THE REGULATION OF MILK PROTEIN GENE EXPRESSION: FROM BASIC SCIENCE TO BIOTECHNOLOGY

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Our laboratory has been studying the mechanisms by which hormones regulate the expression of differentiated function in the normal mammary gland and how these regulatory mechanisms have deviated in breast cancer. Two rat milk protein genes encoding β-casein and whey acidic protein (WAP) have been employed as molecular markers of mammary epithelial cell terminal differentiation (1, 2). The expression of these genes is regulated during mammary gland development by lactogenic hormones and cell-substratum interactions.

In order to decipher the mechanisms responsible for this complex regulation, more than ten years ago we initiated studies of their expression in transgenic mice (3,4). This basic research has led to the identification of the important elements required for mammary-specific gene expression, and provided new insights into the mechanism of synergy of prolactin and glucocorticoids in regulating milk protein gene expression.

Composite response elements containing multiple binding sites for several transcription factors mediate the hormonal and developmental regulation of milk protein gene expression. Signal transduction pathways regulated by the lactogenic hormones result in transcription factor binding and interaction within these composite elements, changes in chromatin structure and milk protein gene expression. In the casein promoters these include binding sites for signal transducers and activators of transcription (Stat)5, Yin Yang (YY)-1, CCAAT/enhancer binding protein(C/EBP) and the glucocorticoid receptor (GR) (5,6). In the whey protein gene promoters these include binding sites for nuclear factor (NF) I, as well as the GR and Stat5 (7). These composite response elements have a modular structure that is conserved in most mammals and sometimes duplicated in the 5' flanking regions of the milk protein genes.

Not all of the important regulatory sequences, however, are located in the regions flanking the milk protein genes; some are in intragenic, noncoding regions. In the B-casein gene, these sequences are located in the 5' untranslated region (UTR), while in the WAP gene they are in the 3' UTR (8).

Using this information it has been possible to design constructs for the targeting of heterologous genes to the mammary gland using the milk protein gene regulatory sequences. In our laboratory this has led to the successful overexpression of a variety of heterologous proteins in milk including biologically active bovine follicle stimulating hormone (9) and insulin-like growth factor I (10), and human surfactant proteins B & C(11). Although the mammary gland is an efficient bioreactor, it is not able to efficiently post-translationally process all proteins, but may instead secrete the partially processed or unprocessed proproteins.

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