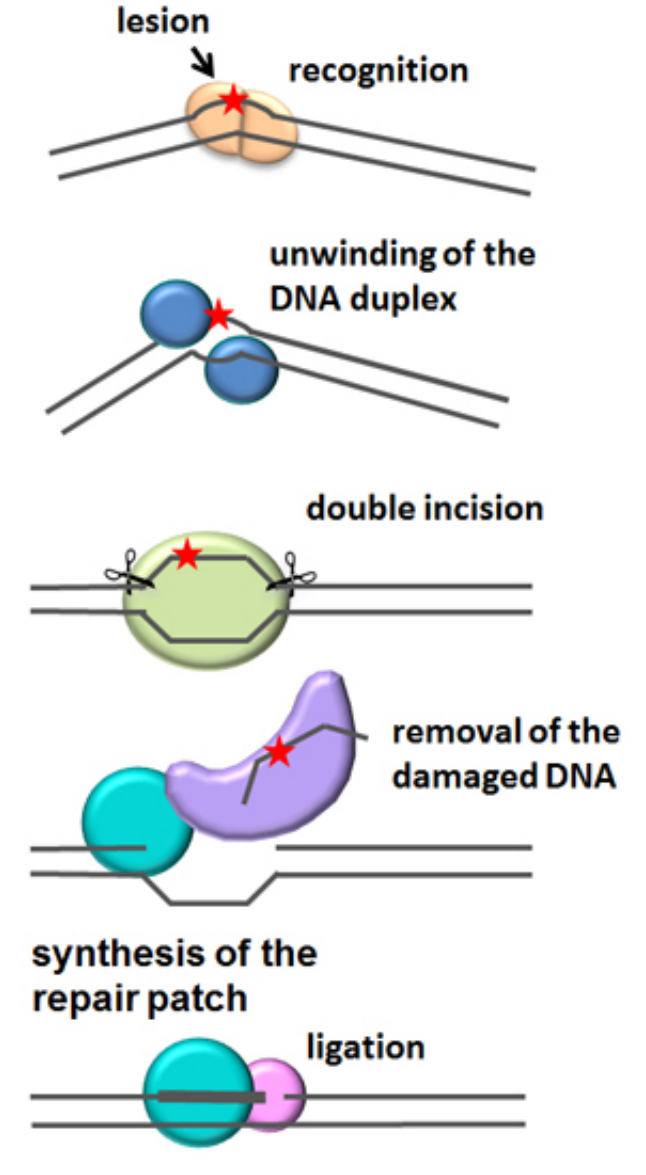
Repair of damaged genetic material in humans

Living organisms across the evolutionary scale protect their genetic material (DNA) by repairing the constant threat of damage posed by environmental radiations, toxic chemicals, and byproducts of cellular metabolism. In the early 60s, Setlow and Howard-Flanders at Yale University found that lesions in DNA were removed, while Hanawalt at Stanford University observed that new DNA was made in damaged cells; these discoveries revealed the ubiquitous pathway of nucleotide excision repair (NER). There are additional repair pathways that deal with specialized types of damage like oxidized bases, DNA strand breaks and crosslinking of DNA strands, discovered in later years.



The serial steps in NER, illustrated in figure, are similar in organisms from unicellular bacteria to

complex mammals and plants, and involve recognition of lesions, adducts or other disruptions of the DNA double helix. The DNA is opened up around the lesion; specialized enzymes called endonucleases then cut the damaged DNA strand on both sides of the lesion, and enzymes called helicases remove the short stretch of DNA containing the damage. Enzymes that make DNA, called DNA polymerases, synthesize a repair patch copying the opposite undamaged strand as a template, and ligases (enzymes that glue DNA ends together) seal the end of the new patch to the existing strand, to restore the DNA to its original form.

NER plays an important role in protecting us against the consequences of persisting DNA lesions, which may cause cell death when DNA polymerases that replicate DNA in dividing cells collide with those lesions. Special translesion synthesis (TLS) polymerases can synthesize DNA containing damage, allowing replication to proceed uninterrupted. However, avoiding cell death can be costly: these TLS polymerases often introduce errors in the DNA sequence, resulting in changes (mutations) in the DNA code that can cause cancer, accelerated aging, and other health problems. For example, patients suffering from the hereditary disease, xeroderma pigmentosum, have mutations in genes that code for enzymes in NER, or a defective TLS polymerase; they are extremely sensitive to sunlight and very likely to develop multiple skin cancers in sun-exposed areas.

Transcription is the process by which the information encoded in DNA is copied to RNA, which carries the message that is used to make proteins. Transcription can be arrested when the DNA is damaged. In the 1980s the Hanawalt laboratory discovered the transcription-coupled repair (TCR) subpathway of NER, dedicated to the removal of lesions from the template DNA strands of actively transcribed genes in all types of cells. This process may protect the information needed to make proteins in cells that have undergone terminal differentiation; these cells, like neurons and mature muscle cells are so specialized that they have lost the ability to proliferate. The overall NER efficiencies in terminally differentiated cells are generally very low in much of the DNA. However, active genes are still repaired by TCR, protecting the genetic information so that transcription can proceed without interruptions or mistakes. TCR also helps to quickly remove lesions that are otherwise repaired slowly and could interfere with DNA replication, causing cell death.

Most of the DNA lesions that are recognized by NER are considered strong mutagens and carcinogens. Ironically, agents that induce these lesions are regularly used in chemotherapy to treat cancer; a problem often found is that the highly mutable tumor cells develop resistance to the drugs. A strategy for overcoming drug resistance combines two or more drugs, for example cisplatin to damage DNA and an NER inhibitor drug to prevent the repair of the lesions. Further studies of NER will yield faster and better therapies.

Publication

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