'Sloppier copier' surprisingly efficient

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The "sloppier copier" discovered by USC biologists is also the best sixth man in the DNA repair game, an article in the journal *Nature* shows.

The enzyme known as DNA polymerase V (pol V) comes in when a cell's DNA is reeling from radiation damage or other serious blows. Pol V copies the damaged DNA as best it can - saving the life of the bacterial cell at the cost of adding hundreds of random mutations.

The July 16 *Nature* study reveals pol V's key attributes: economy of motion and quickness to engage.

The study also solves two other stubborn mysteries about the mechanics of DNA repair: the exact composition of the active form of pol V and the crucial role of a protein filament, known as RecA*, that is always present around DNA repair sites, but was never shown to be directly involved.

The three findings together describe an exquisitely efficient process.

"It's a beautiful mechanism for how cells conserve energy," said first author Qingfei Jiang, a graduate student of senior author Myron Goodman, professor of biological sciences and chemistry at USC College.

Cells multiply by division, which starts with the copying of DNA. Pol V kicks in when a section of damaged DNA baffles the enzymes normally involved in copying.

In experiments with E. coli, Jiang and Goodman showed that the activation signal for pol V is the transfer to the enzyme of two key molecules from RecA*.

RecA* is a nucleoprotein filament: a long line of proteins bound to single-stranded DNA. The molecules that RecA* transfers to pol V are ATP, the energy factory of the cell, and a single RecA* protein among the many that make up the filament.

The copying of damaged DNA is formally called "translesion synthesis," or TLS.

"What is RecA* doing?" had been a vexing question in the field for two decades, since the discovery that the filament was necessary for DNA repair. No one, however, could figure out why.

Goodman's group showed that the role of RecA* is limited but direct: It is needed to donate molecules to activate pol V, but it does not participate in damage-induced DNA copying and does not even need to be next to the repair site.

Instead, RecA* acts as a fuel station to put pol V to action.

With the two extra molecules attached, pol V copies the damaged DNA. As soon as it reaches the end of the damaged section, it falls off and immediately deactivates.

Pol V then waits to be called again.

In addition to saving energy, the process prevents the mistake-prone copier from trying to "repair" normal DNA.

"All the other DNA polymerases [enzymes], when they copy DNA, they

go first from one and then to another DNA and copy it. Not this baby. It has to be reactivated," Goodman said.

"It's a utility player. It's the guy who does the tough jobs."

He added that the discovery "explains one of the key ways that you get mutations when you damage DNA."

Human cells use similar enzymes, Goodman said.

The study of mutations holds fundamental relevance for medicine, evolutionary biology, aging research and other fields.

Goodman's research group discovered pol V in 1999. The "sloppier copier" nickname, coined by USC science writer Eric Mankin, has since been adopted widely.

At the time, Goodman described pol V as a "last-ditch cell defense" that averts death at the cost of frequent copying mistakes, which show up as mutations in the cell's DNA.

Ironically, the sloppier copier may do more for the long-term success of the species than its accurate cousins. Some of the accidental mutations are likely to be helpful. Cells with those mutations will adapt better to their environment, and the mutations will spread through the species by natural selection.

Source: University of Southern California (news : web)

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