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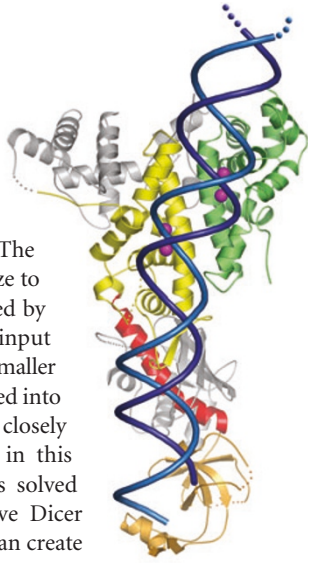
Dicer rules



RNA-mediated interference (RNAi) pathways use short interfering RNAs or microRNAs to produce sequence-specific gene silencing. Hallmark characteristics of these small RNAs are a 3′ overhang and a length of ~21–25 nucleotides (nt). The small RNAs, which are of an ideal size to achieve gene specificity, are generated by Dicer proteins that process longer-input double-stranded (ds) RNAs into the smaller RNA fragments, which are then loaded into silencing complexes. To look more closely into how Dicer creates fragments in this size range, Doudna and colleagues solved the structure of a full-length active Dicer protein from *Giardia*. This protein can create RNA fragments 25–27 nt long. In contrast to higher eukaryotic Dicers, which have accessory domains that contain helicase and dsRNA-binding activities, this Dicer enzyme has only the RNA-binding PAZ domain, which is known to recognize 3′ two-base overhangs, and two RNase III domains (RNase IIIa and IIIb). The structure of the enzyme shows that the PAZ domain is linked to the C-terminal RNase III domains by a long connector helix. The distance between the PAZ 3′ overhang–binding site and the RNase IIIa active site is about 65 Å. The authors model in an ideal RNA duplex and find that when the 3′ end of the RNA falls in the PAZ binding site, the scissile phosphate is in the RNase IIIa active site 25 base pairs away. They propose that Dicer functions like a molecular ruler, with the distance between the PAZ binding and RNase active sites dictating the length of the small RNAs generated. (*Science* **311**, 195–198, 2006) *MM*

Destroying dad's DNA

In most eukaryotes, genomic DNA in chloroplasts or mitochondria is only inherited from the maternal parent. This property makes mitochondrial DNA (mtDNA) a useful tool for tracing maternal lineage and for establishing evolutionary relationships. One possible mechanism for the observed maternal inheritance of mtDNA is simple dilution upon fertilization because an egg is so much larger than a sperm. However, several studies have provided evidence that an active process may be involved in eliminating paternal mtDNA after fertilization. Nishimura and colleagues have now directly monitored what happens to the mtDNA in male Japanese medaka fish (*Oryzias latipes*) by fluorescence spectroscopy. They showed that the number of mtDNA-protein bodies, known as mitochondria nucleoids, is reduced approximately five-fold during the sperm maturation process. In addition, using mtDNA polymorphism as a marker to distinguish paternal and maternal mtDNA, they showed that paternal mtDNA is no longer detectable by PCR 30–105 min after fertilization of the egg, suggesting that paternal mtDNA is actively degraded. This interpretation is further supported by single–sperm cell analysis facilitated by optical tweezers. Notably, the integrity of the paternal mitochondria does not seem to be affected during this period of time, suggesting that paternal mtDNA is digested well before the destruction of the mitochondrial structures. Further studies are now necessary to identify the signals triggering DNA digestion in the paternal mitochondria and the enzymes that are responsible for the degradation reaction. (*Proc. Natl. Acad. Sci. USA* Early Edition, 23 January 2006, doi:10.1073/pnas.050691120) *HPF*

Research highlights written by Hwa-ping Feng, Maria Hodges, Michelle Montoya and Tracy Smith Schmidt.

How proteins evolve

Multistep gene rearrangement is often cited as a likely route for the evolution of new protein topologies, especially in protein families that are related by circular permutation, such as the DNA methyltransferases. However, in such a process it is not clear whether new folds could easily emerge without sacrificing function, or in other words, whether numerous intermediates along the proposed evolutionary pathway would be active enough for viability. A recent study explores this issue by focusing on one frequently suggested mechanism of evolution for the methyltransferase superfamily: gene duplication, in-frame fusion and truncation of the 5′ and 3′ ends. Tawfik and colleagues performed a directed evolution experiment starting with a HaeIII methyltransferase gene library and selected for enzyme activity *in vivo*. They were able to find many genes with duplications and truncations that retained methylation capability. Most of the clones identified corresponded to putative evolutionary intermediates that one might expect to have led to known distinct classes of methyltransferase proteins. However, one set of active sequences did not correspond to any previously identified class of methyltransferase. In this group of isolates, the protein's target-recognition domain was split, with part of the domain found at the N terminus and the remainder of the domain at the C terminus of the protein. They used this set of sequences for homology searches and subsequently identified new methyltransferases in three species of bacteria, enzymes that might have gone unrecognized without considering the permutation-by-duplication evolutionary framework. (*Nat. Genet.* **38**, 168–174, 2006) *TSS*

Processing orders

The anaphase-promoting complex/cyclosome (APC), a ubiquitin ligase, is the central coordinator of cell-cycle progression in mitosis and G1. It achieves this by targeting key cell-cycle regulators for proteasomal degradation through the addition of a chain of ubiquitin molecules. These regulators must be destroyed in the correct order, a process known as substrate ordering. How the APC decides which substrate to modify, and when, has been something of a mystery. Kirschner and colleages now show that the timing of a substrate's degradation is tightly linked to its processivity. A processive substrate can be multiubiquitinated in a single APC binding event, whereas distributive substrates often require multiple rounds of APC binding. The authors find that processive substrates, like the G1 proteins securin and geminin, are degraded more rapidly than distributive substrates, like cyclin A. Additional data suggest that the D box, a sequence motif found in APC substrates that promotes recognition by the APC, is required for effective processive multiubiquitination. The authors suggest that the multiple APC binding events required for multiubiquitination of distributive substrates makes them prone to deubiquitination and forces them to compete with more processive substrates, resulting in delayed degradation. (*Cell* **124**, 89–103, 2006) *MH*