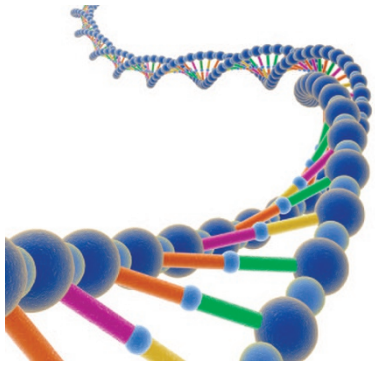
Monkeying with monkey genes

Advances in genome-editing techniques have enabled researchers to create specific genetic modifications in laboratory animals such as mice, rats, fruit flies and zebrafish. This is often done to create models of human diseases that can be studied to learn about their etiology, pathology and mechanisms and to test potential therapeutic strategies. But many human diseases can be appropriately modeled only in primates, and, until recently, genome editing in primates has been largely unsuccessful as well as prohibitively expensive, with the only reported successes in generating transgenic primates achieved by using the technique of virus-mediated gene transfer. The viral vector strategy lacks the efficiency and precision required for broad utility, however. Now, researchers led by Weizhi Ji of the Yunnan Key Laboratory of Primate Biomedical Research (Kunming, China) have successfully applied two advanced genome-editing techniques in monkeys, producing cynomolgus macaques with targeted genomic modifications.

The first technique, dubbed the CRISPR/Cas9 system, uses short RNA sequences to direct gene editing, enabling alterations at the single-base-pair level. Ji's team disrupted two target genes simultaneously in macaque embryos by co-injecting the embryos with Cas9 mRNA and guiding RNA. The embryos were transferred to surrogate female macaques, resulting in 10 pregnancies, one of which was later miscarried. At the time the report was published, one female had delivered twin female offspring at full term by caesarean section and the remaining eight females were mid-gestation. Preliminary analyses of tissues from the infant monkeys showed that the CRISPR/Cas9 system resulted in site-specific gene modification with no off-target effects (*Cell* **156**, 836–843; 2014). Further analyses will be forthcoming when the remaining infants are delivered and when the transgenic monkeys reach adulthood.

Ji's team also investigated the use of the TALEN system in editing macaque genomes. This technique uses special nucleases to bind and cut DNA at a specified genomic location, creating specific mutations. In this case, the targeted gene encodes methyl-CpG binding protein 2 (*MECP2*), mutations of which are



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associated with Rett syndrome, an X-linked disorder that affects human females. Six surrogate females became pregnant after transfer of modified embryos, and one female infant was born and had reached 4 months of age at the time the report was published (*Cell Stem Cell*, **14**, 1–6; 2014). Successful *MECP2* mutagenesis with no off-target effects was reported.

Together, the studies' results show that *in vivo* genome editing is possible in nonhuman primates, which may enable the development of better models of human diseases.

Monica Harrington

LIFESPANS PREDICTED IN A FLASH

A new study suggests that an organism's lifespan is predictable at early adulthood by looking at the activity of its cells' mitochondria.

Mitochondria are the organelles that supply energy to the cell. During energy production, mitochondria produce reactive oxygen molecules, such as free radicals, that can cause stress and damage the mitochondria. It was recently discovered that mitochondria sometimes produce these reactive oxygen molecules in short, repeated bursts; these are called mitoflashes.

Meng-Qui Dong and his colleagues at the National Institute of Biological Sciences in Beijing, China, visualized the mitoflashes produced by mitochondria in *Caenorhabditis elegans* by targeting the energy-producing organelles with a fluorescent protein that glows yellow when viewed under a microscope. In regular worms, two mitoflash bursts occurred: one during the worms' egg-laying period in early adulthood and one during senescence.

The team compared mitoflash rates in two mutant *C. elegans* strains, one with a shorter lifespan, lasting 21 d on average, and the other with a longer lifespan, lasting 30 d or more on average. Remarkably, the pace of mitoflashing in the first mitoflash burst was found to correlate with lifespan in the worms. The shorter-lived worms had more frequent mitoflashes than the longer-lived worms (*Nature* doi:10.1038/nature13012; published online 12 February 2014).

Recognizing that aging is determined not only by genetic factors but also by environmental factors, the researchers next gave different groups of worms various treatments that have been shown to alter the lifespan of *C. elegans*. Conditions that extend the lifespan of the worms, such as exposure to heat shock or starvation, resulted in less frequent mitoflashes during the early-adulthood burst. And conditions that reduce the lifespan of the worms, such as treatment with substances that increase production of reactive oxygen molecules, resulted in more frequent mitoflashes. These results suggest that the bursts of activity in the mitochondria of the worm's cells can accurately predict how long the worm will live. "Mitochondrial flashes have an amazing power to predict the remaining lifespan in animals," Dong told *Nature News*.

A common theory suggests that mitochondria are the biological clock that drives aging. In addition to supplying energy to cells, mitochondria are also involved in cell death and the control of the cell cycle and cell growth. The findings of this study certainly support that theory by demonstrating the intricate link between mitochondrial activity and lifespan. Said Dong, "There is truth in the mitochondrial theory of aging."

Kara Rosania