Gene invaders are stymied by a cell's genome defense

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Gene wars rage inside our cells, with invading DNA regularly threatening to subvert our human blueprint. Now, building on Nobel-Prize-winning findings, UC San Francisco researchers have discovered a molecular machine that helps protect a cell's genes against these DNA interlopers.

The machine, named SCANR, recognizes and targets foreign DNA. The UCSF team identified it in yeast, but given the similarity of yeast and human cells, comparable mechanisms might also be found in humans, where they might serve to lower the burden of inherited human disease and death, the researchers said.

The targets of SCANR are small stretches of DNA called transposons, a name that conjures images of alien scourges. But transposons are real, and to some newborns, life threatening. Found inside the genomes of organisms as simple as bacteria and as complex as humans, they are in a way alien—at some point, each was imported into its host's genome from another species.

Unlike an organism's native genes, which are reproduced a single time during cell division, transposons—also called jumping genes—replicate multiple times, and insert themselves at random places within the DNA of the host cell. When transposons insert themselves in the middle of an important gene, they may cause malfunction, disease or birth defects.

But just as the immune system has ways of distinguishing what is part of

the body and what is foreign and does not belong, researchers led by UCSF's Hiten Madhani, MD, PhD, discovered in SCANR a novel way through which the genetic machinery within a cell's nucleus recognizes and targets transposons. The study was published online February 13 in the journal *Cell*.

"We've known that only a fraction of human inherited diseases are caused by these mobile genetic elements," Madhani said. "Now we've found that cells use a step in gene expression to distinguish 'self' from 'non-self' and to halt the spread of transposons."

Gene Wars Span Eons

Transposons have been barging into genomes and crossing species boundaries throughout evolution. Rapidly evolving bacterial species often use them to transmit antibiotic resistance to one another.

Nearly half of the DNA in the human genome consists of transposons, and the percentage can potentially creep upward with every generation. That's because nearly 20 percent of transposons are capable of replicating in a way that is unconstrained by the normal rules of DNA replication during cell division—although through generations over time, most have become inactivated and no longer pose a threat.

While humans are riddled with transposons, compared to some organisms they've gotten off easy, according to Madhani, a professor of biochemistry and biophysics at UCSF. The water lily's genome is 99 percent derived from transposons. The lowly salamander has about the same number of genes as humans, but in some species the genome is nearly 40 times bigger, due to all the inserted, replicating transposons. To accommodate this DNA, a salamander's cells are large in comparison to a human's cells.

The scientists' discovery of SCANR and how it targets transposons in the yeast Cryptococcus neoformans builds upon the Nobel-Prize-winning discovery of jumping genes by maize geneticist Barbara McClintock, and the Nobel-prize-winning discovery by Richard Roberts and Phillip Sharp that parts of a single gene may be separated along chromosomes by intervening bits of DNA, called introns. Introns are transcribed into RNA from DNA but then are spliced out of the instructions for building proteins.

In the current study, the researchers discovered that the cell's splicing machinery stalls when it gets to transposon introns. SCANR recognizes this glitch and prevents transposon replication by triggering the production of "small interfering RNA" molecules, which neutralize the transposon RNA. The earlier discovery by Andrew Fire and Craig Mello of the phenomenon of RNA interference, a feature of this newly identified transposon targeting, also led to a Nobel Prize.

"Scientists might find that many of the peculiar ways in which genes are expressed differently in higher organisms are, like intron splicing in the case of SCANR, useful in distinguishing and defending 'self' genes from 'non-self' genes," Madhani said.

Provided by University of California, San Francisco