Chapter

Introductory Chapter: Endoplasmic Reticulum-Knowledge and Perspectives

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1. Introduction

The endoplasmic reticulum is one of the most studied and fascinating organelles. It is found in all eukaryotic cells and performs a variety of functions. The organelle was designated by this name by Keith Porter in 1953 on the basis of studies carried out with the electron microscope in cells in tissue culture. Porter was able to differentiate the exoplasm, an adjacent region devoid of organelles, from the neighboring endoplasm. In the endoplasm, he examined a system of interrelated tubules, a reticulum, for this reason, the name "endoplasmic reticulum" (ER).

The collaboration between Keith Porter and George Palade showed that ER exists in all eukaryotic cells and that it consists of different but continuous domains, the smooth and rough ER, whose abundance fluctuates between different types of cells. Palade observed on the surface of the rough ER the ribosomes that synthesized secretory proteins. The secretory proteins would cross an intracellular membrane, instead of the plasma membrane. The verification of this concept led to the discovery of the secretion pathway and the conception of intracellular protein binding to various organelles.

2. Brief history of the endoplasmic reticulum

The history of the endoplasmic reticulum began in 1945 when Porter, Claude, and Fullam [1] observed vesicle-like bodies in cell culture studies using electron microscopy. These elements had a size that varied between 100 and 150 mμ. The most important characteristics of this new cytoplasmic system were described: (1) its reticular disposition and (2) the vesicular nature of the component elements. In later articles, Porter and his colleagues explained the chosen concentration of the vesicular elements of the reticulum in the endoplasm and their insufficiency or absence in the supposedly ectoplasm periphery of the cytoplasm [1–3], a result that subsequently led to the choice of the name "endoplasmic reticulum," designation used in a subtitle in 1948 [3] and finally used in an article published by Porter and Kallman in 1952 [4]. In addition to the reticular arrangement and the endoplasmic position implicit in the name, Porter's studies recognized a number of other significant characteristics for the new cytoplasmic constituent, namely, the usual continuity of the system throughout the endoplasm of normal cells, the extraordinary polymorphism of its components, and the disintegration of the whole system in cytolysis in a set of isolated vesicles.

3. My participation in studies with endoplasmic reticulum

Ten years after my first experience with polyunsaturated fatty acids (PUFA) [5], in 1974, I participated in a project that demonstrated in a reliable way the mechanism of action of stearoyl-CoA desaturase. As an international fellow of the National Institutes of Health (NIH), I started under the direction of Prof. Philip Strittmatter in a project with the objective of analyzing the physical, chemical, and catalytic properties of a desaturating system of fatty acids reconstructed in egg lecithin or vesicles of dimyristoyl lecithin, devoid of detergent. This initial characterization of the mechanism included data on the substrate specificity of the desaturase, the interaction of the substrate with the enzyme, and the possible functions of the phospholipid in the transport of electrons, the binding of the substrate, and the desaturation stage that limits the speed. The ER is the main site for the synthesis of sterols and phospholipids that constitute most of the lipid components of all biological membranes. In addition, many enzymes and regulatory proteins involved in lipid metabolism reside in the ER. The ER, therefore, plays an essential role in the control of the lipid composition of the membrane [6] and the lipid homeostasis of the membrane in all cell types. Stearoyl-CoA desaturase is a microsomal oxidase system required for the biosynthesis of oleic acid. Three protein components of this system (cytochrome b5 reductase, cytochrome bs, and terminal oxidase) were resolved, and an enzymatically active desaturase was reconstituted from the purified components. As a result of these studies, an article was published in J. Biol. Chem. under the title "Microsomal stearoyl-CoA desaturase mechanism of rat liver: studies of substrate specificity, enzyme-substrate interactions and function of the lipids." Undoubtedly, these studies have opened new paths in the fatty acid desaturation reaction [7]. Stearoyl-CoA desaturase (SCD) is an enzyme of the endoplasmic reticulum (ER) that catalyzes the biosynthesis of monounsaturated fatty acids (MUFAs) from saturated fatty acids that are synthesized again or derived from the diet. The SCD along with NADH, the flavoprotein cytochrome b5 reductase, and the electron acceptor cytochrome b5 as well as the molecular oxygen introduced a simple double bond in a spectrum of acyl-CoA fatty substrates interrupted with methylene (**Figure 1**).

The preferred substrates are palmitoyl- and stearoyl-CoA, which are then converted into palmitoleoyl- and oleoyl-CoA, respectively [7]. These products are the most abundant monounsaturated fatty acids (MUFAs) and serve as substrates

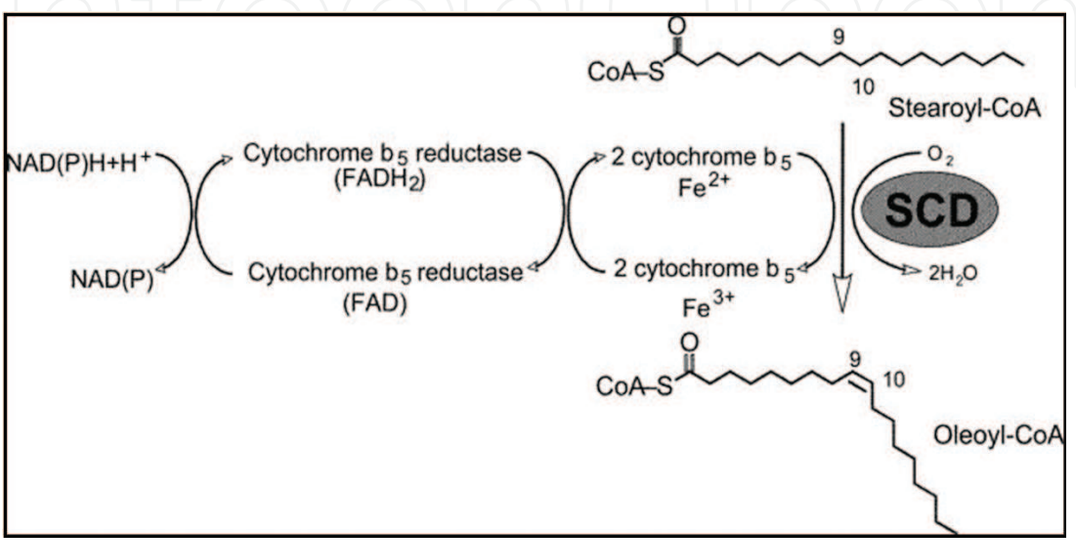

Figure 1.
The pathway of electron transfer in the desaturation of fatty acids by stearoyl-CoA desaturase (SCD).

for the synthesis of various kinds of lipids, including phospholipids, triglycerides (TG), cholesteryl esters, wax esters, and alkyldiacylglycerols. Apart from being the components of lipids, MUFAs have also been implicated to serve as mediators in signal transduction and cellular differentiation, including neuronal differentiation [8]. Recently, oleate has been shown to regulate food intake in the brain [9], and MUFAs may also influence apoptosis and mutagenesis in some tumors [10]. Thus, given the multiple roles of MUFAs, variation in stearoyl-CoA desaturase activity in mammals would be expected to influence a variety of key physiological variables, including cellular differentiation, insulin sensitivity, metabolic rate, adiposity, atherosclerosis, cancer, and obesity.

4. General remarks, conclusions, and perspectives

It has been fascinating to follow the field of endoplasmic reticulum research during almost six decades. Quantitative proteomics and lipidomics analysis are now available for measurement of the main components of the endoplasmic reticulum. From my experience, it is impossible to predict which aspects in endoplasmic reticulum research will dominate in the future.

Acknowledgements

This book is dedicated to the memory of Emeritus Professor Dr. Rodolfo R. Brenner,* the main guide in my research on lipid metabolism: "It will remain forever in the memory of those who had the privilege of knowing him and receiving his teachings." The outstanding scientist was a pioneer in the study of fatty acid desaturases (enzymes that play a prominent role in lipid metabolism and are located in the endoplasmic reticulum).

* On July 3, 2018, the distinguished scientist, Dr. Rodolfo R. Brenner, passed away. He was a Senior Investigator Emeritus of CONICET and the Head Professor Emeritus of UNLP. He held the position of Established Academic of the National Academy of Exact, Physical and Natural Sciences, of the National Academy of Sciences of Buenos Aires, and of the National Academy of Pharmacy and Biochemistry, as well as the Academic of the Medicine Academy of Córdoba, Argentina.

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