DNA Polymerase and Leading and Lagging Strand Synthesis: the Work of Bruce Alberts

The Slow Dissociation of the T4 DNA Polymerase Holoenzyme When Stalled by Nucleotide Omission. An Indication of a Highly Processive Enzyme

The Rapid Dissociation of the T4 DNA Polymerase Holoenzyme When Stopped by a DNA Hairpin Helix. A Model for Polymerase Release following the Termination of Each Okazaki Fragment

Bruce Michael Alberts was born in Chicago, Illinois in 1938. His interest in science began in seventh grade when he had to explore the inside of a television set and explain how it worked. This interest was further stoked during his junior year in high school when he had the chance to play with reagents and set off explosions in science class. He recalls, “we could see chemistry as being real. That was quite different from just reading about chemistry” (1). Alberts enjoyed the hands-on aspects of science so much that he decided to pursue a career that involved chemistry. During his high school’s Career Night, he attended lectures by the two speakers who used chemistry in their jobs: a chemical engineer and a physician. The engineer drew dull pictures of pipes and tanks on the blackboard, whereas the physician spoke about the importance of science for medicine. At that point, Alberts decided to become a physician.

However, Alberts’ hopes for explosions and hands-on experiments were dashed when he arrived at Harvard University in 1956 and realized the course work consisted mostly of memorizing facts and performing simple experiments in laboratory sections. Fortunately, he was invited to work in Paul Doty’s laboratory where he discovered that the college science he had been exposed to was not at all like actual science. Working on deciphering how errors in DNA and RNA base pairing affected their helical structure, Alberts was able to publish his results in the Proceedings of the National Academy of Sciences and Nature (2, 3). Suddenly, medical school did not seem as appealing as pure science, and Alberts decided to pursue a doctorate in biophysics at Harvard after graduating in 1960 with an A.B. in Biochemical Sciences.

Working in Doty’s laboratory on DNA replication, Alberts earned his doctorate in 1965. He then spent the following year as a postdoctoral fellow at the University of Geneva with Alfred Tissières and Richard Epstein studying the phage T4 genes involved in DNA replication. In 1966, Alberts joined the Department of Biochemical Sciences at Princeton University as an Assistant Professor. He eventually became Damon Pfeiffer Professor of Life Sciences in 1973 and was the Acting Chairman of the Department of Biochemical Sciences from 1973 to 1974 and the Associate Chairman from 1974 to 1975. In 1976, Alberts left Princeton to become Professor and Vice Chair of the Department of Biochemistry and Biophysics at the University of California, San Francisco. In 1980, he was awarded an American Cancer Society Lifetime Research Professorship, and in 1985, he was named Chairman of the UCSF Department of Biochemistry and Biophysics.

Greatly influenced by his graduate and postdoctoral studies, Alberts’ research has continued to focus on DNA replication. He is noted particularly for his extensive study of the protein complexes that allow chromosomes to be replicated. For example, while at Princeton, Alberts discovered the T4 gene 32 protein. This proved to be the first example of a single-strand
DNA-binding protein, a structural protein that plays an important role in DNA processes in all organisms (4). The two Journal of Biological Chemistry (JBC) Classics reprinted here deal with Alberts’ explanation of how DNA polymerase can replicate both the leading and lagging DNA strands simultaneously.

In the first Classic, Alberts and Kevin J. Hacker use an assay to monitor the rate of dissociation of the T4 DNA polymerase holoenzyme once it has been stalled by nucleotide omission. They find that the half-life of the stalled holoenzyme is similar to that expected for a holoenzyme processively replicating DNA on the leading strand of a replication fork. This suggested that the holoenzyme can sense a difference between being stopped by omission of a nucleotide and being stopped by the end of an Okazaki fragment. From their results, Alberts and Hacker also concluded that ATP hydrolysis by the holoenzyme’s 44/62 proteins serves to load the ring-like 45 protein onto the DNA. Once loaded, the 45 protein, possibly along with the 44/62 complex, acts as a sliding clamp that tethers the DNA polymerase to the template.

In the second JBC Classic reprinted here, Alberts and Hacker examine the mechanism that allows a DNA polymerase holoenzyme to remain on the DNA template for many minutes when synthesizing DNA (or when stopped by nucleotide omission), while permitting rapid dissociation at the end of each Okazaki fragment. To approach this question, they measured the dissociation of the holoenzyme-DNA complex in the presence of a 15-base pair hairpin helix that mimicked an encounter with the end of a previously synthesized Okazaki fragment. They found that the holoenzyme dissociates with a half-life of 1 s after hitting the hairpin helix, as compared to a half-life of 2.5 min when stalled by nucleotide omission. This rate is sufficient to allow efficient polymerase recycling on the lagging strand. Thus Alberts and Hacker concluded that, upon completing each Okazaki fragment, the holoenzyme senses an encounter with duplex DNA and then switches to a state that rapidly dissociates.

In 1993, Alberts became President of the National Academy of Sciences. He served two terms as President, during which time he was instrumental in a number of initiatives that have had fundamental and far-reaching impacts on the shape of science education in the U. S., including the landmark National Science Education Standards that have been implemented in school systems nationwide. Alberts returned to UCSF as a Professor in 2005 and remains there today.
In addition to his research endeavors and tenure as President of the National Academy, Alberts has long been committed to the improvement of science education, dedicating much of his time to educational projects. He has also served in different capacities on a number of advisory and editorial boards, including Chair of the Commission on Life Sciences, National Research Council. Until his election as President of the Academy, Alberts was President-elect of the American Society of Biochemistry and Molecular Biology, and he is currently President-elect of the American Society for Cell Biology. Alberts is also one of the original authors of *The Molecular Biology of the Cell*, widely considered a leading textbook in its field. His most recent text, *Essential Cell Biology* (1998), is intended to approach this subject matter for a wider audience.

In recognition of his many accomplishments, Alberts has received several awards and honors including the Eli Lilly Award in Biological Chemistry from the American Chemical Society (1972), the U. S. Steel Foundation Award in Molecular Biology from the National Academy of Sciences (1975), the Baxter Award for Distinguished Research in the Biomedical Sciences from the Association of American Medical Colleges (1992), and the UCSF Medal (1994). Alberts is a member of the American Academy of Arts and Sciences, the Royal Society of London, and the National Academy of Sciences.¹

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REFERENCES


¹ Biographical information on Bruce Alberts was taken from Refs. 1 and 5.
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