Food and feed safety assessment principles to evaluate new applications for agricultural biotechnology

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Actors & Outcome

- Taskforce 8:
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- Peer-reviewed by 20 international experts prior to journal submission

New opportunities for agricultural biotechnology

- Transcription factors
- Genes that alter gene expression within a plant
  - Approximately 10% of genes in a plant genome
  - Many traits can be affected as a consequence
- Gene suppression/RNA interference (RNAi)
  - Turn off expression of genes that are normally turned on
- Other modulations of gene expression
- Began with a review of the role of TF and gene-silencing in plant domestication & breeding
  - Some examples follow

Naked grains of maize

- Three image captions:
  - The tga1 gene in maize
  - SBP-domain transcription factor
  - Wang et al., 2005 Nature 436: 714-719

Fruit size in tomato

- Two image captions:
  - Frary et al., 2002. Fv2.2: a quantitative trait locus key to the evolution of fruit size in tomato. Science 289: 85-88

Green Revolution wheats

- Two image captions:
  - The Harvesters, by Pieter Bruegel, 1565
  - Example of tall (L) and dwarf (R) wheats
TF's also involved in stress tolerance

- CBF transcription factors

The expression of several Cbf genes at the Fr-A2 locus is linked to frost resistance in wheat.

Vaghefi et al., 2008

A cluster of 11 CBF transcription factors is located at the frost tolerance locus Fr-A2 in Triticum monococcum.

Miller, Galiba & Dubcovsky, 2006

RNA interference

Gene silencing

- The unifying mechanism behind
  - Natural & engineered virus resistance
  - Other naturally occurring traits

Low glutelin rice

News and Views

Nature 425, 390 (23 May 2003) | doi:10.1038/nature02178

RNA Interference: Cereal adulterity

Christopher Carstens

For people who must restrict their protein intake—such as patients with kidney failure—a mutant rice that is naturally low in proteins called glutelin is beginning to be used as a dietary therapy. Kusaba and colleagues have now discovered how this mutant achieves the glutelin levels. (Plant Cell doi:10.1105/tpc.014820, 2003). The answer involves the increasingly well-known biological phenomenon of RNA interference.


Historical use of intentional gene silencing in agriculture

- 1930’s - Farmers intentionally inoculate their orchards with a mild virus
  - Become resistant to more virulent strains
  - Became the incentive to engineer plants with virus coat protein genes
  - Turns out to silence virus genes via RNAi

Virus-resistant Hawaiian papaya

Non-transgenic Transgenic
Gene-suppression

- Some original GM products are now understood to have resulted from RNAi
  - Flavr Savr tomato

How can RNAi be used in agriculture?

- Virus resistance
- Altered ripening
- Speciality oils
- Pathogen resistance
- Insect control
- Flower color

RNAi summary

- Is a natural phenomenon
- Explains many traits in crop plants
- Is a unifying mechanism that explains many of the observations seen with genetically modified plants
  - Co-suppression
  - Anti-sense RNA
  - Virus resistance by cross protection

Safety

Are plants produced via TFs and RNAi safe for food/feed?

- First set of GM crops produced by introducing a gene that makes a protein
  - Insect and herbicide resistance
  - Safety assessment geared towards safety of the protein
    - Allergenicity
    - Toxicity
  - Safety assessment also uses compositional analysis

Transcription factors

Food/feed safety issues

- TFs only modulate existing pathways and metabolites within a species
  - Relative quantities/timing of plant compounds can be changed, but
  - No novel compounds produced
  - No new allergy or toxin concerns

Therefore, a targeted compositional analysis may be performed to ensure safety of elevated levels of given compounds

High anthocyanin tomato

Gonzalez et al., 2009 Purple as a tomato: towards high anthocyanins tomatoe Trends in Plant Science 14: 207-211
RNAi – Assessing safety

- RNA is ubiquitous and an innocuous part of the diet
  - Tens of thousands in each plant cell
  - Many are perfect complements for essential human genes
  - No indication that a plant-produced siRNA has ever silenced a human gene
- No proteins are produced
  - No concerns with toxins or allergens
    - If ensure no start codons are present
- Is specific only to target gene sequence
  - No concerns over effects to non-targets

Picotee patterns in flowers are due to RNA

Overall Recommendations

- The current comparative assessment process is appropriate to evaluate TF/RNAi transgenics
- The currently employed targeted analytical composition methodologies are fully capable of detecting biologically significant unintended effects
  - Unintended ≠ dangerous

Specific Recommendations

- The TFs engineered into plants may come from a source organism with a history of safe use
  - When a history of safe use cannot be established, a Tier 1 protein safety assessment should be applied to assess safety of the TF protein.

- The safety assessment of crops developed by the modulation of endogenous plant gene expression should focus on a comparative assessment/compositional analysis to the non-transgenic version
  - In the case of a stress-tolerance trait, the comparator should also be grown, to the extent possible, under conditions that the crop has been engineered to tolerate, to ensure that no adverse compositional changes affecting safety for consumption have occurred

Bon appetit!