Nutrigenes, Functional Genomics and Systems Biology

Sheila Ernest,*† Michelle Carter,** Angela Hosack,‡ David Rosenblatt,‡ Elizabeth Ross** and Joseph H. Nadeau*‡

*Department of Genetics, Case Western Reserve University School of Medicine, Cleveland, Ohio; †Center for Computational Genomics, Case Western Reserve University, Cleveland, Ohio; **Laboratory of Neurogenetics and Development, Weill Medical College, Cornell University, New York, NY; and ‡Departments of Human Genetics, Medicine, Pediatrics and Biology, McGill University, Montreal, Quebec, Canada

ABSTRACT Traditionally, the classic reductionist approach attributes functions to individual genes. For instance, this has involved the analysis of motifs or the amino acid sequences of single gene products. It is unclear how the products of particular collections genes act together to provide higher order functionality in health and disease. To address this higher order problem, the function of collections of genes, as opposed to “one gene at a time” has to be studied. Accordingly, a model system is needed to test systems biology. In our studies, we used the homocysteine-folate metabolism as a model system.

KEY WORDS: • systems biology • perturbations • homocysteine-folate metabolism • neural-tube defects • mice

Homocysteine-folate metabolism as a model system

We used homocysteine-folate (HCY-folate) metabolism as an ideal model system because it contains many useful attributes: 1) it is relevant to common and important human diseases, such as neural tube defects (NTD) (1,2), vascular disease (3) and cancer (4); 2) its core pathway is known (Figs. 1, 2); 3) it contains intermediate phenotypes that are measurable, such as metabolite levels and enzyme activity; 4) it is influenced by environmental factors, such as diet (5,6); and 5) it contains targets for pharmacologic interventions, such as anticancer drugs (5). A key point in testing systems biology is to monitor consequences or responses of specific causes or perturbations. We have been developing a platform based on collections of NTD mutant mice and dietary supplementation in combination with HCY-folate metabolism to begin studying complex biological systems.

We first assessed the effect of genetic perturbations on HCY-folate metabolism using NTD mice with a series of single gene mutations (PAX3, GLI3, APOB, PTCH and SKI). We monitored the response of HCY-folate metabolism to these genetic perturbations by measuring serum metabolite levels and gene expression. Increased serum homocysteine levels and

1 Presented at the Experimental Biology Meeting, April 11–15 2003, San Diego, CA. The symposium was sponsored by The American Society for Nutritional Sciences and supported in part by an educational grant from Nestle and a USDA-NRI conference grant. The proceedings are published as a supplement to The Journal of Nutrition. This supplement is the responsibility of the guest editors to whom the Editor of The Journal of Nutrition has delegated supervision of both technical conformity to the published regulations of The Journal of Nutrition and general oversight of the scientific merit of each article. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, editor or editorial board of The Journal of Nutrition. Guest Editors for the symposium publication are Naima Moustaid-Moussa and Jay Whelan, Department of Nutrition, The University of Tennessee, Knoxville, TN.

2 To whom correspondence should be addressed. E-mail: jhn4@cwru.edu.

0022-3166/03 $8.00 © 2003 American Society for Nutritional Sciences.
altered expression profiles of HCY-folate metabolism genes were detected in mice with partial protein deficiencies in the WNT and hedgehog signal transduction (GLI3 and PAX3) and lipid transport (APOB) (7). This systems approach revealed functional relations between pathways which otherwise were not evident and may contribute to the pathogenesis of birth defects.

We then studied the effect of genetic and physiological perturbations on HCY-folate metabolism using a single gene mouse mutant model, Crooked tail (Cd), whose developmental defects are suppressed with a folate-supplemented diet (8). Crooked tail mice model the human folate-responsive NTD, permitting an assessment of the ways in which dietary supplementations suppress the adverse developmental outcomes of single gene mutations. A combination of metabolic assays and expression profiles were used to survey wild-type heterozygous Cd/+ and homozygous Cd/Cd mice on control, folate-supplemented and folate-deficient diets. The mutation and the diet were used as genetic and physiological perturbations, respectively. Surprisingly, the Cd mutation had no significant effect on HCY levels, suggesting that folate might correct the defect through a mechanism that may not involve HCY per se. Interestingly, cluster analyses revealed that gene expression and metabolite profiles of homozygous Cd/Cd mice parallel that of folate-deficient mice, suggesting that homeo[yosity for the Cd mutation might be a functional folate deficiency without alterations in HCY levels. These studies illustrate the ways in which gene expression and metabolic assays can be combined with perturbations of physiological and developmental systems to define the complex networks of functional interactions that relate genetic mutations with disease outcomes (unpublished results).

In summary, the HCY-folate metabolism has many useful attributes for studies on systems biology in mouse models of human disease and provides a unique opportunity to integrate genetics, expression and metabolite profiles and complex phenotypes.

LITERATURE CITED