A different perspective on GM food

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As a cell biologist, I am very discouraged by the nature of the ongoing "debate" on the introduction of genetically modified (GM) plants into the marketplace. This discussion has usually pitted irrational emotional arguments against the apparently rational notion that genetic engineering is just like traditional plant breeding, only more specific. In particular, I believe that insufficient attention has been paid to three important issues: first, introduction of the same gene into two different types of cells can produce two very distinct protein molecules; second, the introduction of any gene, whether from a different or the same species, usually significantly changes overall gene expression and therefore the phenotype of the recipient cell; and third, enzymatic pathways introduced to synthesize small molecules, such as vitamins, could interact with endogenous pathways to produce novel molecules. The potential consequence of all of these perturbations could be the biosynthesis of molecules that are toxic, allergenic, or carcinogenic. And there is no *a priori* way of predicting the outcome. In what follows I outline these concerns and argue that GM food is not a safe option, given our current lack of understanding of the consequences of recombinant technology.

The biological activity of a protein can be modified by gene splicing, which alters the primary amino acid sequence, and by the post-translational attachment of such moieties as phosphate, sulfate, sugars, or lipids. The nature of these modifications is markedly dependent upon the cell type in which the protein is expressed. For example, if the β-amyloid precursor protein, which is involved in Alzheimer's disease, is expressed in glial cells, it contains covalently attached chondroitin sulfate; but when it is expressed in brain nerve cells the protein contains a much simpler sugar[1]. This is because each cell type expresses a unique repertoire of enzymes capable of modifying protein structure by mRNA splicing or at the post-translational level. In the case of the β-amyloid precursor protein, its adhesive properties are altered by the attachment of different carbohydrates[2]. With our current state of knowledge, however, there is no way of predicting either the modifications or their biological effects. Therefore, a toxin that is harmless to humans when made in bacteria could be modified by plant cells in many ways, some of which might be harmful.

My second concern is the potential for the introduction of a foreign gene to either evoke the synthesis of toxic, carcinogenic, teratogenic, or allergenic compounds, or downregulate the synthesis of a beneficial plant molecule. Introduction of one gene usually alters the gene expression pattern of the whole cell, and typically each cell type of the organism will respond differently. One example involves the transfection of a receptor gene into human cells. In this case, the protein was a closely related isoform of an endogenously expressed gene[3]. Monitoring the pattern of gene expression using microarray technology showed that mRNA levels for 5% of the genes were significantly upregulated or downregulated. Recent studies in transgenic plants showed that the over-expression of a gene involved in pectin synthesis had no effect in tobacco, but caused major structural changes and premature leaf shedding in apple trees[4]. Although these sorts of unpredicted changes in gene expression and function are frequently observed, they have received very little attention. Furthermore, they are not unexpected. The maintenance of a specific cell phenotype involves a very precise balancing act of gene regulation, and any perturbation might be expected to change the overall patterns of gene expression. The problem, as with secondary modifications, is that there is currently no way to predict the resultant changes in protein synthesis.

Third, the introduction of genes for all or part of a new enzymatic pathway into plants could lead to the synthesis of unexpected or even totally novel products through an interaction with endogenous pathways. Some of these products could be toxic. For example, retinoic acid (vitamin A) and its derivatives are used in many signaling events that control mammalian development[5]. As these compounds have effects at ultra-low concentrations, a GM plant making vitamin A might also produce retinoic acid derivatives, which act as agonists or antagonists in these pathways, resulting in direct toxicity or abnormal embryonic development. A relevant example is a genetic manipulation carried out in bacteria during the 1980s to increase the yield of tryptophan for use as a nutritional supplement. The resultant product caused a novel illness that was highly correlated with the aberrant appearance of specific trace contaminants[6].

Given that GM plants will sometimes produce different amounts of proteins, and perhaps totally new proteins, as compared with the parental species, what are the possible results? A worst-case scenario would be that an introduced bacterial toxin is modified to make it toxic to humans. Prompt toxicity might be rapidly detected once the product entered the marketplace if it caused a unique disease, and if the food were labeled for traceability, as were the GM batches of tryptophan. However, cancer or other common diseases with delayed onset would take decades to detect, and might never be traced to their cause. Conversely, plant flavonoids and related molecules have great health benefits[7], and there is evidence that these can be depleted in GM crops[8].

If the above concerns are valid, what can be done to address them? Secondary modifications could be assayed by monitoring of the introduced gene product by mass spectroscopy; changes in gene expression could be assayed by DNA chips; and metabolically active molecules could be measured biochemically. The problem is, of course, that unless we know exactly what to look for, we are likely to miss the relevant changes. To me, the only reasonable solution is to require that all GM plant products destined for human consumption be tested for long-term toxicity and carcinogenicity before being brought to market. These safety criteria must be met for many chemicals and all drugs, and the magnitude of harm caused by a widely consumed toxic food could well be much greater than that from any single drug. However, even extensive animal testing might not detect the consequences of deficiencies in beneficial plant products. As GM crops offer potential benefits, it would be in the industry's best interest to more thoroughly examine these products before continuing with their introduction into the food supply.

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