THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 284, No. 44, Issue of October 30, p. e19, 2009

Printed in U.S.A.

Classics

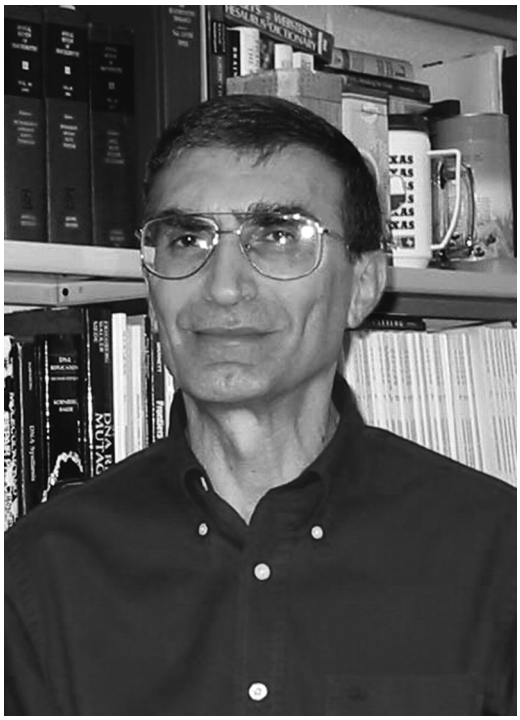
A PAPER IN A SERIES REPRINTED TO CELEBRATE THE CENTENARY OF THE JBC IN 2005

JBC Centennial
1905–2005
100 Years of Biochemistry and Molecular Biology

DNA Repair Mechanisms: the Work of Aziz Sancar

Action Mechanism of *Escherichia coli* DNA Photolyase. III. Photolysis of the Enzyme-Substrate Complex and the Absolute Action Spectrum
(Sancar, G. B., Jorns, M. S., Payne, G., Fluke, D. J., Rupert, C. S., and Sancar, A. (1987) *J. Biol. Chem.* 262, 492–498)

Reconstitution of the Human DNA Repair Excision Nuclease in the Highly Defined System
(Mu, D., Park, C.-H., Matsunaga, T., Hsu, D. S., Reardon, J. T., and Sancar, A. (1995) *J. Biol. Chem.* 270, 2415–2418)



Aziz Sancar

Aziz Sancar was born in Savur, Turkey in 1946. Although both his parents were illiterate, they valued the importance of education and did their best to see that Sancar received a good one. They succeeded, and he excelled in many scientific subjects in high school. However, he also dreamed of playing on Turkey's national soccer team, and this dream almost came true when, as a senior in high school, he was invited to attend tryouts to be a goalie on the national under-18 team. Ultimately he decided not to accept the invitation, later explaining, "upon serious consideration, I decided I wasn't tall enough to be an outstanding goalie, and instead I concentrated on my studies" (1).

After graduating in 1963, Sancar enrolled at Istanbul Medical School with the idea of becoming a doctor. However, after taking a biochemistry class during his 2nd year, he decided to become a research biochemist. Surprisingly, when he discussed his desire to pursue a Ph.D. with his biochemistry professor, he advised Sancar to practice medicine briefly before plunging into research, reasoning that anyone who spends the time getting a medical degree should at least practice for a couple years. So, Sancar spent 2 years as a rural physician near his hometown of Savur.

In 1973, Sancar came to the United States to study with Claud Rupert in the molecular biology department of the University of Texas at Dallas. While in Turkey, Sancar had developed an interest in photoreactivation, the process by which DNA damaged by UV light is repaired by longer wavelength blue light. Rupert had identified photolyase, the enzyme that mediated the process by catalyzing the opening of the cyclobutane ring in pyrimidine dimers, and Sancar was eager to work him. The main topic of study in the Rupert laboratory in the early 1970s was the nature of photolyase's chromophore. To that end, Sancar spent several

years cloning and characterizing the gene for photolyase (2). After finally succeeding, he set out to purify the protein, but Rupert told him he had done enough research for his thesis and advised him to write his dissertation and graduate.

After earning his Ph.D. in 1977, Sancar applied to three different laboratories hoping to continue studying DNA repair. All three laboratories rejected him. However, he learned that Dean Rupp at Yale University was interested in cloning repair genes, and although he didn't have a postdoctoral position available, he was looking for a technician. Sancar accepted the job and joined the lab. Working with Rupp, Sancar identified and cloned several *Escherichia coli* repair genes, including the *uvrA*, *uvrB*, and *uvrC* genes involved in excision repair (3–5). He then purified the three uvr proteins and reconstituted the UVRABC nuclease, which he termed "excision nuclease" or "excinuclease" (6).

In 1982, Sancar left Yale to become an associate professor of biochemistry at the University of North Carolina, Chapel Hill. There he resumed his work on photolyase and discovered that the enzyme contains two chromophores: $FADH^-$ and a pterin (7–9). He also proposed a model for the reaction mechanism of photolyase repair, which is the subject of the first *Journal of Biological Chemistry* (JBC) Classic reprinted here.

At the time the Classic was published, there were two possible mechanisms for the repair reaction: the first involved energy transfer from a sensitizer to pyrimidine dimers, and the second involved electron transfer between the pyrimidine dimer and the photosensitizer. By determining the absolute action spectrum of the enzyme, Sancar and his colleagues were able to determine that the flavin cofactor of the enzyme is fully reduced *in vivo* and that, upon absorption of a single photon in the 300–500 nm range, the photolyase chromophore donates an electron to the pyrimidine dimer causing its reversal to two pyrimidines. Eighteen years after publishing this Classic paper, Sancar was able to capture the excited flavin intermediate and observe the photolyase electron transfer, definitively proving his model (10).

Sancar also continued studying other DNA repair pathways and soon turned his attention to excision repair in humans. The second JBC Classic is a result of Sancar's studies on xeroderma pigmentosum, a hereditary disease caused by a defect in nucleotide excision repair as a result of mutations in one of several genes: XPA through XPG. In the paper, Sancar and his colleagues purified the components known to be required for the incision reaction and reconstituted the excision nuclease activity with these proteins. Using this system, they determined that the excised fragment remains associated with the post-incision DNA-protein complex, suggesting that accessory proteins are needed to release the excised oligomer.

Sancar is currently the Sarah Graham Kenan Professor of Biochemistry and Biophysics at the UNC School of Medicine. He has received many honors and awards in recognition of his contributions to science, including the Presidential Young Investigator Award from the National Science Foundation (1984) and the highest awards from the American Society for Photobiology (1990) and the Turkish Scientific Research Council (1995). Sancar was also the first Turkish-American member of the National Academy of Sciences (2005).

Nicole Kresge, Robert D. Simoni, and Robert L. Hill

REFERENCES

1. Zagorski, N. (2005) Profile of Aziz Sancar. *Proc. Natl. Acad. Sci. U.S.A.* **102,** 16125–16127
2. Sancar, A., and Rupert, C. S. (1978) Cloning of the *phr* gene and amplification of photolyase in *Escherichia coli*. *Gene* **4,** 295–308
3. Sancar, A., Wharton, R., Seltzer, S., Kacinski, B., Clarke, N., and Rupp, W. D. (1981) Identification of the *uvrA* gene product. *J. Mol. Biol.* **148,** 45–62
4. Sancar, A., Clarke, N., Griswold, J., Kennedy, W., and Rupp, W. D. (1981) Identification of the *uvrB* gene product. *J. Mol. Biol.* **148,** 63–76
5. Sancar, A., Kacinski, B. M., Mott, L., and Rupp, W. D. (1981) Identification of the *uvrC* gene product. *Proc. Natl. Acad. Sci. U.S.A.* **78,** 5450–5454
6. 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**, 249–260
7. Sancar, A., and Sancar, G. B. (1984) *Escherichia coli* DNA photolyase is a flavoprotein. *J. Mol. Biol.* **172,** 223–227
8. Jorns, M. S., Sancar, G. B., and Sancar, A. (1984) Identification of a neutral flavin radical and characterization of a second chromophore in *Escherichia coli* DNA photolyase. *Biochemistry* **23,** 2673–2679
9. Johnson, J. L., Hamm-Alvarez, S., Payne, G., Sancar, G. B., Rajagopalan, K. V., and Sancar, A. (1988) Identification of the second chromophore of *Escherichia coli* and yeast DNA photolyases as 5,10-methenyltetrahydrofolate. *Proc. Natl. Acad. Sci. U.S.A.* **85,** 2046–2050
10. Kao, Y.-T., Saxena, C., Wang, L., Sancar, A., and Zhong, D. (2005) Direct observation of thymine dimer repair in DNA by photolyase. *Proc. Natl. Acad. Sci. U.S.A.* **102,** 16128–16132