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Short hairpins to silence genes

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Endogenous genes could soon be 'silenced' by engineered strands of hairpin-shaped RNA, giving hope for a novel approach in the treatment and prevention of disease. In the April 15 issue of Genes and Development, Patrick Paddison and colleagues from Cold Spring Harbor Laboratory, New York, hijacked a natural cellular mechanism by driving the expression of short strands of RNA that will form hairpins once transcribed; the hairpins then block the activity of specific genes in *Drosophila,* mouse and human cells.

The use of RNA to interfere with gene expression has become a growth industry since the finding that injecting double-stranded RNA corresponding to a specific gene into a nematode blocked the activity of the gene; this relies on an enzyme that encounters the RNA and breaks it up into smaller pieces that act as small-interfering (si) RNAs. A complex of proteins then gathers up the siRNAs and destroys any RNA in the cell with a matching sequence, including messenger RNA from the corresponding gene, thus 'silencing' the targeted gene.

The production of long double-stranded RNAs can lead to cell death, however, and short RNAs are sometimes unstable. So, Paddison *et al.* developed short hairpin RNA (shRNA) sequences to silence specific genes - inspired by findings in worms that showed some genes are naturally regulated by a similar mechanism. They observed that a variety of genes in normal and cancer cell lines could be silenced using this method. In addition, transgenic cells with genes coding for the relevant shRNA can be created, producing lines of cells with long-lasting gene silencing.

"In many cases, this strategy could translate from benchtop, to animal model, to clinic much more quickly than traditional medicinal chemistry," said Greg Hannon, lead researcher.

"There hasn't been a tool this sharp in a long time", Doug Conklin, a member of the team concluded.

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