THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 281, No. 5, Issue of February 3, p. e5, 2006
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

Salih Wakil's Elucidation of the Animal Fatty Acid Synthetase Complex Architecture

The Architecture of the Animal Fatty Acid Synthetase. I. Proteolytic Dissection and Peptide Mapping
(Mattick, J. S., Tsukamoto, Y., Nickless, J., and Wakil, S. J. (1983) *J. Biol. Chem.* 258, 15291–15299)

The Architecture of the Animal Fatty Acid Synthetase. II. Separation of the Core and Thioesterase Functions and Determination of the N-C Orientation of the Subunit
(Mattick, J. S., Nickless, J., Mizugaki, M., Yang, C. Y., Uchiyama, S., and Wakil, S. J. (1983) *J. Biol. Chem.* 258, 15300–15304)

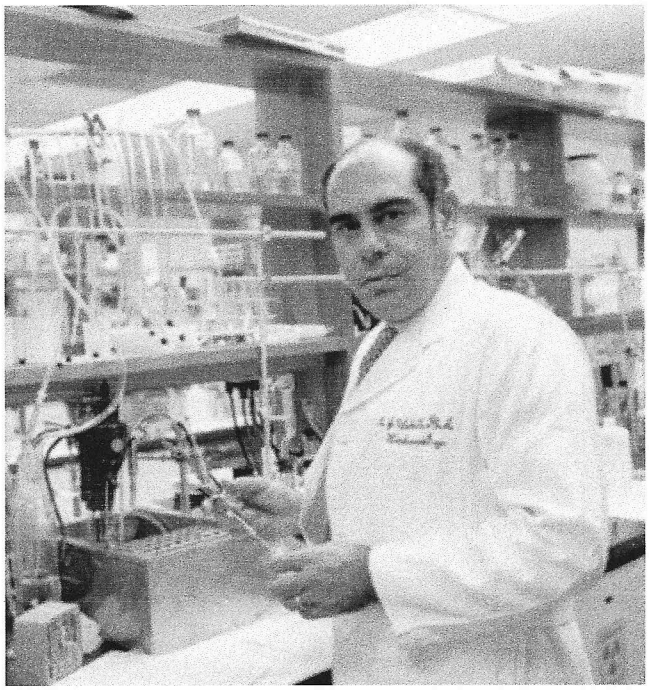
The Architecture of the Animal Fatty Acid Synthetase. III. Isolation and Characterization of Beta-Ketoacyl Reductase
(Wong, H., Mattick, J. S., and Wakil, S. J. (1983) *J. Biol. Chem.* 258, 15305–15311)

The Architecture of the Animal Fatty Acid Synthetase Complex. IV. Mapping of Active Centers and Model for the Mechanism of Action
(Tsukamoto, Y., Wong, H., Mattick, J. S., and Wakil, S. J. (1983) *J. Biol. Chem.* 258, 15312–15322)

Salih Jawad Wakil was born in 1927 in Kerballa, Iraq. Because he placed third in the nation on the baccalaureate examination out of high school, he received a scholarship to the American University in Beirut. While at the American University he met Stanley Kerr, who introduced him to biochemistry and gave him the opportunity to work in his laboratory. After graduating in 1948, Wakil was accepted at the University of Washington, which he assumed was located in the U. S. capital. However, he arrived in the United States only to learn that he would have to take a 3-day train journey from New York to his university in Washington State. In Seattle, Wakil worked with Donald Hanahan and finished his graduate studies in biochemistry in 3½ years. Next, he decided to do postdoctoral training at the Enzyme Institute of the University of Wisconsin, where he began to work on fatty acid oxidation. It was there that he helped to elucidate the steps by which fatty acids are oxidized and showed that fatty acids are synthesized and oxidized by different pathways.

Wakil was named assistant professor in 1956, but joined the Department of Biochemistry at the Duke University School of Medicine in 1959 and rose to the rank of professor there (1965). At Duke, Wakil investigated fatty acid synthesis in *Escherichia coli*. He and Roy Vagelos, who was featured in a previous *Journal of Biological Chemistry* (JBC) Classic (1), independently studied the role of acyl carrier protein as well as several of the individual reactions of fatty acid elongation. Wakil left Duke in 1971 to become professor and chairman of the Verna and Marrs McLean Department of Biochemistry and Molecular Biology at Baylor College of Medicine in Houston,Texas. At Baylor, Wakil studied the multifunctional enzyme, fatty acid synthetase. The characterization of this enzyme complex is the subject of the four JBC Classics reprinted here.

In vertebrates, the fatty acid synthetase complex exists as a dimer of what Wakil believed were identical subunits derived from a single large mRNA. The complex contains the seven enzymatic activities needed for the assembly of fatty acids: (i) acetyl transacylase, (ii) malonyl transacylase, (iii) β-ketoacyl synthetase, (iv) β-ketoacyl reductase, (v) β-hydroxyacyl dehy-



Salih J. Wakil

dratase, (vi) enoyl reductase, and (vii) palmitoyl thioesterase, as well as an acyl carrier peptide to which the nascent chain is attached. These Classics, which were printed as a back-to-back series in one issue of the JBC, present Wakil's comprehensive proteolytic analysis of chicken fatty acid synthetase in which he assigned relative locations for the enzymatic activities in the complex.

In the first Classic, Wakil and his colleagues used seven different proteases to digest the synthetase. They found that the sum of the molecular weights of each set of fragments generated by the proteases corresponded to the size of the synthetase subunit rather than the native dimer, indicating that the synthetase was indeed a homodimer. The researchers also reported that the subunit is arranged into three major domains of M_r = 127,000, 107,000, and 33,000.

Wakil describes the cleavage of chicken fatty acid synthetase by α-chymotrypsin in the second Classic. The complex was cleaved into two fragments. The larger 230-kDa fragment contained all the core activities involved in the assembly of the fatty acyl chain whereas the smaller 33-kDa fragment retained the thioesterase activity which releases the complete product. Using amino acid sequence analysis, Wakil showed that the thioesterase domain is located at the carboxyl terminus of the synthetase monomer.

In the third Classic, Wakil used trypsin and subtilisin to cleave fatty acid synthetase and isolated a polypeptide containing only β-ketoacyl reductase activity. Using a kallikrein/subtilisin double digestion, Wakil and his colleagues also isolated another fragment containing β-ketoacyl reductase activity as well as the phosphopantetheine prosthetic group. From this, Wakil concluded that the acyl carrier protein moiety is located in the 15-kDa segment that separates the β-ketoacyl reductase from the thioesterase domain.

In the fourth and final Classic, Wakil presents an architectural model for the synthetase based on his results from the previous three papers. In Wakil's model, domain I functions as a site for acetyl and malonyl substrate entry and acts as the site of carbon-carbon condensation. Thus, this domain contains the amino terminus of the polypeptide and the β-ketoacyl synthetase and acetyl and malonyl transacylases. Domain II, the reductive domain, contains the β-ketoacyl and enoyl reductases, probably the dehydratase, and the 4′-phosphopantetheine prosthetic group of the acyl carrier protein. Finally, domain III contains the thioesterase activity. Based on his observations, Wakil concluded that even though each subunit contains all the activities needed for fatty acyl synthesis, the actual synthesizing unit consists of one-half of one subunit interacting with the complementary half of the other subunit. This is shown in the model in Fig. 2. Wakil, along with Bornali Chakravarty, Ziwei Gu, Subrah-

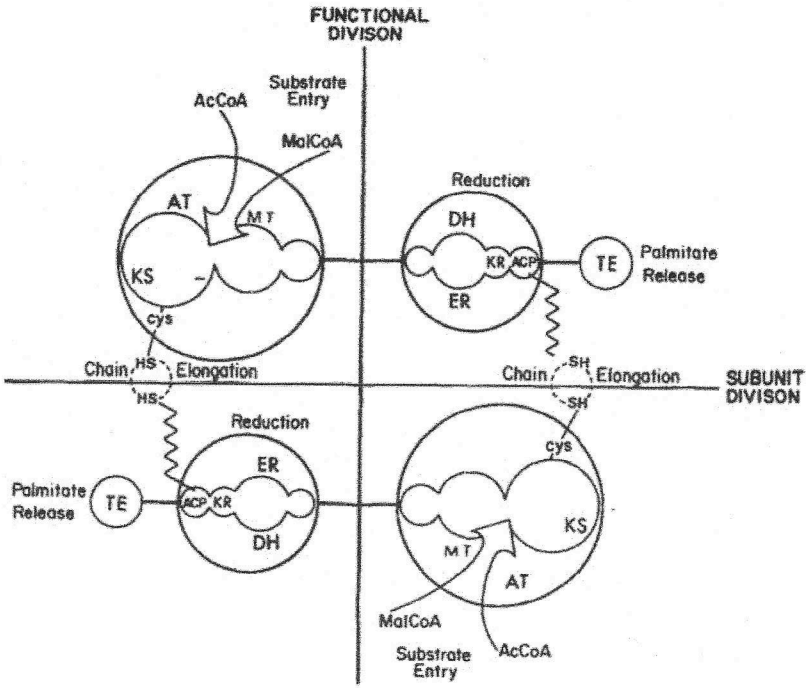


Fig. 2

manyam S. Chirala, and Florante A. Quiocho, subsequently solved the crystal structure of the thioesterase domain of human fatty acid synthetase (2).

Today, Wakil remains at Baylor where he is Distinguished Service Professor and Bolin Professor in the Department of Biochemistry and Molecular Biology. Most recently, his focus has been on acetyl-CoA carboxylase (ACC), which exists in two forms, ACC1 and ACC2. He has developed a transgenic mouse, which does not produce ACC2, and as a result can eat 20–30% more food and weighs 10% less than mice that produce the enzyme.

In honor of Wakil's contributions to the field of fatty acid metabolism, he has received many awards and honors. These include the Paul Lewis Award from the American Chemical Society (1967), the Chilton Award of the University of Texas Southwestern Medical Center (1985), the Kuwait Prize of the Kuwait Foundation for the Advancement of Sciences (1988), the Yamanouchi USA Foundation Award (2001), and the Bristol-Myers Squibb Freedom to Discover Award (2005). In 1990, Wakil was the first Baylor College of Medicine faculty member to be elected to the National Academy of Sciences.

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

REFERENCES

1. JBC Classics: Majerus, P. W., Alberts, A. W., and Vagelos, P. R. (1965) *J. Biol. Chem.* **240,** 618–621; Majerus, P. W., Alberts, A. W., and Vagelos, P. R. (1965) *J. Biol. Chem.* **240,** 4723–4726 (http://www.jbc.org/cgi/content/full/280/35/e32)
2. Chakravarty, B., Gu, Z., Chirala, S. S., Wakil, S. J., and Quiocho, F. A. (2004) Human fatty acid synthase: structure and substrate selectivity of the thioesterase domain. *Proc. Natl. Acad. Sci. U. S. A.* **101,** 15567–15572