The Biochemical Disposal of Cholesterol: the Work of David Russell

Cloning, Structure, and Expression of the Mitochondrial Cytochrome P-450 Sterol 26-Hydroxylase, a Bile Acid Biosynthetic Enzyme

Cloning and Regulation of Cholesterol 7α-Hydroxylase, the Rate-limiting Enzyme in Bile Acid Biosynthesis

David W. Russell was born in Dallas, Texas. He attended the University of Texas, Austin, where he worked on protein synthesis in the laboratory of Joanne M. Ravel. After graduating in 1975, Russell went to the University of North Carolina, Chapel Hill, and performed dissertation research with Linda L. Spremulli in which he characterized ribosome anti-reassociation factors. He completed his Ph.D. in chemistry in 1980.

From North Carolina, Russell traveled to the University of British Columbia as a Damon Runyon Cancer Research Fund postdoctoral fellow and worked in the laboratory of 1993 Nobel laureate and Journal of Biological Chemistry (JBC) Classic author Michael Smith (1). Two years later he joined the University of Texas Southwestern faculty as an assistant professor in the department of molecular genetics. He was promoted to associate professor in 1986, professor in 1990, and became the McDermott Distinguished Chair of Molecular Genetics in 1992.

Once at UT Southwestern, Russell began a 5-year collaboration with 1985 Nobel laureates Michael S. Brown and Joseph L. Goldstein, who were featured in a previous JBC Classic (2). The trio worked on cloning the low density lipoprotein receptor gene and determining the molecular basis of familial hypercholesterolemia, one of the most common human genetic disorders.

In 1987 Russell started an independent research program and began elucidating the biochemical pathways that mammalian cells use to degrade cholesterol and other sterols. Mammalian cells lack the ability to directly degrade the four-membered ring structure of cholesterol, so they instead use a pathway that results in the conversion of the molecule into bile acids. This complex biosynthetic pathway involves a series of 16 enzymes that modify both the
ring structure and side chain of cholesterol, resulting in the formation of the primary bile acids, cholic acid and chenodeoxycholic acid.

The first step in the oxidation of the cholesterol side chain involves the introduction of a hydroxyl function at the 26-position. This reaction is catalyzed by the mixed function monoxygenase, sterol 26-hydroxylase. In the first JBC Classic reprinted here, Russell and his colleagues use protein sequencing and molecular cloning techniques to isolate and characterize a cDNA encoding the rabbit mitochondrial sterol 26-hydroxylase. Their deduced amino acid sequence confirmed that the protein was a mitochondrial cytochrome P-450 that shares sequence similarity with the mitochondrial cholesterol side chain cleavage and steroid 11β-hydroxylase cytochrome P-450 enzymes. The researchers also did RNA blotting experiments, which demonstrated that the 26-hydroxylase mRNA is present in many tissues at different levels of abundance, and Southern blotting experiments, which indicated that the protein is probably encoded by a unique copy gene in the rabbit genome. This paper has been cited more than 1000 times.

Russell followed up these experiments by isolating several other enzymes in the degradative pathway, including the microsomal cytochrome P-450 cholesterol 7α-hydroxylase (7α-hydroxylase). This enzyme catalyzes the rate-limiting step in bile acid biosynthesis and is involved in the introduction of a hydroxyl moiety at the 7-position of cholesterol. At the time the paper was published, it was known that the activity of 7α-hydroxylase was subject to feedback regulation by sterols, but it was not known whether changes in enzyme activity were the result of changes in the amount of enzyme or actual changes in its activity levels.

Following up on a preliminary report describing the purification and cloning of the rat 7α-hydroxylase (3), Russell and his colleagues purified rat 7α-hydroxylase and determined its partial protein sequence. They also showed that the enzyme's mRNA is found only in the liver and that the levels of this mRNA increased when bile acids were depleted by dietary cholestyramine and decreased when bile acids were consumed. From these experiments, Russell was able to conclude that bile acids and sterols altered the transcription of the 7α-hydroxylase gene, explaining the previously observed feedback regulation of bile acid synthesis. Russell and his colleagues were one of three groups that were able to purify 7α-hydroxylase and clone its cDNA. Of the three papers describing the findings, two, Russell's and one by John Chiang (4), were published in the JBC.

Today Russell remains at UT Southwestern and continues to investigate lipid metabolism. His laboratory has isolated more than a dozen genes that encode enzymes involved in cholesterol breakdown and has identified the molecular bases of six human genetic diseases characterized by abnormal cholesterol and lipid metabolism.

In addition to his research achievements, Russell has made significant contributions to the education and training of scientists. Together with Joseph Sambrook, he co-authored “Molecular Cloning,” a popular molecular biology manual published by Cold Spring Harbor Laboratory Press. Russell is an associate editor for the Journal of Biological Chemistry and serves on the editorial boards of Cell Metabolism, Journal of Lipid Research, and Trends in Biochemical Sciences. In the past he has served on the editorial boards of Biochemistry, Annual Reviews of Biochemistry, Journal of Biological Chemistry, and Molecular Endocrinology. Russell has also received several honors and awards including the 1985 Louis N. Katz Award from the American Heart Association, the 1993 Kilby Science Place Award from Texas Instruments, the 1999 Ernst Oppenheimer Award from the Endocrine Society, and the 2002 Adolph Windaus Prize from the Falk Foundation in Germany. He was elected to the National Academy of Sciences in 2006.

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REFERENCES


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