FUNCTIONAL MEDICINE UPDATE
SEPTEMBER 2007
ISSN 1092-1761
Vol. 27, No. 9

"Omics" Research and Cellular Function

Smell is an ancient sensory system present in organisms from bacteria to humans. In the nematode *Caeonorhabditis elegans*, gustatory and olfactory neurons regulate aging and longevity. Using the fruit fly, *Drosophila melanogaster*, a research team based at the Huffington Center on Aging at Baylor College of Medicine demonstrated that exposure to nutrient-derived odorants can modulate life span and partially reverse the longevity-extending effects of dietary restriction. The identification of a nutrient-related olfactory cue (odorants from live yeast) and a gene involved in olfaction (*Or83b*) indicates that olfaction affects adult physiology and aging in *Drosophila*, possibly through the perceived availability of nutritional resources, and that olfactory regulation of life span is evolutionarily conserved. REF #1

Metabolomics takes a global view of an organism; it attempts to understand physiological status of a laboratory sample or organism in light of its full biochemical physiological potential. Since metabolomic measurements are directly reflective of the current physiological or biochemical state of a sample, it yields very different, and potentially more useful, information than other omics sciences. When used in conjunction with other omics sciences, it offers additional perspectives on cellular function.

The great strength of metabolomics lies in the ability to impose concepts of concentration variance onto metabolic maps. This powerful attribute is an outcome of the use of the concept of metabolic networks rather than focusing on predefined pathways. Biochemical profiling is a rapidly developing science. It is already clear that the metabolomic perspective gives a clear and unambiguous picture of cellular physiology. REF #2

Nutritional proteomics (or nutriproteomics) is the application of proteomics methodology to nutrition-related research, but also represents the interaction of bioactive food ingredients with proteins. The proteome, defined as the protein complement expressed by a genome, implies a static nature but is in reality highly dynamic. Proteomics may be defined as the different methodologies used to describe the structural diversity with the underlying biological processes. New strategies surrounding proteomics should provide opportunities for establishing useful new biomarkers for the validation of efficacy and safety of nutrients with health-promoting effects. REF #3

Hypertension as an Example of Altered Cellular Function

Primary hypertension results from the interplay of internal derangements (primarily in the kidney) and the external environment. Recent evidence, as well as classic studies, point to the interaction of sodium and potassium as the dominant environmental factor in the pathogenesis of primary hypertension and its associated cardiovascular risk. A review recently published in *The New England Journal of Medicine* examines this interdependency and its influence on blood pressure.

Human kidneys are poised to conserve sodium and excrete potassium. Prehistoric humans, who consumed a sodium-poor and potassium-rich diet, were well-served by this mechanism. This mechanism, however, is unfit for the sodium-rich and potassium-poor modern diet. The end result of the failure of the kidneys to adapt to this diet is an excess of sodium and a deficit of potassium in hypertensive patients. Potassium depletion inhibits insulin secretion and is associated with glucose intolerance.

A modified diet that approaches the high potassium-to-sodium ratio of the diets of human ancestors is a critical strategy for the primary prevention and treatment of hypertension. Apart from educating the public, an agreement by the food industry to limit the deviation of the cationic content of processed foods from their natural counterparts is essential. REF #4

The Licorice-Blood Pressure Connection

Use of licorice (*Glycyrrhiza glabra*) dates back to at least 1000 BC. In Europe in the 15th century, licorice became an established treatment for dyspepsia. But, during the second half of the 20th century, licorice prompted scientific interest not so much for its therapeutic value, but more because of its significant adverse side effects. A classic paper published in the Journal of Clinical Endocrinology and Metabolism in 1978 examined the effect of licorice on the hypothalamic-pituitary-adrenal axis of normal individuals. The findings of this study suggested that licorice ingestion led to a prompt and sustained increase in urinary unconjugated cortisol without obvious effect on plasma cortisol, plasma adrenocorticotrophic hormone (ACTH), or urinary steroid metabolite excretion. REF #5

When licorice or carbenoxolone is administered therapeutically, or when licorice is ingested habitually or given to healthy volunteers, the resultant syndromes share most of the clinical and biochemical features of primary aldosteronism. Clinical manifestations include those of sodium retention (peripheral edema, breathlessness, and hypertension) and hypokalemia (polyuria due to nephrogenic diabetes insipidus, proximal myopathy, lethargy, paresthesiae, muscle cramps, headaches, and tetany). Biochemical markers for excessive activation of mineralocorticoid receptors in the distal nephron include hypokalemic alkalosis and suppression of plasma renin activity. Interestingly, individuals vary markedly in their susceptibility to licorice-induced mineralocorticoid excess. Hypermineralocorticoidism, as well as these other adverse effects, have been demonstrated in animal studies in addition to their appearance in human subjects. REF #6-7

A Controversial Article on Rosiglitazone

A meta-analysis was published earlier this year in *The New England Journal of Medicine* about the effect of rosiglitazone (widely used to treat patients with type 2 diabetes mellitus) and the risk of myocardial infarction and death from cardiovascular causes. After examining 42 trials and analyzing data by means of a fix-effects model, authors Steven Nissen and Kathy Wolski concluded that rosaglitazone was associated with a significant increase in the risk of myocardial infarction, as well as an increase in the risk

of death from cardiovascular causes that had borderline significance. The authors stated that the study had been limited by a lack of access to original source data, but their discussion included some interesting points:

- One potential contributing factor may be the adverse effect of the drug on serum lipids. The FDA-approved rosiglitazone product label reports a mean increase in low-density lipoprotein (LDL) cholesterol of 18.6% among patients treated for 26 weeks with an 8 mg daily dose, as compared with placebo.
- PPAR agonists such as rosiglitazone have very complex biologic effects, resulting from the activation or suppression of dozens of genes.
- Piglitazone appears to have more favorable effects on lipids, particularly triglycerides, than does rosiglitazone.
- The use of blood glucose measurements as a surrogate end point in regulatory approval must be carefully reexamined.

GlaxoSmithKline publicly disagreed with the conclusions of the *NEJM* article, citing incomplete evidence and a methodology with significant limitations. REF #8-9

The Mediterranean Diet and Fasting Indices of Glucose Homeostasis: The ATTICA Study

The *Journal of the American College of Nutrition* recently published a study that was undertaken to examine the association between the adherence to the Mediterranean diet and fasting indices of glucose homeostasis in adults without any clinical evidences of cardiovascular disease who were randomly selected from the general population. The "ATTICA" epidemiological study was carried out in the province of Attica (Greece) from May 2001 to December 2002; 3042 inhabitants agreed to participate.

In this non-interventional study of the general "free-eating" population, the researchers observed that adherence to the Mediterranean diet was related to better fasting indices of glucose homeostasis (fasting plasma glucose, insulin levels, and HOMA-IR) in normoglycemic people, but not in diabetic or pre-diabetic (IFG) individuals, after controlling for several potential confounding factors. These results were in agreement with the results of several intervention trials. REF #10

Nutrient Sensing and Metabolic Decisions

Cells have several sensory systems that detect energy and metabolic status and adjust flux through metabolic pathways accordingly. Dr. Bland discusses a review article in which the authors describe the sensing and response to macronutrients, particularly glucose, amino acids and fatty acids, or the products of their catabolism. The review brings together information about five different nutrient-sensing pathways, highlighting their similarities, differences, and roles in disease. REF #11

Clinician/Researcher of the Month

Jeffrey M. Smith
Author, *Genetic Roulette: The Documented Health Risks of Genetically Engineered Foods*
www.seedsofdeception.com
www.responsibletechnology.org
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Jeffrey Smith is a best-selling author and a leading spokesperson on the health dangers of Genetically Modified Organisms (GMOs). He has counseled world leaders, influenced the first state laws regulating GMOs, and has united leaders to support *The Campaign for Healthier Eating in America,* an industry and consumer movement to remove GMOs from the natural food industry. Mr. Smith has recently published his second book, *Genetic Roulette: The Documented Health Risks of Genetically Modified Foods*. His first book, *Seeds of Deception: Exposing Industry Lies about the Safety of the Genetically Engineered Foods You're Eating* captured public attention in 2003.

Mr. Smith is the executive director of the Institute for Responsible Technology, a public education nonprofit that works on major public initiatives with scientists and concerned citizens from around the world to shine a spotlight on the dangers of GMOs. When not traveling and speaking throughout the world, Mr. Smith resides in Iowa, surrounded by genetically modified soybeans and corn.

Dr. Bland and Mr. Smith have a detailed discussion about current practices related to genetically engineered crops and worldwide instances of immune-system response and concern. It is important to note that Mr. Smith is not opposed to the use of technology in general. He refers to a future in which the agricultural community can safely and reliably manipulate crop DNA for the benefit of human health and the environment. His research into current practices, however, has revealed a flawed and primitive system that could result in health consequences throughout large populations. REF #11-24

In closing: "Junk" DNA
As a follow-up to his discussion with Jeffrey Smith, Dr. Bland discusses an article titled *Tagging the Rice Transcriptome*, which was recently published in *Nature Biotechnology*. Rice is the world's most important crop. A once orderly picture of the rice transcriptome has given way to a complex landscape of RNA species, including siRNAs, microRNAs, antisense genic transcripts, and intergenic transcripts. Dr. Bland finds author Antoni Rafalski's final words compelling and quotes him directly: "A significant fraction of intergenic space in the rice genome, sometimes thought of as 'junk,' is functionally active. From a biotechnological perspective, transgenic modifications that disrupt transcription of any of these intergenic regions may have unintended consequences. Although the genic environment of transgenes is routinely surveyed in the process of governmental approval, better insight into which sequences in the rice genome are transcribed and thus presumably functionally important, will facilitate efforts to avoid transgene insertions within expressed regions." REF #25

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