THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 284, No. 46, Issue of November 13, p. e21, 2009

Printed in U.S.A.

Classics

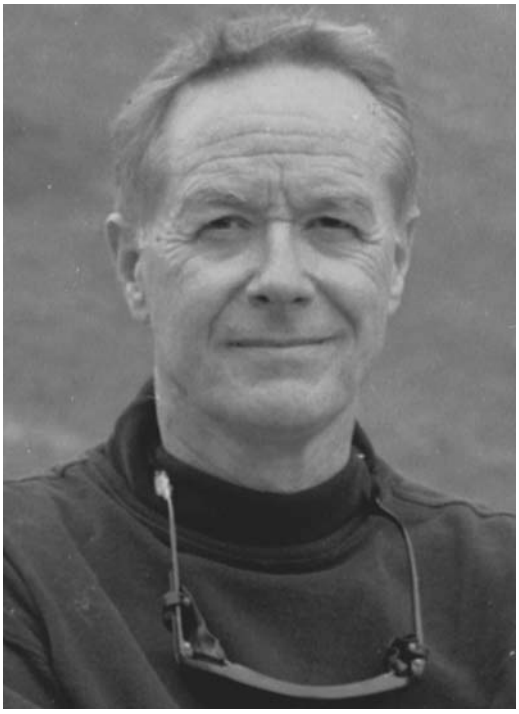
A PAPER IN A SERIES REPRINTED TO CELEBRATE THE CENTENARY OF THE JBC IN 2005

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

Looking at DNA through the Electron Microscope: the Work of Jack Griffith

Electron Microscopic Visualization of the RecA Protein-mediated Pairing and Branch Migration Phases of DNA Strand Exchange
(Register, J. C., 3rd, Christiansen, G., and Griffith, J. (1987) *J. Biol. Chem.* 262, 12812–12820)

Formation of DNA Loop Replication Fork Generated by Bacteriophage T7 Replication Proteins
(Park, K., Debyser, Z., Tabor, S., Richardson, C. C., and Griffith, J. (1998) *J. Biol. Chem.* 273, 5260–5270)



Jack Griffith

Jack D. Griffith was born in Logan, Utah, in 1942. He attended Occidental College in Los Angeles and received his B.A. in physics in 1964. Griffith then enrolled at the California Institute of Technology where he worked with *Journal of Biological Chemistry* (JBC) Classic author James Bonner (1) studying chromosome structure with electron microscopy (EM).

In the late 1960s, scientists were using a technique called metal shadow casting to visualize molecules via EM. The method involved spraying a layer of metal on the molecule. Because the sample was slightly raised, it got coated with more metal than its supporting film, which allowed the molecule's outline to be seen with an electron microscope. A variation on the technique in which the sample was coated with denatured protein was used to visualize DNA. This provided a good way to look at the shape of DNA, but the specific proteins bound to the DNA were obscured by the thick coating. For his Ph.D. work, Griffith developed the EM technology needed to directly visualize bare DNA and DNA-protein complexes. His methods involved carefully controlled rotary shadow casting with tungsten and mounting the DNA on very thin carbon films.

After graduating in 1969, Griffith did a 1-year postdoctoral fellowship with Benjamin Siegel at Cornell University and a 3-year fellowship with JBC Classic author Arthur Kornberg (2) at Stanford University. Using the methods Griffith developed at Caltech, Griffith, Kornberg, and Joel A. Huberman published a paper showing an EM image of *Escherichia coli* DNA polymerase I bound to DNA (3). This was not only the first EM image of DNA bound to a known protein, but it also showed that electron microscopy had the potential to provide quantitative information about macromolecular assemblies involving DNA.

Griffith stayed at Stanford as a research scientist until 1978 when he became an associate professor at the Lineberger Comprehensive Cancer Center and the Department of Microbiology and Immunology at the University of North Carolina at Chapel Hill. At UNC, he designed a research program in which he used EM and biochemical tools to study DNA. The two JBC Classics reprinted here demonstrate some of those studies.

In the first Classic, Griffith and his colleagues investigated the role of the *E. coli* RecA protein in homologous recombination. RecA catalyzes this process by promoting pairing and strand exchange between homologous DNA molecules. The scientists used EM to follow reactions in three homologous DNA pairs: supertwisted double-stranded (ds) DNA and linear single-stranded (ss) DNA; linear dsDNA and circular ssDNA; and linear dsDNA and colinear ssDNA. They found that all three reactions undergo a three-step pathway. First, the RecA protein-ssDNA filament makes contact with a homologous dsDNA (joining). Second, both DNA partners are at least partially enveloped within the nucleoprotein filament, and if the DNA topology is favorable, exchange of DNA strands then ensues (envelopment/exchange). Finally, upon completion of strand exchange, this complex is resolved and the products are released.

In the second Classic, Griffith teamed with JBC Classic author Charles C. Richardson (4) and used EM to examine the architecture of the DNA and DNA-protein intermediates involved in replication reactions employing the T7 replication proteins. This study showed the first direct evidence of the presence of a DNA loop at the replication fork and provided a long sought after proof of the Alberts trombone model of looping of the lagging strand during replication. One of Griffith and Richardson's co-authors on this paper, Stanley Tabor, is the son of long time JBC editor Herbert Tabor.

Griffith remains at the University of North Carolina at Chapel Hill as Kenan Distinguished Professor of Microbiology and Immunology and Biochemistry. He has received many honors and awards for his contributions to science including the Ellison Senior Scholar Award (2001–2005), the ASBMB Herbert A. Sober Award (2002), the Grand Gold Medal of Comenius University, Slovak Republic (2006), and the Glenn Foundation Award (2007). He was also elected to the American Association for the Advancement of Science (2001) and the American Academy of Arts and Sciences (2005) and served on the *Journal of Biological Chemistry* editorial board from 2002 to 2007.

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

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