10-YEAR ANNIVERSARY

Keeping genes quiet

RNA interference (RNAi), the use of double-stranded RNAs (dsRNAs) to inhibit the expression of specific genes, had been successfully used in various organisms, including plants and invertebrates, but it was not thought to work in mammals. This is because the introduction of dsRNAs longer than 30 nucleotides activates the interferon response, which mediates the general degradation of RNAs by activating RNase L. However, a study by Tuschl and colleagues in 2001 showed, for the first time, that genes can be effectively silenced by RNAi in mammalian cell lines.

To assess whether RNAi can be used in mammals, the authors transfected different cells lines with luciferase reporter genes together with 21- or 22-nucleotide small interfering RNAs (siRNAs) that were specific for the reporter genes. The expression of the reporter genes was inhibited by the siRNAs in a sequence-specific manner, albeit at lower levels than was observed in transfected *Drosophila melanogaster* cells. The introduction of longer (50–500 bp) dsRNAs specific for the reporter genes also induced sequence-specific gene silencing, but this could only be detected when taking into account the non-specific effects of silencing mediated by the interferon response. Together, these results indicated that RNAi is effective in mammalian cells, but the silencing effect of longer dsRNAs is difficult to detect *in vivo*.

So can RNAi be used to inhibit endogenous RNAs? Although not effective for suppressing vimentin, possibly owing to using a non-optimal-sequence siRNA, the introduction of cognate siRNAs for lamin A/C, lamin B and nuclear mitotic apparatus protein successfully decreased their expression. This confirmed that RNAi is not an oddity specific to plants and invertebrates, but can also be used in mammalian cells to rapidly inhibit gene expression. As a result, RNAi is today one of the most widely used tools to study gene function.

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“RNAi ... can also be used in mammalian cells to rapidly inhibit gene expression.”

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