Introduction: Milk Lipid Synthesis: Chain Length Determination and Secretory Differentiation

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In 1967 Stuart Smith and R. Watts, working with Ray Dils at the National Institute for Research in Dairying at Reading, found that there was very little difference in the fatty acid composition of the adipose tissue of different species, while in contrast milk fat had an average fatty acid chain length of 11.7 in rabbits, 14.2 in rats, 15.3 in mice, and 17.2 in guinea pigs [1]. Smith and Dils had previously shown that fatty acids with a chain length from 6 to 14 carbons could be synthesized by mammary tissue from lactating rabbits, making it clear that *de novo* fatty acid synthesis in the mammary gland differed fundamentally from that in other organs [2]. Evidence for an independent tissue specific factor in the mammary gland that terminated chain elongation early was obtained in several laboratories [3]. By 1969 Smith had moved to the Children's Hospital Medical Center of North Carolina to work with Sandy Abraham; both he and Ray Dils continued to work on this factor, which became known as thioesterase II. It was a difficult job, finally successful in 1978 [4]. In the paper reproduced here, the pathway to purification of this factor as well as the general mechanisms of fatty acid synthesis are described [5].

Smith describes the circumstances under which he gave the talk at the 74th Annual Meeting of the American Dairy Science in 1979 that resulted in this publication: "That meeting, held on the campus of Utah State University in Logan, included a symposium on Milk Synthesis. I recall that Nick Kuhn from the

University of Birmingham, England, (my alma mater), also gave a talk on lactose synthesis. I don't remember many details of the meeting except that I arrived at sunset on a small prop plane from Salt Lake City to find that the tiny airport was completely deserted, not a taxi in sight. I was rescued by the pilot of our plane who drove me in his car directly to my hotel in town. Now that's service you will not find anywhere these days!"

He goes on: "During the five year period leading up to the talk it was established that the animal fatty acid synthase was a 'multifunctional polypeptide' in which all of the enzymes of that biosynthetic pathway were integrated into a single polypeptide. Little did we know that it would take another 30 years before the detailed structure of the complex would be established [6, 7]. Nevertheless, at the time of the meeting in Logan, we had come to appreciate that all tissues use the same enzyme system for *de novo* fatty acid biosynthesis (the fatty acid synthase), regardless of the products made. In the case of the lactating mammary gland, the ability to make medium-chain saturated fatty acids was dependent on the presence of a tissue-specific thioesterase (termed 'thioesterase II') that, remarkably, was able to interrupt the chain elongation process by accessing and hydrolyzing the thioester bond linking these intermediates to the protein. We now know that the resident thioesterase (termed 'thioesterase I'), which normally terminates chain elongation at 16 carbon atoms, is secured to its neighboring domain by a relatively long flexible tether, which presumably allows it to be displaced by the external thioesterase II thus allowing access to intermediate chain length intermediates. Nevertheless, the details of how this is achieved are still to be worked out."

One of the next big questions is how the activity of this enzyme is regulated. There is increasing evidence at

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the molecular level that fatty acid synthase is not the only enzyme involved in synthesis of fatty acids whose mRNA is increased at the onset of lactation. Rudolph and his colleagues in Colorado have found, in the mouse mammary gland, that many genes involved in the synthesis of fatty acids are significantly upregulated at the onset of lactation [8, 9], including members of the pentose phosphate shunt, enzymes for the mitochondrial synthesis and transport of citrate, enzymes that supply malonyl CoA to fatty acid synthase, fatty acid synthase itself, and enzymes involved in the desaturation and elongation of fatty acids. In addition, SREBP-1c, the precursor of a transcriptional regulator of most of these enzymes, is also upregulated, leading to the hypothesis that SREBP is responsible for regulating *de novo* fatty acid synthesis in the mammary gland. Bauman and his colleagues at Cornell University, studying a phenomenon known as milk fat depression, have evidence that a causative dietary lipid, trans-10, cis-12 conjugated linoleic acid, apparently works through the SREBP pathway in dairy cows [10]. Clearly we have additional work to do to understand how milk lipid synthesis is regulated, but the role of SREBP may provide important clues as we pursue this problem.

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