A Is For . . .

RNA Silencing

RNA silencing *An antiviral defense mechanism, common to plants and animals, that recognizes and destroys copies of foreign double-stranded RNA; also termed RNA interference.*

In a 1990 review, Richard Jorgensen wrote of his attempts to alter flower color in petunias by introducing exogenous transgenes. Instead of intensifying the color, however, what happened was that the flowers showed variegated pigmentation or no pigmentation at all.

The inference from this was that not only were the transgenes inactive, but somehow the introduced DNA sequences also affected expression of endogenous genes. The phenomenon was termed co-suppression.

A few years later, plant researchers began to report that plants respond to replicating RNA viruses by targeting viral RNAs for destruction. It was soon observed that an engineered virus (replicon) containing DNA sequences homologous to endogenous genes could induce silencing of the endogenous genes at a post-transcriptional level.

Independent studies in animals and fungi described similar systems, which led to the recognition that all were based on the same essential mechanism, now called RNA interference or RNA silencing. To date, the most useful outcome of this understanding has been the ability to rapidly survey gene functions by shutting off genes one at a time.

How RNA silencing operates in an organism is still obscure, but there are some clues. First, the “foreign” RNA must be double-stranded. This may constitute a signal that a foreign or aberrant element is spreading through the genome.

Second, experiments suggest that double-stranded RNA is cut into short segments by an unidentified enzyme that acts independently of the base-pair sequence. The enzyme, referred to as “Dicer,” produces multiple short interfering RNAs (siRNA).

Each of the siRNA joins a multicomponent nuclease (RNA-induced silencing complex, RISC) which becomes activated by unwinding the RNA duplex. This complex then recognizes and binds other mRNA through sequence complementarity and can potentially cleave the mRNA. Furthermore, through various means, including recycling of the siRNA or synthesis of secondary copies, the effect is amplified.

As in clonal selection in vertebrate immune systems, such amplification is key to the effectiveness of RNA silencing in suppressing foreign genetic elements, so that exposure to only a few molecules of dsRNA triggers a widespread effect. In plants and invertebrates, moreover, the process can clearly spread from cell to cell.

It has become clear that RNA silencing is an ancient mechanism, having appeared before the divergence of plants and animals, to protect the organisms’ genetic code. Transposable elements constitute 45% of the human genome, so the interplay of transposons and RNA silencing has helped shape the structure of the genome itself.

Recent analyses suggest RNA silencing also may have integral functions in regulating endogenous genes.

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