sembles of nuclear spins have demonstrated (*11*). The operations on qubits could be performed with applied magnetic fields while the measurement would be done optically. The structure of the interacting system would have to be carefully designed to control the interactions between qubits.

The molecules in the experiments of Hettich *et al.* (*4*) were distributed at random, but nanomanipulation has been progressing so quickly that such a control might very soon become real. Combining nanoscale structures with single molecules to process quantum information would then open a wide realm of fascinating opportunities.

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PERSPECTIVES: RNA EVENTS

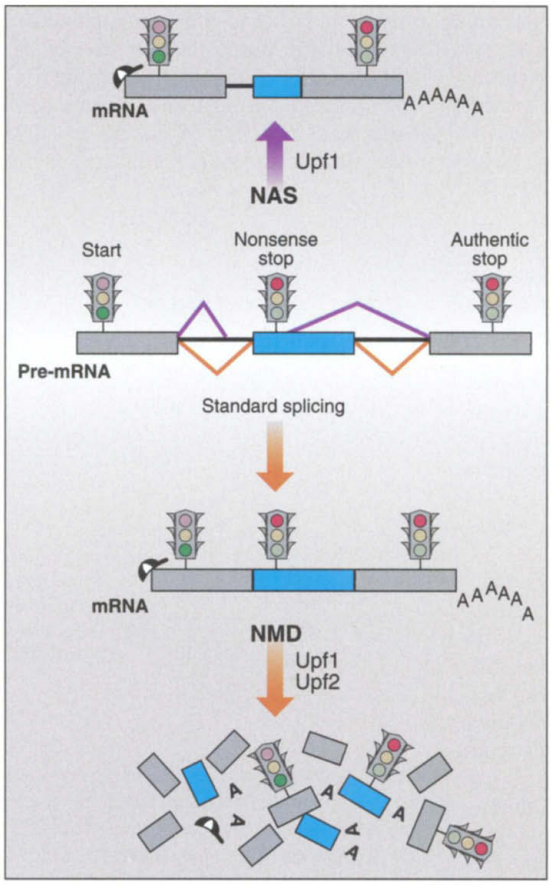
No End to Nonsense

Melissa J. Moore

Two of the hottest topics in eukaryotic gene expression research involve absolute nonsense: nonsense-mediated mRNA decay (NMD) and nonsense-associated altered splicing (NAS). "Nonsense" in this case refers to a type of mutation in mRNA transcripts that causes the protein synthesis machinery to terminate prematurely their translation into proteins. Nonsense mutations were originally thought to affect only the length, and therefore the function, of the encoded protein. However, it is now apparent that they can dramatically decrease the half-lives of mutant mRNAs as well as alter the pattern of precursor mRNA (pre-mRNA) splicing (see the figure). The molecular basis of the latter phenomenon (NAS) is particularly mysterious, because it is generally accepted that nonsense mutations cannot be recognized as nonsense until after the splicing process is complete. Two papers, one by Mendell *et al.* on page 419 of this issue (*1*) and another by Wilkinson and co-workers in a recent issue of *Molecular Cell* (*2*), now begin to unravel this mystery by showing that NMD and one type of NAS (reading frame–dependent NAS) are functionally distinct processes that rely on different, but overlapping, sets of proteins.

NMD is the quality control system by which mRNAs containing premature stop (nonsense) codons are selectively eliminated by eukaryotic cells. It is thought that by removing these defective mRNAs, NMD protects cells from potential damage due to inappropriately truncated proteins. To date, a number of proteins required for NMD have been identified in a variety of organisms, and analysis of how they regulate this process is well under way (*3*, *4*). NAS, on the other hand, has proven much more controversial (*5*–*7*). Although numerous examples of NAS have been described, most of these can be readily explained by conventional mechanisms involving chance disruption of RNA sequences called exonic splicing enhancers (ESEs). ESEs are target sites for proteins that help to define pre-mRNA splice sites; their disruption by almost any type of mutation can cause altered splicing. Therefore, the promotion of alternate splicing by most nonsense mutations is simply due to the destruction of a key recognition element for the splicing machinery and has nothing to do with the ability of nonsense mutations to be recognized subsequently as stop signals during protein synthesis. Recently, however, Wilkinson and co-workers convincingly demonstrated that NAS of certain T cell receptor gene transcripts does require that the mutations act as protein synthesis stop signals (*2*, *8*). They showed that certain nonsense mutations only mediated alternate splicing if they were "in frame" with a start signal, meaning that they had to be detected by the protein translation machinery. In addition to the T cell receptor case, available evidence suggests that nonsense mutations can alter splicing in a reading frame–dependent manner in other systems as well (*9*–*12*).

One aspect of T cell receptor NAS that is particularly difficult to reconcile with our current understanding of eukaryotic gene expression is that this type of NAS depends on the mRNA reading frame, something that is not established until after splicing is complete. A pressing challenge, therefore, is to understand how the apparent downstream process of reading-frame recognition can feed back to alter the apparent upstream process of pre-mRNA splicing. Given that reading frame–dependent NAS is triggered by the same signals that trigger NMD, one possibility is that NAS is an indirect consequence of NMD. If so, then both phenomena should be dependent on the same subcellular machinery. What both groups now show is that this is not what actual-



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Circumventing stop signals. Alternate fates of mRNA transcripts containing nonsense mutations. **(Top)** Shown is a pre-mRNA harboring a nonsense stop signal within an internal exon (colored box). In the majority of such molecules, introns (lines) are removed at the usual sites, resulting in retention of the nonsense mutation in the mature mRNA. Such aberrant mRNAs are then subject to degradation by NMD. **(Bottom)** In some cases, however, a nonsense mutation can activate an alternate splicing pathway (NAS), yielding a stable mRNA lacking the mutation. These two effects of nonsense mutations are dependent on different protein factors. Whereas NMD requires both Upf1 and Upf2, reading frame–dependent NAS is Upf2-independent.

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ly occurs. Depletion of two factors requisite for NMD, Upf1 and Upf2, abrogated NMD of mutant T cell receptor mRNAs. In contrast, reading frame–dependent NAS proved resistant to Upf2 depletion (*1, 2*). Yet, because both processes do require Upf1, there is clearly some mechanistic overlap between them.

In their study, Mendell *et al.* used RNA interference (RNAi) to eliminate Upf1 and Upf2 from their test cells. RNAi can be initiated in mammalian cells by incubating them with small pieces of double-stranded RNA, one strand of which is complementary to a target mRNA. These small double-stranded RNAs cause the targeted mRNA to be degraded. RNAi allows the researcher to "knock down" individual mRNAs, and thereby remove the proteins they encode, without having to introduce mutations at the DNA level. After determining a knockdown phenotype, one generally wants to know what specific part of the target protein is responsible for the eliminated activity. Thus, having shown that Upf1 is necessary for both NMD and reading frame–dependent NAS, Mendell *et al.* (*1*) wondered whether Upf1 plays the same role in both processes. To address this question, they used a strategy known as "allele-specific RNAi." By changing the sequence of the Upf1 gene encoded on a plasmid, they created a version of Upf1 that was not subject to RNAi by the double-stranded RNAs used to knock down the endogenous protein. They could then rescue both NMD and NAS in the RNAi-induced cells by introducing this altered plasmid. This strategy allowed them to determine the effects of two different substitution mutations in conserved regions of Upf1. One of these mutations supported NAS, but failed to rescue NMD. Thus, the functions of Upf1 in NAS and NMD are genetically separable, again demonstrating that these two processes are related yet mechanistically different.

Although the two new studies rule out one possible mechanism for reading frame–dependent NAS, we are left with many more unanswered questions. Of utmost interest is the unknown mechanism by which recognition of the mRNA reading frame can feed back to alter pre-mRNA splicing. One way to address this problem is to identify the proteins required. Identification of Upf1 as the first such factor thus represents a crucial step toward this goal.

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PERSPECTIVES: EVOLUTION

Jaws of the Fates

Georgy Koentges and Toshiyuki Matsuoka

In his poem about the lonely "Maldive Shark," Herman Melville describes the daunting jaws of a serious meat-eater, which serve as an asylum for the sleek little pilot fish, azure and slim, hiding in his "jaws of the Fates." The "jaws of the Fates" may act rather unpredictably in the uncharted oblivion of the Indian Ocean, but Depew *et al.* (*1*) report a remarkable catch—the genes that dictate the fates of jaws—on page 381 of this issue. These authors turn lower jaws into upper jaws by simultaneously inactivating the homeobox genes *Dlx5* and *Dlx6* of mice. Such a spectacular transformation of "jaw identity" unveils a family of genes that are crucial for directing formation of the vertebrate face. This gene family may have been subject to profound modifications during vertebrate evolution and in certain human congenital diseases. The *Dlx5* and *Dlx6* genes are now implicated in the elaboration of vertebrate lower jaws, from the ferocious feeding machinery of the great white shark to the sophisticated hearing system of mammals.

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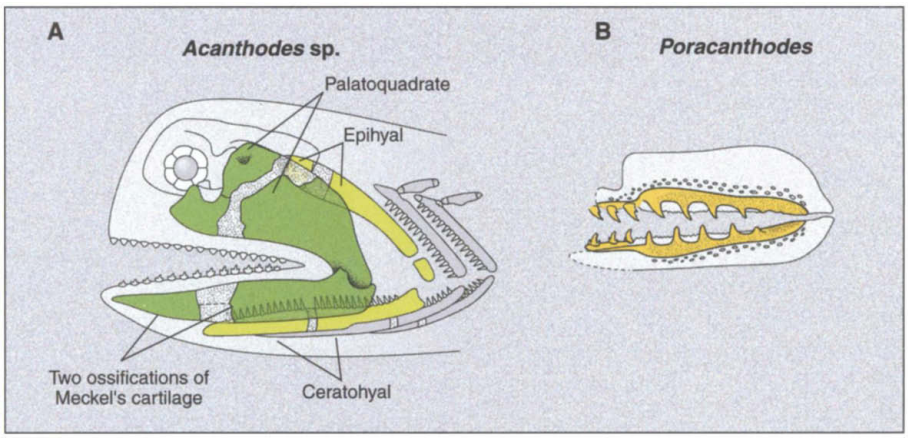
A complex series of cellular and molecular interactions underlies the assembly of the vertebrate face. Most structures are formed by the neural crest, a tissue that emanates from the early embryonic brain and populates the so-called branchial arches (*2*). Branchial arches are a segmental series of bulges in the embryonic head and are predecessors of all facial elements. Within the first (mandibular) branchial arch, jaw elements develop from three bulges: the mandibular, maxillary, and frontonasal processes that are filled by neural crest cells from different origins (midbrain and hindbrain) (*3*). Widespread mixing between them supports the notion that jaw neural crest is exposed to instructive signals from its environment that establish a proximodistal axis to the jaw-forming branchial arch (*3*). Such external cues are translated into a code of neural crest proximodistal "identity," leading to the precisely orchestrated formation of skeletal and muscular elements. Much evidence implicates the *Hox* homeobox genes as the encoders of "rostrocaudal identity" in all branchial arches posterior to the jaw-forming arch. However, until now no genes have been proven to act as true selector genes for proximodistal identity of neural crest cells in branchial arches.



A more symmetrical smile. (**A**) Skeleton of the head of a jawed vertebrate, *Acanthodes*, showing symmetry between upper and lower jaw elements (green) and hyoid elements (yellow). The upper jaw (palatoquadrate) and lower jaw are both subdivided in two by a cartilaginous bridge. (**B**) Jaws of the acanthodian *Poracanthodes* with symmetrical jaws and dentition (yellow). The success of jawed vertebrates is partly attributable to the morphological independence (that is, asymmetry) of upper and lower jaws encoded by differentially expressed *Dlx* genes. Elaboration of this developmental code imbued vertebrates with hearing machinery and a wide variety of feeding capabilities. [Adapted from (*8*)]

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