Regulation of Cholesterol Metabolism: The Work of Robert D. Simoni

Robert D. Simoni began his foray into the world of lipids and membranes when he was in graduate school at the University of California, Davis, studying fatty lipid synthesis in plants with Paul Stumpf. Fewer than ten years later, Simoni started his own research program at Stanford University, exploring the biochemistry of cell membrane structure and function. The two Journal of Biological Chemistry (JBC) Classics articles reprinted here review some of Simoni’s research on the regulation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which catalyzes the rate-limiting step in the synthesis of sterol and non-sterol isoprenoid products.

The Membrane Domain of 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Confers Endoplasmic Reticulum Localization and Sterol-regulated Degradation onto β-Galactosidase
(Skalnik, D. G., Narita, H., Kent, C., and Simoni, R. D. (1988) J. Biol. Chem. 263, 6836–6841)

Oligomerization State Influences the Degradation Rate of 3-Hydroxy-3-methylglutaryl-CoA Reductase
(Cheng, H. H., Xu, L., Kumagai, H., and Simoni, R. D. (1999) J. Biol. Chem. 274, 17171–17178)

Robert Dario Simoni was born in San Jose, California, in 1939. He attended San Jose State College, where he fluctuated between majors and even considered dentistry school but failed the requisite dentistry dexterity test. He eventually settled on biology and chemistry and graduated in 1962. Simoni then enrolled at the University of California, Davis, and earned a Ph.D. in biochemistry in 1966, studying fatty lipid synthesis in plants with Paul Stumpf.

After graduating, Simoni received a National Science Foundation postdoctoral fellowship, which he used to study membrane solute transport systems with JBC Classics author Saul Roseman (1) at The Johns Hopkins University. In 1971, Simoni joined the Department of Biological Sciences at Stanford University as an assistant professor. He rose through the ranks and eventually became the Donald Kennedy Chair in the School of Humanities and Sciences, a position he still holds today.

Simoni’s research at Stanford focuses on the biochemistry of cell membrane structure and function, the interaction of membrane proteins, and membrane lipids. The two JBC Classics articles reprinted here review some of Simoni’s research on the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR).
HMGR catalyzes the rate-limiting step in the synthesis of sterol and non-sterol isoprenoid products. This is one of the key regulatory steps in the biosynthetic pathway. HMGR is bound to the endoplasmic reticulum via an 8-membrane-spanning domain, whereas its catalytic domain resides in the cytosol (2). The enzyme is regulated at the transcriptional and translational levels, as well as at the level of protein degradation. Increased sterols, either biosynthetic or exogenously supplied, simultaneously decrease the rates of synthesis of the enzyme and decrease its degradation rate.

The first Classics article shows that the enzyme’s increased degradation rate in response to sterols is dependent on its membrane anchor. Simoni and colleagues created a fusion construct consisting of the HMGR membrane domain and *Escherichia coli* β-galactosidase (which replaced the HMGR catalytic domain). They found that the hybrid protein exhibits normal endoplasmic reticulum localization and normal sterol-enhanced degradation. From these results, the authors concluded that the membrane domain of HMGR is necessary and sufficient to confer sterol-regulated degradation.

However, the second Classics article provides evidence that the membrane domain of HMGR, although necessary for sterol-enhanced degradation, is not sufficient. Simoni and colleagues created additional fusion constructs, combining the HMGR membrane domain with other heterologous proteins. These chimeric proteins gave mixed results with respect to sterol-enhanced degradation, suggesting that the cytosolic domain has some influence on degradation rates and sterol responsiveness. For example, fusing the HMGR membrane domain to the FK506-binding protein (FK506BP) yielded a construct that did not exhibit sterol-enhanced degradation. However, if a double-headed ligand of FK506 was added to cells expressing HMGR-FK506BP, the fusion protein formed oligomers, and normal sterol-enhanced degradation was restored. Thus, the authors concluded that, although the membrane domain of HMGR is necessary for sterol-enhanced degradation of HMGR, the oligomeric state of the cytosolic domain also determines the sterol response. In retrospect, Simoni and colleagues realized that the β-galactosidase fusion proteins created in the first Classics article were able to form tetramers and thus met the requirement that the HMGR cytosolic domain be an oligomer.

In addition to his research activities, Simoni has been intricately involved with JBC for more than twenty-five years. In 1985, he became a member of the Editorial Board, and, in 1987, he became an associate editor, a position he still holds today. Simoni also served as Deputy Editor of the Journal from 1999 to 2010 and was very important in the development of JBC online. With Simoni’s guidance, JBC became the first science journal to appear online, and its debut launched a revolution in science publishing. Now, virtually every biomedical science journal has a digital version. Simoni continues to lead efforts in digital innovation.

Simoni has received numerous awards and honors for his contributions to science. These include the Stanford University Dean’s Award for Distinguished Teaching (1976) and the American Society for Biochemistry and Molecular Biology’s William C. Rose Award (1998). Simoni was also the inaugural holder of the Donald Kennedy Chair in the School of Humanities and Sciences at Stanford University (2000) as well as a Fulbright Fellow (1977–1978). He is a scholar of the Japan Society for Promotion of Science (1987) and a member of the Johns Hopkins University Society of Scholars (1988).

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