Managing Biotransformation: Introduction and Overview

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A description of the family of human detoxification enzymes, cytochrome P450s, first appeared in the literature in 1962.1 Until that time it was known that foreign compounds were somehow detoxified by specific physiological processes, but the nature of these processes had not been elucidated. In the absence of an understanding about this superfamily of detoxification enzymes (now known to be generated by 57 genes, many of which show multiple polymorphisms), there was much speculation as to how an individual actually eliminated lipophilic compounds, both exogenous and endogenous. It is now recognized that the enzymes in the CYP450 superfamily have roles not only in the detoxification of drugs and other xenobiotics, but also in the metabolism of nutrients and endogenous molecules such as essential fatty acids, phytoneurtrients, steroid hormones, and vitamins D and A.2

Over the past 40 years, we have learned that what is termed phase 1 activation of lipophilic compounds is carried out by enzymes in the CYP450 family. This phase 1 biotransformation of a molecule creates an activated intermediate that is either directly eliminated from the body or, more commonly, becomes a substrate for one of the phase 2 conjugation enzymes and is then eliminated. The phase 2 conjugases, which include sulfation, amino acid conjugation, glutathione conjugation, glucuronidation, methylation, and acetylation activities, are also highly polymorphic. In both the phase 1 and phase 2 detoxification enzyme families, some enzymes are constitutively expressed and some are inducible. Importantly, certain environmental and nutritional agents have been found to influence the induction and activities of specific phase 1 and phase 2 enzymes.1,4

Murray has described some of the effects of diet on detoxification by pointing out that constituents of the diet regulate the expression and function of both CYP450 and conjugation genes, which impact lipophilic molecule elimination and may also significantly influence disease pathogenesis. He concludes that “food constituents modulate CYP expression and function by a variety of mechanisms, with the potential for both deleterious and beneficial outcomes.”5 This suggests that diet may have a “detoxifying” influence if the constituents of the diet properly support balanced phase 1 and phase 2 detoxification functions.

Recently, however, Clemens and Pressman suggested that “detoxification diets provide empty promises”6 because “these approaches are contrary to scientific consensus and medical evidence and are not consistent with the principle that diets should reflect balance, moderation, and variety.” While the principles of balance, moderation, and variety are excellent guidelines for constructing public health policies, they may not be specific enough for constructing the proper diet for a patient with a specific alteration in his or her functional capacity for detoxification.

Genetic polymorphisms that result in highly variable individual responses to toxin exposure, to dietary influences, and to drug treatment may be useful in identifying people at risk for many different kinds of diseases and adverse effects.7 For example, exposure to specific toxins and the absence of proper support for detoxification functions are both thought to increase the risk for neurodegenerative conditions such as Parkinson’s disease,8,9 and in both situations genetic variability is common. It is well known that individuals who consume a poor-quality diet and/or excess alcohol—and concomitantly take acetaminophen—have a much higher risk of both hepatic and neurological injury from the medication.10 It is also clinically well established that diet plays an important role in the etiology of hepatic encephalopathy.11,12 Diet therapy that influences both intestinal and hepatic detoxification enzyme function is part of the standard of care for patients with this condition.11,12

Grapefruit juice,13 red wine,14 and crucifers15 have been shown to contain constituents that influence specific CYP450 activity that can alter drug metabolism and elimination. Certain foods and spices (e.g., black pepper)16 can also influence phase 2 activities. Oral supplementation with the amino acid glycine has been found to support phase 2 glycination and glucuronidation,17 which may improve detoxification in certain individuals. Some of these characteristics have been clinically exploited to develop a nutritional regime that will reduce the rapid first-phase detoxification of drugs, such as with cyclosporine, which is used to prevent tissue rejection in transplant patients.

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The clinician is thus challenged to investigate the potentially toxic burdens patients might be exposed to, ranging from pollution or xenobiotics in their homes, work, or local environments; to prescribed or recreational drugs; to the quality of their diets. Each potential exposure raises the questions frequently mentioned by Sidney Baker, MD: “Is there something for which this person has a special, unmet need? Is there something to which this person is having an adverse or toxic reaction (ie, the person is getting too much of)?” It is now recognized from molecular and cellular biology research that diet and lifestyle choices can influence both the level of exposure to potentially toxic substances and detoxification functions. Some key examples of these mechanisms include:

1. alteration of the absorption of toxins (ie, fiber intake);
2. alteration of gut microbial function (ie, probiotics, prebiotics);
3. alteration of the genetic expression of CYP 450s and conjugates (ie, glucosinolates);
4. alteration of post-translational, site-specific phosphorylation of CYPPs through specific kinase modulation (ie, sulforaphane);
5. post-translational and other possible influences on detoxification enzyme function (ie, pH, methylation with folate and vitamin B12, oxidation, and non-enzymatic glycation);
6. modulation of transcription by factors such as orphan nuclear receptors and cell-signaling pathways (eg, PPAR, RXR, T3, 1, 25 vitamin D3, Pregnane X, NrF 2) and by phytochemicals (eg, carnosol epigallocatechin gallate, curcumin).

In essence, this contemporary view of the role that diet plays in detoxification suggests that specific dietary signals are translated to the genes through a complex process involving reporter gene activation through specific nuclear transcription factors and cell-signaling pathways. These nuclear transcription factors control the cell-specific expressions of various detoxification enzymes. Various environmental substances send “stress” messages to the genome that induce specific detoxification responses. Intracellular reduction/oxidation potential (ie, cellular bioenergetics) plays a role in determining the degree of the response to the toxin. A quick response to a toxic exposure that short-circuits the need to induce protein synthesis in response to a toxic stress signal is mounted through the kinase activation pathway, which in turn is also sensitive to various phytochemicals and dietary factors.

Clearly, the diet–detoxification connection represents a specific example of clinical nutrigenomics. Muller and Kersten defined nutrigenomics as “the understanding that micronutrients and macronutrients (ie, cellular bioenergetics) play a role in determining the degree of the response to the toxin. A quick response to a toxic exposure that short-circuits the need to induce protein synthesis in response to a toxic stress signal is mounted through the kinase activation pathway, which in turn is also sensitive to various phytochemicals and dietary factors.”

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The papers you are about to read will explore some of these—and many other—fascinating ideas in greater depth. The IFM symposium itself provided an exciting look at some overarching concepts about the links between diet and detoxification that can now be supported by the emerging science:

1. Numerous genetic differences can influence both phase 1 and phase 2 detoxification functions.
2. Multiple environmental agents and drugs can affect the detoxification process.
3. Many nutrients and phytochemicals can influence both phase 1 and phase 2 detoxification function.
4. The multiple, complex interactions that can involve genetics, detoxification function, and environmental exposures (food, drugs, toxicants) can magnify the effects mentioned in points 1, 2, and 3 above.
5. Dietary influences on detoxification may play a role in the diet-cancer association.

Taken as a whole, the information provided in this series of papers demonstrates that the proper diet for a specific patient can influence detoxification function in a clinically important manner. Our review of this impressive body of evidence suggests strongly that this important topic in clinical nutrition and its relationship to medicine have not been adequately emphasized in either teaching or clinical practice. Detoxification diets may have significant value in promoting more effective physiological responses to toxic stressors that come either from the exogenous or endogenous environments.

References
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