasts in an undifferentiated state as well as upregulate a pool of mRNAs that includes some whose protein products encode pro-myogenic factors. Lawrence Gardner's lab has found that the efficiency of NMD is also inhibited ~2.5-fold during hypoxia (as determined using β -globin-based NMD reporters in a comparison of prostate cancer PC3 cells grown as monolayers to PC3 cells grown as three-dimensional tumors) so as to promote tumorigenesis. This seems to have the effect of stabilizing NMD substrates that promote the response to stress (including genes that are responsive to the unfolded-protein response), allowing cells to adapt to their newly established environmental conditions. During the differentiation of neural stem cells, the group of Miles Wilkinson has demonstrated that NMD is downregulated in part by the expression of a neural-specific microRNA, miR-128, that partially degrades mRNA encoding the key NMD factor UPF1. As a consequence, the efficiency of NMD is abrogated approximately twofold (as measured using a luciferase-activity reporter assay during 4 d of PC12 pheochromocytoma-cell neurogenesis) so as to upregulate the abundance of mRNAs that include those encoding proteins promoting post-mitotic neuronal differentiation. As a final but certainly not the last example, Max Popp in my lab has shown that a sufficient level of DNA damage induced by commonly used chemotherapeutics, such as doxorubicin, inhibits NMD approximately twofold by triggering the caspase-mediated cleavage of some but not all of UPF1 protein, thereby upregulating the half-lives of mRNAs encoding proteins that mediate programmed cell death. Notably, in each case, the modest inhibition of

NMD is necessary but not sufficient for the appropriate cellular response. Max demonstrated this explicitly in the case of programmed cell death by recapitulating, in the absence of DNA damage (i.e., in the absence of doxorubicin), the physiologic level of cleaved UPF1 observed in the presence of doxorubicin by co-expressing tobacco etch viral (TEV) protease and UPF1 engineered to contain a TEV protease cleavage site.

Data from the group of Ari Helenius has offered a twist to this theme: various plus-stranded RNA viruses may have evolved mechanisms to reduce the degradation of their own transcripts by inhibiting the cellular NMD machinery, and these viruses would be sub-optimally served if their inhibitory mechanism severely debilitated host-cell viability. Furthermore, following an immune response, Jonathan Dinman's lab has found that the low efficiency with which various cytokine receptor-encoding mRNAs are targeted for NMD as a consequence of microRNA-promoted -1 programmed ribosomal frameshifting (measured using dual luciferase reporters of the CCR5 mRNA to be 4.5%–11% depending on cell type) pushes cells towards immune desensitization as a way for individual cells to fine-tune their return to homeostasis.

In summary, the effects of post-transcriptional regulatory pathways that have more than one target transcript are often more than the sum of the effects of targeting individual transcripts. This is certainly the case for NMD. Given new technologies able to detect transcript levels that vary by less than twofold, we now realize that cells utilize NMD to only modestly alter the expression of groups of genes. By encoding pools of NMD targets that can respond appropriately to a variety of cellular changes, cells are able to tune their metabolic state with a robust versatility.

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