Chapter 25
Evaluation of Genetically Engineered Crops Using Proteomics

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25.1 Introduction

The question addressed in this chapter is whether the use of transgenesis to improve a plant variety (through the expression of a new desired trait) can lead to unintended effects, that is, effects going beyond that of the original genetic modification, and which could have an impact on human and animal health. Such pleiotropic effects could be due to altered expression of untargeted genes leading to metabolic changes, or could be the consequence of an unexpected metabolic effect of a novel gene product.

Genetically-engineered (GE) varieties are assessed for their food and feed safety and nutritional quality in a comparative manner using parental or near isogenic lines as reference (the latter being considered as safe). It is aimed at identifying differences between these comparators and subsequently at evaluating the implications in terms of human and animal health. Current tools to perform such comparative safety assessments are targeted compositional analyses, animal nutrition, and classical toxicology evaluations, as well as agronomic evaluations. A major principle and guiding tool for the food safety assessment of GE crops is the concept of substantial equivalence according to principles outlined in the Organization for Economic Cooperation and Development consensus documents (OECD 2006).

In the last decade, new large-scale profiling methodologies have been developed that allow, in theory, a holistic search for alterations in GE crops. Numerous publications have examined whether the use of transgenesis as a plant breeding tool

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could lead to unexpected changes in the transcriptome or metabolome (see Ricroch et al. 2011). That these two biological levels (transcripts and metabolites) have been most frequently examined is not surprising considering the above-mentioned potential sources of unexpected effects linked to the insertion of a transgene.

However, proteomics have also been used in a number of studies that are summarized here and which yield fairly convergent conclusions. Relevant questions also discussed here are: from a basic research point of view, are proteomics a powerful nontargeted approach to detect unintended effects in GE crops? Do proteomics lead to different conclusions from transcriptomics and metabolomics? Does our current experience with proteomics indicate that current methodologies are robust and sufficiently standardized to be used routinely for reglementary GE crop assessment?

25.2 Proteomic Analysis of GE Varieties of Crop Plants

The main data from the publications discussed below are summarized in Table 25.1, which also briefly lists the methodologies used.

25.2.1 Grapevine

Sauvage et al. (2007) used two-dimensional electrophoresis (2DE) to study changes in leaf protein content from GE grapevine plants over- and under-expressing alcohol dehydrogenase (experimental nonmarketed lines). MS identification of peptides indicated that only a few proteins had a different abundance in the GE lines. Interestingly, these proteins were mainly from the chloroplasts and involved in sugar-phosphate metabolism. It should also be noted that a consistency in the range of 53–72% of matching spots was found between the triplicates with a given sample.

25.2.2 Maize

MON810 is a transgenic trait providing resistance to certain lepidopteran pests (such as the European corn borer). This trait has been introgressed in a large number of corn varieties.

The grain proteomes of two field-grown MON810/non-GE variety pairs were found to be almost identical, with few spots showing quantitative changes in the 1–1.8-fold range (Coll et al. 2010a). These differences were all variety-specific (not present in both variety pairs). These data confirmed a previous study (Albo et al. 2007) on two different field-grown MON810 varieties. Another previous study (Zolla et al. 2008) found more differences between two MON810 variety pairs. In the latter study, field versus growth chamber growth conditions were also

Table 25.1 2-DE and proteomic comparison of GE varieties with non-GE varieties

Species	References	Varieties or traits/growth	Differences in GE versus control	Methods
Grapevine	Sauvage et al. (2007)	Control, sense, and antisense for alcohol dehydrogenase/ greenhouse	Leaves. Changes in abundance in 14 proteins mainly from chloroplast and sugar-phosphate metabolism	2-DE. Gel Image Analysis. MALDI-TOF-MS. LC-MS/MS
Maize	Albo et al. (2007)	Two MON810/non-GE variety pairs/field	Grain proteomes mainly identical	2-DE. MALDI-TOF. LC-MS/MS
	Balsamo et al. (2011)	Four MON810/non-GE pairs (Brazilian varieties)/controlled environmental conditions	Leaves. Quantitative differences in 5 proteins (not consistent in all experiments). 7 exclusive spots for one pair, 5 for the other	2-DE. MALDI-TOF-MS
	Barros et al. (2010)	Two GE lines (MON810 and tolerant to glyphosate) and respective controls/different fields and years	Quantitative differences in 5 grain proteins. Environment exerting greater effects	2-DE
	Batista and Oliveira (2010)	MON810 and non-GE/field/ individual or pooled plants	Natural plant-to-plant variability for grain proteins	2-DE. Gel Image Analysis
	Coll et al. (2010a)	Two MON810/non-GE variety pairs/field	Grain proteomes mainly identical, with few spots showing quantitative changes in the 1–1.8 fold range	2-DE. Gel Image Analysis. LC-MS/MS
	Coll et al. (2011)	Two MON810/non-GE variety pairs/real agricultural conditions	Quantitative differences in a particular variety pair not exceeding 1.2% of the grain proteins spots. Approx. 40% non matching proteins between two conventionally varieties	2-DE. Gel Image Analysis. LC-MS/MS
	Zolla et al. (2008)	Two MON810/non-GE variety pairs/field + growth chamber	Grain. Differences in both variety pairs. Growth conditions induced more changes	2-DE. LC-MS/MS

(continued)

Table 25.1 (continued)

Species	References	Varieties or traits/growth	Differences in GE versus control	Methods
Pea	Chen et al. (2009)	Two pea lines producing a bean alpha-amylase inhibitor	Seed. 33 proteins differentially accumulated	2-DE. Gel Image analysis. MALDI-TOF-TOF
	Islam et al. (2009)	Two pea lines producing a bean alpha-amylase inhibitor and non-GE/greenhouse	About 30 seed protein changes in abundance in each GE/non-GE pair (different in both pairs): minor differences for one pair, quantitative and qualitative differences for second	2-DE. Gel Image Analysis. LC-MS/MS
Potato	Lehesranta et al. (2005)	Range of diverse varieties, landraces and GE lines (empty vector or potato sense and antisense). Mal1 gene or antis. S-adenosylmethionine decarboxylase gene/field	Tuber. GE: quantitative differences in a total of 9 proteins out of 730 Qualitative and quantitative differences in 1,077 out of 1,111 when comparing varieties and landraces	2-DE. Gel Image Analysis. LC-MS/MS
Rice	Takahashi et al. (2005)	Expression of a homolog of maize HC-toxin reductase, conferring tolerance to several stresses/cell cultures	Proteome of cultured cells: higher levels for 5 spots out of 668	2-DE. Image gel analysis
Soybean	Brandao et al. (2010)	Glyphosate-tolerant and non-GE	Differences (at least 90% variation) for 10 seed proteins)	2-DE. Gel Image Analysis. MALDI-TOF-MS.
Tomato	Corpillo et al. (2004)	Hybrid variety expressing the nucleoprotein gene of TSW virus (TSWV-*N*)+*nptII* for selection and non-GE/growth chamber	Seedlings. No major changes	2-DE. MALDI-TOF-MS

Tomato and tobacco	Di Carli et al. (2009)	*Lycopersicon esculentum* (cv. MicroTom) and *Nicotiana benthamiana* producing recombinant antibodies against cucumber mosaic virus and tomato spotted wilt virus, resp.	Leaves. Quantitative differences (average less than 2.4) in 10 proteins out of 2,000 spots	2-DE. Gel Image Analysis. MALDI-TOF-MS. LC-MS/MS
Wheat	Scossa et al. (2008)	Bread wheat overexpressing a GE low MW glutenin subunit gene and non-GE	Seeds. Differential accumulation of several classes of endosperm proteins, paralleled by corresponding changes in transcript levels	

compared and more changes detected than in the case of the genetic modification. Concerning the differences, these authors speculated that genome rearrangement occurred, but other explanations seem equally likely such as the use of not fully isogenic comparator lines. It is, however, difficult to explain the discrepancy between the results by Zolla et al. (2008) and by Coll et al. (2010a) inasmuch as the latter team also used one of the two pairs used by the former.

More recently, another study on two variety pairs of MON810 and the comparable non-GE counterpart grown in real agricultural conditions has been published (Coll et al. 2011). A very small number of quantitative differential spots was found in a particular variety pair, not exceeding 1.2% of the proteins analyzed by 2DE. The differences between two conventional varieties were much greater (approx. 40% nonmatching proteins). It should be mentioned that the same team found similar results when using a transcriptomic approach in leaf (Coll et al. 2008, 2010b).

Barros et al. (2010) performed a transcriptomic, proteomic, and metabolomic comparison of kernels of two GE maize lines (MON810 and one line tolerant to the herbicide glyphosate) with the respective control lines. When plants were grown in the same location over three seasons, the authors found more differences in gene expression, protein distribution, and metabolite content between seasons than differences linked to the genetic modification. That environment exerts a greater effect was also shown by the distinct profiles observed when plants were grown for one season in three different locations.

The occurrence of natural plant-to-plant variability (not linked to a genetic modification) was investigated by Batista and Oliveira (2010). They compared 2DE protein patterns from MON810 and comparator lines obtained either from individual plants or from pooled plants. For individual samples, five different ears of five different maize plants were harvested. They observed, for some spots, a high quantitative variability between individual samples from one line and this variability was masked when plants were pooled. For other spots, variability existed between individual samples and also between pools.

Leaf proteome was compared in two pairs of GE (MON810) and non-GE isogenic Brazilian varieties grown under controlled environmental conditions (Balsamo et al. 2011). Leaf proteomic profiles of the four GE varieties were similar to their non-GE counterparts. Observed quantitative differences (in five spots) were not reproducible in all six 2DE performed. Reproducible qualitative differences were as follows: in the first pair, 1 exclusive spot in the GE line and 6 in the non-GE line; in the second pair, 1 exclusive spot in the GE line and 4 in the non-GE line. Thus, 12 exclusive proteins were observed in total; all of these leaf proteins were variety-specific. Previous studies also found similar maize leaf transcriptome patterns in GE and their non-GE counterparts (Coll et al. 2008, 2009).

25.2.3 Pea

Islam et al. (2009) performed a proteomic study on two pea lines producing a bean alpha-amylase inhibitor (AI1). About 30 seed protein spots were found to differ in abundance between each GE/comparator pair, but they were generally different between

pairs, although the GE lines produced AI1 at similar levels. These differences were minor for one pair, but strikingly quantitatively and qualitatively different (appearance and disappearances of 36 protein spots) for the second pair. According to the authors, differences of a "similar magnitude" exist between different pea cultivars.

Chen et al. (2009) found that 33 proteins differentially accumulated in AI1-expressing lines compared with the parental line. They concluded that three of these differences were associated with the production of AI1 and the remaining 30 differences were due to the transformation events. Seed storage proteins, which are common food allergens, were among the protein exhibiting changes in their amounts. This illustrates the interest of using 2DE protein analysis and proteomics to detect new allergens in food (see below).

25.2.4 Potato

Important differences, both qualitative and quantitative, were found in the tuber proteome of field-grown varieties and landraces, and such differences were limited (quantitative) between the pairs constituted by experimental GE lines modified in cell wall structure or in ethylene/polyamine metabolism and their comparators (Lehesranta et al. 2005). It should be noted that the same and related lines, plus lines expressing a sense and antisense fructokinase gene were also studied using metabolomics (Defernez et al. 2004) or targeted composition analysis (Shepherd et al. 2006), with similar conclusions.

25.2.5 Rice

Takahashi et al. (2005) used in vitro cultured cells from experimental GE rice over-expressing the *YK1* gene, the homologue of maize HC-toxin reductase (HCTR) in rice. Out of a total of 668 polypeptides visualized by 2DE, 5 were increased in cells over-expressing *YK1* with respect to the control line, which included stress-related proteins such as osmotin-like protein and osr40c1 (an abscisic acid-responsive protein normally associated with salt tolerance).

25.2.6 Soybean

Using 2DE, Brandao et al. (2010) compared soybean GE (tolerant to the herbicide glyphosate) and non-GE comparator seeds. They found differences (greater than 90% variation in protein spot area and/or intensity) for ten proteins, six of them with differences in area or intensity and four of them in volume and intensity. Two proteins could not be identified. The other eight proteins identified by MS were seed storage proteins of glycinin and β-conglycinin types (responsible for the main nutritional, physicochemical, and physiological properties of soybeans), actin,

sucrose-binding protein (involved in the storage of nutrients and sugar binding) and allergen Gly mBd 28 k (less than twofold increase).

25.2.7 Tomato

Corpillo et al. (2004) considered a virus-resistant GE tomato line to be "substantially equivalent" to its non-GE counterpart from both proteomic and agronomic points of view, because no reproducible differences could be found in peptide abundance in the GE line versus the control line.

Di Carli et al. (2009) used two transgenic plant models, a dwarf tomato line and tobacco, producing recombinant antibodies against two plant viruses. In each model, around 10 proteins out of around 2,000 spots were found to accumulate differentially in the transgenic lines. The variation ratio was less than 2.4 on average. Most of the differentially accumulated proteins were related to photosynthesis or plant defense.

25.2.8 Wheat

Scossa et al. (2008) performed, in parallel, a transcriptional and proteomic comparison of seeds from a GE bread wheat line (over-producing a low molecular weight glutenin subunit) with respect to the nontransformed line. Differential accumulation of several classes of endosperm proteins was observed, and paralleled by corresponding changes in transcript levels. The authors interpreted these observations as a compensatory mechanism of the strong over-expression of the transgenic glutenin gene (a consequence of the diversion of amino acid reserves).

25.3 Proteomic Analysis of *Arabidopsis thaliana* Relevant to GE Plant Safety

A. thaliana is a basic research model plant that can also provide information about the potential impact of transgenesis (Wienkoop et al. 2010).

A line containing the selectable bar marker gene (encoding phosphinotricin acetyl transferase) was used in several studies. Ren et al. (2009a) concluded that differences in metabolic profiles (major contributors were altered levels of alanine and threonine) were due to the bar gene. However, 2DE analysis on 12 bar-containing lines showed little consistent differences in the 4–14 protein spots that changed quantitatively in these lines (Ren et al. 2009b).

Natural variability can also be important in *A. thaliana* ecotypes. After growing various ecotypes under controlled growth conditions, and using 2DE to analyze

seed proteins, Ruebelt et al. (2006) found that nearly half the spots were present or absent depending on the ecotype. In addition, 95% of the spots consistently found in all ecotypes were found to vary quantitatively. The seed proteome of 12 transgenic lines (using three different genes and three different promoters) were also compared to their parental line and to 12 ecotype lines, with no evidence for unintended changes.

25.4 Allergen Detection

Evaluation of their allergenicity potential is part of the reglementary safety assessment before marketing. 2DE of protein extracts may provide a complementary approach as shown by the following examples.

Batista et al. (2007) performed 2DE of flour protein extracts from a glyphosate-tolerant soybean and its non-GE comparator. Blots were probed with sera from soybean-sensitive individuals. MS was also used to identify IgE-binding proteins. Allergen production apparently remained unaltered as a consequence of the genetic modification.

Nakamura et al. (2010) also used 2DE-based techniques to compare an experimental GE potato line (producing an Arabidopsis transcription factor) with a control. The patterns of IgE-binding proteins were almost identical, with, however, several quantitative differences in these proteins (identified by MS/MS).

Satoh et al. (2011) used a similar approach in the case of GE rice. Salt-soluble proteins were probed with patient sera and antigen-specific animal sera. No differences were found between GE or non-GE lines.

25.5 Discussion

These proteomic studies are heterogeneous and have to be considered as exploratory. Considering all sources of difficulties in data interpretation (such as plant to plant variation, the possibility that comparator lines are not necessarily fully isogenic, experimental errors, etc.), care has to be taken as to their biological signification. These studies form merely a compilation of data; no normalized and validated approaches are available for routine assessment of GE plants.

Nevertheless, some lessons can be learned from these studies. Some differences are found in the proteome of GE varieties compared to control varieties. However, these differences can be generally considered as quantitatively minor and, when data are available, comparison of various conventional varieties consistently shows more differences. This is due, on one hand, to the biodiversity of existing varieties and, on the other, to the fact that GE lines have been selected from the laboratory to the field by phenotypic comparison with a close comparator. In addition, for marketed varieties, the transgenic trait has usually been introgressed into elite lines

(these crosses contribute to the elimination of unintended genomic modifications). In some studies, environmental factors (such as field location or year of sampling) have consistently been shown to exert a greater impact than transgenesis.

As shown by Ricroch et al. (2011), metabolomics are the prevalent "omic" approach to assess GE crops, followed by transcriptomics. Few laboratories have used different omics comparatively. Therefore, an exhaustive comparative assessment of these techniques is not yet possible. Nevertheless, when data are available, there is no indication that proteomics will arrive at different general conclusions regarding the extent of unintended impact of transgenesis.

Perhaps the most useful role for 2DE protein analysis would be for allergenicity predictions. Proteomic and mass spectrometry methods can be used for qualitative and quantitative estimation of the allergen levels, including new ones.

None of these proteomic assessments has raised new safety concerns about marketed GE varieties. This is not surprising considering the experience acquired after 16 years of GE crop marketing. However, considering the highly polarized opinions on GE crops and a certain distrust in data provided by seed companies, it is important that new approaches such as transcriptomics, proteomics, and metabolomics have been used by public research laboratories.

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