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INTEGRATED ANALYSIS OF GENE NETWORKS CONTROLLING FEED INTAKE AND ENERGY METABOLISM IN CHICKENS

NON-TECHNICAL SUMMARY: The gene networks responsible for expression of major production traits in poultry are currently unknown. Although hatching represents the most abrupt metabolic challenge, there have been no attempts to functionally map the metabolic pathways induced by nutrients in the chick's first meal. Furthermore, we know very little about the metabolic, hormonal or neuroendocrine factors that regulate feed intake or nutrient utilization during the immediate and post-hatch period, a critical time which influences the broiler chicken's growth rate and muscle yield. We have recently developed powerful genomic (high-density chicken DNA microarrays) and computational tools for genome-wide gene expression profiling across multiple tissues in the chicken. This project will provide an integrated analysis of transcriptional snapshots taken during a major metabolic perturbation--a single cycle of fasting and re-feeding--in newly hatched chicks and market age broilers. These genome-wide gene expression scans will be used to develop a blueprint of the basic gene networks that control feed intake and energy metabolism of the broiler chicken. Knowledge gained from this functional genomics project can be used to tackle many of the adverse problems associated with intensive genetic selection for production traits (i.e., excessive fattening, skeletal abnormalities and metabolic disorders). Furthermore, new information on genetic control of feed intake and nutrient utilization via different metabolic pathways can be used to improve poultry management practices.

OBJECTIVES: The gene networks responsible for expression of major production traits in poultry are currently unknown. Recently, we have developed powerful genomic (high-density chicken DNA microarrays) and computational (gene network analysis) tools that allow examination of gene expression patterns across multiple tissues of the chicken on a genome-wide scale. The main goal of this project is to provide an integrated analysis of transcriptional snapshots taken during a major metabolic perturbation (a single cycle of fasting and re-feeding) in newly hatched chicks and market age broilers. Although hatching represents the most abrupt metabolic challenge, there have been no attempts to functionally map the metabolic pathways induced by nutrients in the chick's first meal. Furthermore, we know very little about the metabolic, hormonal or neuroendocrine factors that regulate feed intake or nutrient utilization during the immediate and critical post-hatch period, which influences the chicken's growth rate and muscle yield. Transcriptional scans of the liver and hypothalamus will reveal a coarse view of the major gene networks and regulatory pathways that respond to the strong metabolic challenge caused by an acute bout of feed deprivation and re-feeding. Genome-wide gene expression scans will enable us to develop a blueprint of the basic gene networks that control feed intake and energy metabolism of the broiler chicken. First, we will use our chicken cDNA microarrays to analyze transcriptional profiles in the liver and hypothalamus of newly hatched chicks during a strong metabolic perturbation--the fasting and refeeding response. Next, we will analyze transcriptional profiles in the liver and hypothalamus of market

age chickens during a strong metabolic perturbation--the fasting and refeeding response. Finally, we will verify the expression patterns of key metabolic and regulatory genes revealed by microarray analysis by an independent method (i.e., qRT-PCR or TaqMan analysis). These gene expression data will be used to develop descriptive models of the major gene networks that control feed intake and energy metabolism in the broiler chicken. Knowledge gained from this functional genomics project can be used to tackle many of the adverse problems associated with intensive genetic selection for production traits like feed efficiency and body composition.

APPROACH: One of the greatest challenges facing application of functional genomics in solving agricultural problems is extracting useful information on genetic interactions from large gene expression data sets. The key to developing models of gene regulatory networks is estimation of regulatory strengths of gene-to-gene interactions. The perturbation method is widely used for gene network modeling. One common metabolic perturbation delivered to a whole animal is an acute cycle of fasting and refeeding which can be used to reveal shifts in utilization of energy substrates (carbohydrates, fat or protein) and activation of different metabolic pathways. We will use time-series perturbation studies combined with gene network modeling to reveal the major topography of genes that control feed intake and important metabolic pathways. We have developed a powerful high-density microarray for chickens--the 14K Del-Mar Chicken Integrated Systems Microarray--for expression profiling across multiple tissues. In the first experiment, we will establish global gene expression profiles during early post-hatching development and assess the effects of fasting and refeeding after hatching on gene expression profiles in liver and hypothalamus during the early post-hatch period. The first perturbation experiment will include ten groups of newly-hatched chicks that were fasted for 24 or 48 hr and then refeed after a 48 hr fast. Liver and hypothalamic samples will be taken from fully-fed control groups at one day of age, after either a 24 or 48 hr fast, and at 4, 24 or 48 hr after refeeding. The second perturbation experiment will use market age broiler chickens (6 weeks of age) subjected to the extreme nutritional states of ad libitum feeding, prolonged fasting and refeeding. Liver and hypothalamic samples will be collected from chickens provided commercial grower ration ad libitum (fed), chickens fasted for 16 hr, chickens fasted for 48 hr, and chickens that were refeed for 4, 24 or 48 hr after the 48 hr fast. The transcriptional profiles in the liver and the hypothalamus will be determined with our 14K chicken microarray. Each RNA sample will be labeled once with Cy3 and once with Cy5 in a "dye swap" hybridization design. The expression levels of a number of differentially expressed genes revealed by microarray analysis will be verified with quantitative real-time RT-PCR (TaqMan) analysis. Gene expression measurements from the integrated microarray experiments will be rank normalized with our Bayesian analysis of microarrays program and gene expression patterns identified with the spanning tree gene clustering method. Model parameters will be estimated from time-course expression scans with microarrays (coarse data) and then true (model-based) gene levels refined with TaqMan qRT-PCR data. Based on the spanning tree structure of functional gene clusters, we will reconstruct networks of the measured genes and build models to estimate regulatory strengths and directions of gene interactions. Accordingly, it will be possible to determine the evolution of gene networks which control feed intake and energy metabolism in broiler chickens.

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