RNA interference : OFF switch for gene expression in eukaryotes

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The central dogma of molecular biology is the flow of genetic information from DNA to RNA (transcription) and from RNA to protein (translation). In eukaryotes (organisms with a nucleus), post-transcriptional gene regulations are interesting and mysterious events. This short review focuses on post-transcriptional regulations mediated by double-stranded RNA (dsRNA).

RNA interference (RNAi)

RNAi is a form of sequence-specific gene silencing induced by the introduction of dsRNA. The ability of dsRNA to induce silencing was first discovered in the nematode *C. elegans* [1], and similar events have since been observed in a variety of eukaryotes.

Technological aspect

RNAi is a physiological response useful for experimental control of gene expression.

The application of RNAi began at basic researches in *C. elegans*, *Drosophila* (fly), plants, *Trypanosoma* (protist), etc. In these organisms, long dsRNA (roughly > 500 base pairs) is commonly utilized for the silencing experiment. There are several methods of introducing dsRNA into organisms. *In vitro*-synthesized dsRNA can be introduced by micro-injection, feeding or transfection. Alternatively, scientists can make transgenic organisms that express dsRNAs from transgenes.

By contrast, the introduction of long dsRNA causes non-specific harmful effects in mammalian cells. In order to avoid this problem, RNAi experiments in mammalian systems are now performed with small RNAs mimicing an intermediate dsRNA in RNAi [2] or precursors of micro-RNAs.

Mechanism

RNAi results in a reduction in the steady state level of the targeted endogenous mRNA. In animals, major steps in the RNAi response are thought to occur at a post-transcriptional level. The mechanisms of RNAi and related post-transcriptional gene silencing (PTGS) have been aggressively studied.

In several model organisms including *C. elegans* [3], scientists screened for mutants whose RNAi/PTGS responses are defective. These genetic screens have identified some important genes required for RNAi/PTGS.

An interesting discovery was that plants exhibiting PTGS contain small RNAs, about 25 nucleotides (nt) length, derived from the sequence of the silenced gene [4]. This small RNA appears to be a key of RNAi/PTGS. Subsequent studies in *Drosophila* have shown that the introduced dsRNAs are processed by a ribonuclease III activity and converted into small RNAs (small interfering RNAs; siRNA) [5, 6]. The siRNAs are incorporated into a complex termed RNA-induced silencing complex (RISC), and the RNA-protein complex is thought to recognize and destruct the target mRNA [7]. Additionally, RNA-dependent RNA polymerase (RdRP) activities seem to be required for

RNAi/PTGS responses in some (but not all) organisms.

Physiological aspect

Viruses and transposons (mobile elements) are parasites rich in nucleic acids. Viruses shuttles between hosts and the environment, and transposons can mobilize within each individual cell of hosts. Studies in plants have suggested that the PTGS response is similar to an anti-viral response. Somewhat similarly, a portion of the RNAi machinery appears to overlap with a mechanism of transposon silencing in *C. elegans*.

There is another intersection. RNAi pathways share features with a developmental gene regulatory pathway that involves natural dsRNA encoding genes, recently named micro-RNA (miRNA) genes. Natural miRNA genes encode RNA products (about 70 nt) which are predicted to fold into stable stem-loop structures that are processed into mature miRNAs (about 22 nt). RNA-protein complexes containing the mature miRNAs are thought to inhibit translation of the target mRNA in animals or destruct the target mRNA in plants.

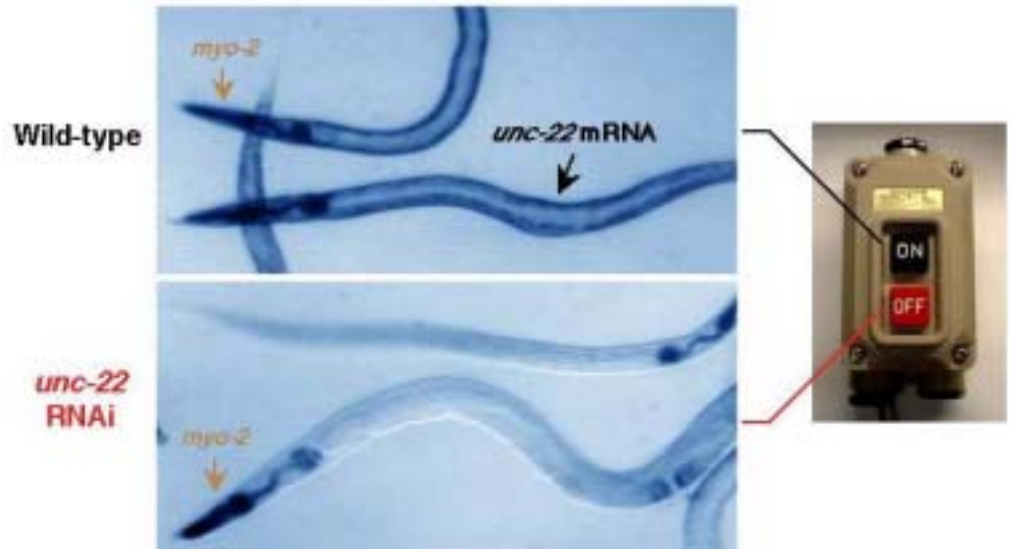

Figure 1. The introduction of dsRNA causes a reduction in the level of target mRNA. Nematodes were treated with a dsRNA homologous to a muscle-expressed gene (*unc-22*). The expression of *unc-22* mRNA was analyzed with *in situ* hybridization.

References in this review

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