Increasing our Understanding of Milk Fat Synthesis using Functional Genomics

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Using new science to investigate aspects of specific milk fats found to have positive health benefits to humans is one of the recent efforts of Cornell University researcher Dr. Dale Bauman. Consumer awareness of animal food products has increased in recent years. Advertising campaigns for milk and cheese have produced many widely viewed television commercials, not to mention celebrities donning white milk moustaches in magazines. With this, fad diets bounce back and forth over the amount of dairy products that should be included in our diets. Regardless, dairy products are an important source of dietary nutrients and make up over 12% of farm cash receipts in the U.S. Because of these facts, scientific research to improve the quality of milk and the efficiency of milk production abounds within academia and industry. Many consumers are not aware of these dairy research efforts or the many factors, such as cow management, environment, and diet composition that can affect the quantity and composition of the milk produced by a cow. For example, milk fat, while being a concern to consumers, remains the most variable nutrient in milk. The amount of fat in milk and its fatty acid composition is influenced by the cow's diet and nutrition. Dr. Bauman, is interested in further understanding the nutritional regulation of milk fat synthesis and possible management of the amount of fat and its composition using a relatively new technology known as functional genomics.

Functional genomics is a way to explore factors that influence production, cow physiology and health situations at the gene level. It links changes in the way genes are expressed under different treatments or conditions to actual cell functions or physiological functions such as milk production, muscle growth, or immune response, for example. External circumstances, like change in diet or stress, can send signals to cells to turn some genes on and other genes off or even change their functions. These altered expressions of genes can be seen as increased or decreased milk production, a difference in concentration of milk fat, protein, or other nutrients in the milk, or many other characteristics or functions within a cow.

Dr. Bauman's group is interested in the relationship between nutrients consumed by cows and what genes are "turned on" and "off" by these diet changes and the resulting effects on cell processes. To do this, Dr. Bauman's group has been using a bovine mircoarray developed by the National Bovine Functional Genomics Consortium (NBFGC) which is used to look at simultaneous changes in thousands of genes at once resulting from experimental changes such as diet changes. This microarray contains 18,000 genes from various bovine cells and tissues. Microarrays are glass slides that are spotted with DNA from thousands of genes and allow researchers to look at the expression of those thousands of genes at once to determine which genes were turned on or off in cells or tissues between certain times or treatments.

The main focus of Dr. Bauman's research concerns a family of unique fatty acids called conjugated linoleic acids (CLA) known to have beneficial health effects. Research studies have found CLAs to be anti-carcinogenic (anti-cancer) and anti-atherogenic (anti-arteriosclerosis). They can also reduce cholesterol and alter the partitioning of nutrients throughout the body. Most CLA in the human diet comes from ruminant-derived foods, mainly dairy products such as milk, ice cream, cheese, and butter. Dr. Bauman's group is interested in two different isomers, or forms of CLA. One form is *cis*-9, *trans*-11 CLA (Figure 1a) the major CLA in milk fat. It has been valuable in health maintenance and the prevention of chronic diseases. For example, this CLA form reduces the risk of cancer and coronary heart disease in biomedical studies with animals used to model human diseases. The other CLA form that they are investigating is *trans*-10, *cis*-12 CLA (Figure 1b), which provides anti-obesity effects and regulates milk fat production. Although the effects of CLAs is well known, the mechanisms underlying their actions are not well understood.

By using functional genomics, this team wanted to identify the actual genes that change during CLA-induced milk fat depression. To do this, they infused the abomasums of cows with *trans*-10, *cis*-12 CLA and fed cows different diets that naturally alter the milk fatty acid composition and content. Mammary gland tissue biopsies were obtained during each treatment and compared on microarrays and by quantitative real-time RT-PCR (reverse transcription-polymerase chain reaction), a sensitive measure used to determine the magnitude each gene is expressed.

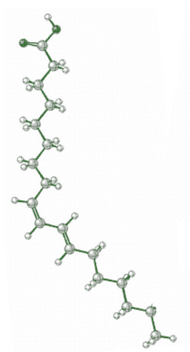

Figure 1a. Molecular model of *cis-9, trans-11* conjugated linoleic acid.

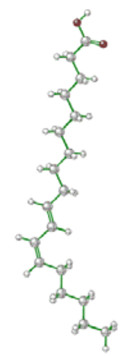

Figure 1b. Molecular model of *trans*-10, *cis*-12 conjugated linoleic acid.

Previous investigations have observed a coordinated down-regulation of enzymes involved in milk fat synthesis. These include genes involved in the uptake of fatty acids from blood, trafficking of fatty acids within the cell, desaturation of fatty acids, synthesis of new fatty acids, and triglyceride synthesis and packaging. The microarray procedure identified changes in undiscovered regulatory pathways that may be responsible for coordinating this response. Bauman's group has verified that the Sterol Response Element Binding Protein 1 (SREBP1) transcription factor and its associated activating proteins are down-regulated during CLA and diet-induced milk fat depression. SREBP1 coordinately regulates all of the steps of FA metabolism, therefore it down regulates uptake, trafficking, new fatty acid synthesis and desaturation. They are currently verifying other newly identified regulatory responses. They are also continuing gene expression profiling for situations involving nutritional regulation of milk fat synthesis with a particular focus on genes involved in cellular signalling, the switches in cells that turn on and off many cellular processes.

Functional genomics provides a powerful approach to understanding complex physiological mechanisms such as the interaction between dietary nutrients and changes in gene expression. Understanding the basic mechanisms of physiological regulation of production traits at the cellular level will be valuable in developing improved strategies in animal nutrition, management, and breeding. Work involving CLAs may lead to milk that has greater levels of CLAs to provide us options for healthier diets.