IN THE NEWS

Human clones imminent?

"Two renegade fertility specialists yesterday unveiled plans to clone a human embryo within a month and predicted the world's first cloned baby would be born next year" (*The Guardian*). The fertility specialists in question are Severino Antinori and Panayoiotis Zavos, who made their announcement on 7 August at the US National Academy of Sciences (NAS) in Washington. The news comes eight days after the US House of Representatives voted to ban all human cloning and, although the decision has to be approved by the Senate before the ban becomes law, the reaction of the scientific community to yesterday's announcement might influence the Senate's vote. Ian Wilmut, who led the team that cloned Dolly the sheep, warned **"Expect the same outcome in humans as in other species: late abortions, dead children and surviving but abnormal children"** (*BBC News*), whereas others **"denounced [human reproductive cloning] as dangerous and immoral"** (*The Guardian*). Dr Antinori — made famous by helping a 62-year-old woman to have a baby — plans to carry out the human cloning in a secret Mediterranean location. **"Cloning will help us put an end to so many diseases, give infertile men the chance to have children. We can't miss this opportunity,"** he said (*BBC News*). Dr Boisselier, the director of Clonaid — a company that might have already experimented with human cloning — believes that **"It is our own choice to use our genes the way we want to"** (*The New York Times*). Despite the vetoes from the scientific and ethical communities, the NAS panel was told that **"the cloning would go on, regardless of whether […] any country makes it a crime"** (*The New York Times*).

Magdalena Skipper

GENE EXPRESSION

Dicing with development

The advantages of double-stranded RNA (dsRNA)-mediated interference (RNAi) as a tool for knocking out genes are well known, but its biological function remains a mystery. Now two research teams might have solved part of this mystery by discovering that the enzyme Dicer — a type III RNase, which cleaves dsRNAs into small, 22-nucleotide (nt) RNAs (siRNAs) that are thought to mediate RNAi — also generates short, single-stranded RNAs that regulate development.

In *Caenorhabditis elegans*, small temporal (st)RNAs — encoded by *let-7* and *lin-4* — are 22 nt long and are cleaved from a larger precursor RNA that probably adopts a stem–loop structure. They regulate stage-specific development by binding to the 3′ untranslated regions (UTRs) of their target RNA transcripts to repress their translation. Although previous work in plants and *Drosophila* had identified the developmental phenotypes associated with *Dicer-* and *rde-1-* related genes (*rde-1* mutants don't respond to RNAi), no dsRNAs or small RNAs that might function in these developmental pathways had been identified. Because the processing of stRNA precursors in *C. elegans* resembles the processing of dsRNAs that mediate RNAi, Grishok and colleagues looked for homologues of genes in the RNAi pathway in worms and screened them for developmental phenotypes similar to *lin-4* and *let-7*. The authors found that inhibition of two genes closely related to *rde-1* — *alg-1* and *alg-2* — as well as inhibition of the *C. elegans Dicer* homologue *dcr-1*, resulted in phenotypes similar to those of *lin-4* and *let-7* mutants.

To test whether *alg-1*, *alg-2* and *dcr-1* act by targeting *lin-4* and *let-7*, the authors constructed reporter genes that contained the 3′ UTR of two genes — *lin-14* and *lin-41* — that are repressed by *lin-4* and *let-7*, respectively. Grishok *et al.* reasoned that if knocking down *alg-1*, *alg-2* or *dcr-1* prevented *lin-4* and *let-7* maturation, then reporter expression would be upregulated. Indeed, RNAi knockdown of *dcr-1, alg-1* and *alg-2* led to the upregulation of reporter gene expression, indicating that *lin-4* and *let-7* stRNAs were either not produced or were not functional. Furthermore, mutations in *lin-14* and *lin-41* suppressed *dcr-1*, *alg-1* and *alg-2* phenotypes, and the 70-nt RNA precursors of *let-7* and *lin-4* accumulated in worms injected with *dcr-1* dsRNA — only the *lin-4* precursor accumulated in *alg-1* and *alg-2* RNAi mutants.

Hutvágner and colleagues focused on *let-7* in their study, and having identified its RNA precursor, they showed that it is processed into a mature stRNA in *Drosophila* embryo lysates. Importantly, they found that the ends of the processed *let-7* stRNAs have a structure that is indicative of RNase-III-type cleavage — consistent with the involvement of Dicer in this processing. They also showed that *let-7* processing in *Drosophila* embryo lysates is ATP dependent, just like Dicer-dependent dsRNA cleavage.

As *Dicer* mutants are not yet available in *Drosophila*, the authors knocked down the human homologue of *Dicer* in HeLa cells by using recently reported siRNAs (see Highlights, July 2001). On doing so, they detected lower levels of mature *LET7*, accompanied by an accumulation of its precursor RNA.

So, *Dicer* lies at the intersection of the stRNA and the RNAi pathways, but downstream of *Dicer* the two pathways diverge — in *C. elegans*, the RNAi pathway involves *rde-1*, whereas the stRNA pathway involves *rde-1* homologues *alg-1* and *alg-2*. Despite some similarities, the two pathways are quite different: in RNAi, dsRNAs prevent gene expression by marking their targets for degradation, whereas single-stranded stRNAs regulate translation of their targets. Future work might unveil the molecular mechanisms that underlie these differences.

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References and links

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FURTHER READING Rougvie, A. E. Control of developmental timing in animals. *Nature Rev. Genet.* **2**, 690–701 (2001)

WEB SITES Craig Mello's lab | Phillip Zamore's lab

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