NSA

Molecular Biology for the Novice – A Workshop for Nutritionists

Genomic strategies in the study of nutrition

PR Ebert

Dept of Zoology and Entomology and Dept of Biochemistry and Molecular Biology, University of Queensland, St Lucia QLD 4072

Background – The rapid development of high throughput analytical tools and freely available genomic databases promises to transform every field of biology, including studies of nutrition. What, however, is the reality behind the hype?

Objective – I will describe the technologies that are currently available for genomic analysis and mention the benefits and limitations of each. Because nutritional studies will pose unique challenges, I will refer to limitations of the techniques as they apply to studies of nutrition.

Design – I will specifically refer to the application of genomics to toxicology and pharmacology as a model for similar nutritional studies. The nature of the questions to be addressed in toxicogenomics and pharmacogenomics are similar to those of nutrigenomics, but the comparative simplicity of the questions to be asked and the robustness of responses to be measured reduce the challenge immensely.

Outcomes – Research strategies to be discussed will include genome wide expression profiling of genes and proteins as well as profiling of metabolites. Also to be discussed will be the complementary techniques of genetic mapping of metabolic disorders, gene knockout/suppression and transgenesis.

Conclusions – The primary difficulty of the application of genomics to the study of nutrition will be to associate specific components in the complex milieu of the diet to complex changes in gene expression across the genome and relate this to chronic phenotypic changes in an individual. The challenges are not to be underestimated, but the real promise of genomics is to provide a framework for the seamless integration of cognate fields. Thus, by embracing the tools of genomics, the field of nutrition will benefit more directly from the insights of related fields.

NSA
The New Nutrition: Molecular Nutrition and Nutriomics

The regulatory architecture of the human genome

JS Mattick
Institute for Molecular Bioscience, University of Queensland, QLD 4072

The draft human genome sequence has provided the first detailed view of the landscape of human genetic programming, with the emphasis to date being on identifying protein-coding genes and determining their biochemical and biological function. However, complex dynamical objects cannot be described just in terms of their components, but must rather be addressed in terms of their integrated function, which includes both the assembly and control of the system. It is these (largely hidden) ontological, physiological and metabolic networks that ultimately determine the emergent effects of variation in endogenous genetic programming and its intersection with environmental variables, including nutrition.

Such considerations have motivated the first tentative steps to describe complex cellular and organismal phenomena, including metabolic networks and protein interaction networks, in terms of "scale-free" networks, a concept derived from the connection characteristics of modern electronic networks. However, analysis of integrated systems suggests that regulatory networks which control function are in fact "accelerating" networks, i.e., that regulation must scale non-linearly (usually quadratically) with function. This has been confirmed by analysis of regulatory genes in prokaryotes, which scale quadratically with genome size, the observed upper limit of which (~12Mb) correlates with the extrapolated point at which new regulators are predicted to exceed new functional genes, suggesting that protein-based regulatory systems have reached their limit in these organisms.[1]

The current orthodoxy holds that genes are generally synonymous with proteins, and therefore that proteins not only fulfil the structural and functional roles within cells, but are also the main agents by which cellular dynamics are controlled, in conjunction with cis-regulatory elements and environmental signals. This is true in prokaryotes, whose genomes are very largely comprised of contiguous protein coding sequences. It is assumed that this is also true in multicellular organisms, despite the fact the proportion of protein-coding sequences declines as a function of complexity and is only a small minority of the genomic programming of complex organisms like mammals. This assumption has led to several logical extensions and subsidiary assumptions, in particular that the increased complexity of eukaryotes is explained by the combination of regulatory factors intersecting with more complex promoters, with the corollary that the majority of non-protein-coding sequences in eukaryotic genomes are either cis-regulatory elements or evolutionary debris (i.e. junk).[1]

This may not be correct. Around 98% of the transcriptional output of the human genome is non-protein-coding RNA (derived from introns of protein-coding genes and from non-protein-coding genes, of which increasing numbers are being discovered), and at least half of the human genome is transcribed.[1,2] Therefore either the human genome is replete with useless transcription, or these RNAs are fulfilling some unexpected function. In addition it is becoming evident that a significant proportion of the noncoding regions of the human genome is under evolutionary constraint, some of it much more highly conserved than proteins.[3] Such observations and the increasing number of complex genetic phenomena being shown to be directed by regulatory RNAs, suggests that the complex organisms may have evolved a more advanced genetic operating system, which occupies the majority of our genome sequence, and in which ncRNA signals constitute a highly parallel network of digital, feed-forward regulatory signals that control differentiation and development.[1,2] Variation in this regulatory architecture may be equally if not more important than variation in the (protein) components in determining the differences between individuals and species, including quantitative trait variation, sensitivity to environmental parameters and susceptibility to disease.

References

1. Mattick JS. RNA regulation: a new genetics? Nature Rev Genet 2004;5:316-23
2. Mattick JS. Noncoding RNAs: the architects of eukaryotic complexity. EMBO Rep 2001;2:986-91.
3. Bejerano, G, Pheasant M, Makunin I, Stephen S, Kent WJ, Mattick JS, Haussler D. Ultra-conserved sequences in the human genome. Science 2004; in press.