KUNGL. VETENSKAPS-AKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES

The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry 2015 to **Tomas Lindahl, Paul Modrich** and **Aziz Sancar** "for mechanistic studies of DNA repair".

The Nobel Prize 2015 **in Chemistry**

The cell's toolbox for DNA repair

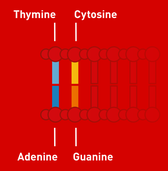
From one cell to another, from one generation to the next. The genetic information that governs how human beings are shaped has flowed through our bodies for hundreds of thousands of years. It is constantly subjected to assaults from the environment, yet it remains surprisingly intact. Tomas Lindahl, Paul Modrich and Aziz Sancar are awarded the Nobel Prize in Chemistry 2015 for having mapped and explained how cells repair DNA and safeguard genetic information.

Every day, our DNA is damaged by UV radiation, oxygen radicals and carcinogenic substances, but the DNA molecule is unstable even without these external attacks. Thousands of spontaneous changes happen in a cell's genetic material every day. In addition, errors occur each time DNA is copied during cell division, which takes place millions of times a day in the human body.

A number of molecular systems ensure that our genetic material does not degrade into chemical chaos by continuously monitoring and repairing DNA. 2015's Nobel Prize in Chemistry honours three pioneers who have mapped the detailed molecular events underlying a number of these repair systems. Their work has provided knowledge about the causes of several inherited diseases, about mechanisms behind ageing and cancer, and given clues to the design of new cancer treatments.

Gigantic molecules form our genetic material

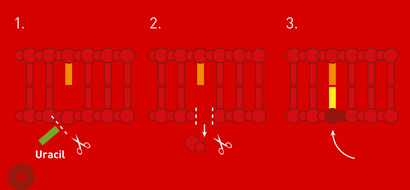
Our genetic material consists of double-stranded DNA, which is built from nucleotides with four different bases. Adenine always pairs with thymine, and guanine with cytosine. Together, they form base pairs. If we were to stretch out all the DNA in the cells of one human body, it would reach to the sun and back about 250 times.



Modrich illustrates mismatch repair

Paul Modrich has shown how the cells correct errors that occur when DNA is copied during cell division. This mechanism, *mismatch repair*, reduces the error frequency in DNA replication by about a thousand-fold. Congenital defects in mismatch repair cause an inherited form of colon cancer, among other things.

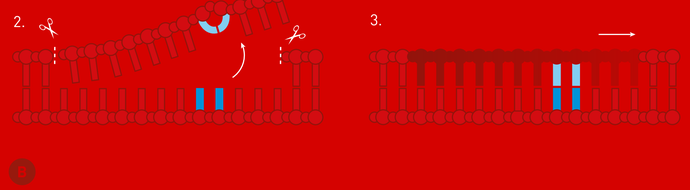
1. The DNA replication machinery has inserted a cytosine where there should be a thymine. The error is discovered by two enzymes, MutS and MutL. Another enzyme, MutH, detects methyl groups on one of the DNA strands. This is the older strand that served as the original during the copying process. This strand, the correct one, is retained, and the new faulty copy is cut.
2. A piece of DNA containing the error is removed.
3. DNA polymerase fills in the gap and DNA ligase seals the DNA strand.



Lindahl discovers that DNA is unstable

In the early 1970s, researchers believed that DNA was an extremely stable molecule, but Tomas Lindahl demonstrated that DNA decays at a rate that should have made life on Earth impossible. This insight led him to the discovery of a molecular machinery, *base excision repair*, which continuously counteracts DNA's collapse.

1. A chemical weakness in DNA is the cytosine base, which may lose an amino group and form uracil that cannot base pair with guanine. An enzyme, glycosylase, detects the error and excises the uracil.
2. Once the base has been removed, other enzymes remove the rest of the nucleotide from the DNA chain.
3. The gap is filled by DNA polymerase and the chain is sealed together by DNA ligase.



Sancar shows how cells repair UV damage

Towards the end of the 1970s, when Aziz Sancar started to investigate how cells repair UV damage, he discovered the mechanism for *nucleotide excision repair*. People who are born with defects in this repair system develop skin cancer if they are exposed to the sun. Nucleotide excision repair may also correct defects caused by hazardous substances, such as those found in cigarette smoke.

1. For example, UV radiation can cause two thymines to bind together incorrectly.
2. The enzymes *UvrA*, *UvrB* and *UvrC* find the damage and cleave the affected DNA strand on each side of the damage. Twelve to thirteen nucleotides are removed.
3. DNA polymerase fills in the gap that has been created and DNA ligase seals the DNA strand so the damage is repaired.

Tomas Lindahl
Swedish citizen. Born 1938 in Stockholm, Sweden. Emeritus group leader at Francis Crick Institute and Emeritus director of Cancer Research UK at Clare Hall Laboratory, Hertfordshire, UK.

Paul Modrich
U.S. citizen. Born 1946 in Raton, NM, USA. Investigator at Howard Hughes Medical Institute and James B. Duke Professor of Biochemistry at Duke University School of Medicine, Durham, NC, USA.

Aziz Sancar
Turkish and U.S. citizen. Born 1946 in Savur, Turkey. Sarah Graham Kenan Professor of Biochemistry and Biophysics, University of North Carolina School of Medicine, Chapel Hill, NC, USA.

FURTHER READING More information on the Nobel Prize in Chemistry 2015: *http://kva.se/nobelchemistry2015* and *http://nobelprize.org* **POPULAR SCIENCE ARTICLES:** ● **Howard Hughes Medical Institute,** Biography Paul Modrich. *www.hhmi.org/scientists/paul-l-modrich* ● **Weston, K.** (2014) Country Life: Repair and Replication, in *Blue Skies and Bench Space: Adventures in Cancer Research.* Long Island, New York, Cold Spring Harbor Laboratory Press. ● **Zagorski, N.** (2005) Profile of Aziz Sancar, *Proc. Nat. Acad. Sci. USA, 102*(45), 16125–16127. **VIDEO:** ● **Howard Hughes Medical Institute** (2003) Mismatch repair. *www.hhmi.org/biointeractive/mismatch-repair* ● **Interview with T. Lindahl** (2015) Cancer Research UK. *www.youtube.com/watch?v=FHInqiEQig0&index=16&list=PL_bJU93S6g0sCs1CQ_eh2o_z7ztU-0kE-* **SCIENTIFIC ARTICLES:** ● **Lahue, R. S., Au, K. G.** and **Modrich, P.** (1989) DNA Mismatch Correction in a Defined System, *Science, 245*(4914), 160–164. ● **Lindahl, T.** (1974) An N-Glycosidase from Escherichia coli That Releases Free Uracil from DNA Containing Deaminated Cytosine Residues, *Proc. Nat. Acad. Sci. USA, 71*(9), 3649–3653. ● **Sancar, A.** and **Rupp, W. D.** (1983) A Novel Repair Enzyme: UVRABC Excision Nuclease of Escherichia coli Cuts a DNA Strand on Both Sides of the Damaged Region, *Cell, 33*(1), 249–260. ● **More references can be found in the Scientific Background:** *http://kva.se/nobelchemistry2015*

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