Plant metabolic engineering: are we ready for phase two?

Editorial overview

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Approximately 40 million hectares of transgenic crops will be planted worldwide in 1999. Included in this will be close to 50% of the soybean acreage in the US, over 70% of the canola acreage in Canada, 20% of the US corn crop and over one third of the cotton acreage in the US. Clearly, transgenic crops are already making an immense impact on agriculture, particularly in North America. This year, land area greater than all of Great Britain or the US state of Iowa will be planted with transgenic crops.

Over 90% of the transgenic seeds which are planted for commercial production have been genetically engineered to provide either herbicide or pest tolerance. These traits represent the first phase of crop metabolic engineering. The traits now available in most transgenic crops provide farmers with either lower costs of production or higher yields or both. For example, glyphosate or other herbicide tolerant crops require less overall herbicide use, and often have higher yields due to less competition from weeds.

Phase two of plant metabolic engineering is just beginning but can be expected to have even larger eventual impact on agriculture than phase one. Phase two can be considered the engineering of plants, not for higher yields, but to provide new or improved products or more complex traits. This second phase promises to have a larger economic impact on agriculture because it will provide farmers with the opportunity to produce higher-value products for new markets. Over the past several decades, the number one problem for farmers in most of the developed world has been the low prices which they have received for agricultural commodities. The low prices in turn stem from the high efficiency of modern agriculture and the over-capacity of our agricultural production systems. Governments have responded to these issues with a variety of price supports and acreage ‘set-aside’ programs which together have cost taxpayers many billions of dollars each year. Although the herbicide or pest tolerant crops produced during phase one provide substantial benefits to farmers who use them, these improvements have not addressed the central issue of low prices. Although low farm commodity prices benefit consumers, this trend has also greatly transformed agriculture from its previous small farm structure toward an ever-larger scale business controlled by conglomerates. The technological successes of agriculture which are, to a large extent, based on basic and applied plant research have contributed to the trend toward ever lower commodity prices. The long-term effect has lead to the transfer of income out of our rural communities and into a smaller number of hands. Phase two of plant metabolic engineering presents the opportunity for plant biologists to help begin a reversal of this trend.

Plants as plants

Plants can be considered as sophisticated chemical factories which use sunlight as a power source and atmospheric CO₂ as the feedstock. With these abundant and inexpensive inputs, together with a highly evolved agriculture, our crops produce complex organic molecules such as starch at a cost of $0.2/kg and oils at a cost of $0.5/kg. For centuries, plants have also provided feedstocks for the chemical and pharmaceutical industry. In 1930, 30% of the industrial organic chemicals were derived from plants, but by 1960 this proportion had been reduced to less than 1% as the petrochemical industry developed cheaper or improved alternatives; however, two major factors suggest this trend may reverse. First, the costs of agricultural products have declined steadily over the past 75 years, whereas oil prices have generally increased such that a kilogram of corn now can be produced for approximately the same cost as a kilogram of crude oil. Second, we now have the ability through genetic engineering to tap into the vast chemical diversity produced biologically. Within the plant kingdom alone, over 25,000 different organic chemical structures are produced and the microbial world provides even more opportunities. The demonstration that, using bacterial genes, polyhydroxybutyrate can be produced in plant leaves at levels up to 14% of dry weight [1] was a dramatic demonstration of the potential to radically alter plant metabolism toward the production of new products. Biologically produced products can provide the chemical industry with much greater diversity and oxidation states than the comparatively limited, highly reduced hydrocarbon structures found in crude oil.

Can plants really take over synthesis of many products we now obtain from petrochemicals? Or, are we ready for phase two of plant metabolic engineering?

Although a number of areas are under development, engineering of plant fatty acid composition is perhaps the most advanced toward commercial production of new plant products. There are now two examples of transgenic plant oils in commercial production which have been modified using a single gene. Calgene developed high-lauric acid canola which can be used in a variety of applications including specialty foods and soap and detergent manufacture. High-lauric canola lines are now being planted in several countries around the world. DuPont developed a
transgenic soybean variety with >85% oleic and low saturated fatty acids [2]. Such oils are both healthier for human consumption and are extremely stable, making them useful as biodegradable lubricants. The class of fatty acid modification enzymes known as di-iron are now recognized as responsible for most of the chemical diversity found in the >500 fatty acid structures found in plants. The article by Napier et al. (pp 123–127) provides information on a number of recent developments in the identification of useful genes for fatty acid modification from this class of enzymes.

Despite the two recent commercial successes with modifying plant oils using a single gene, a number of other attempts to engineer oilseed fatty acid composition have resulted in sobering results. Plants have been transformed with genes which produce fatty acids with unusual double bond positions, conjugated double bonds, hydroxy, acetylenic, or epoxy, functions. In all these cases, although the genes were isolated from plants which accumulate the unusual fatty acids at levels of 70–90%, the production level in the transgenic plants has in most cases been only 5–20%. Since enzyme expression levels do not seem to be limiting, other unknown limitations need to be uncovered. The article by Nuccio et al. (pp 128–134), provides similar examples from the efforts to increase synthesis of osmoprotectants. Thus, it is clear that in almost all cases, phase two of plant metabolic engineering will be technically more complex than phase one. Here are a few more reasons why:

**One**

In many cases it will be necessary to manipulate several genes simultaneously. All of the phase one engineered crops in commercial production are based on a single gene which provides the valuable trait. It is clear from the examples mentioned above, however, that in many cases a single gene will be insufficient to achieve high-level production of desired chemicals. The article by Hitz (pp 135–138) provides some insight into the costs associated with engineering of multiple genes. It is clear that having these tightly linked is the best way to avoid expensive and time-consuming breeding efforts.

**Two**

We must learn much more about plant biochemistry and the interrelationships of metabolic pathways than we currently know. Research on plant biochemistry and metabolism has been comparatively neglected in recent years while most scientists and funding agencies emphasized molecular biology and genetics. To fully exploit the abilities of plants we need a new generation of researchers who are also skilled in the complexities of plant metabolism. As one example, Lange and Croteau’s (pp 139–144) article illustrates that the pathways which produce plant isoprenoids are just now being elucidated. The enzyme which catalyzes the first reaction of plastid isoprenoid synthesis was discovered only two years ago and all the steps to form isopentenyl diphosphate are still not understood. The plant secretory glands found in specialized trichomes of species such as mint represent a structure able to produce high concentrations of relatively pure organic compounds which otherwise might be toxic to the plant. Interestingly, trichomes of other plant species also represent some amazing chemical factories. For example, trichomes of some *Lycopersicon* species secrete sticky glucose fatty acid esters which can represent 25% of the leaf dry weight [3] and cotton fibers represent specialized cellulose fiber factories which derive from glandular trichomes. Lange and Croteau point out that almost nothing is known about what determines the number or type of trichomes produced by a leaf surface.

**Three**

The costs of producing a new product in plants can be complex. Hitz points out that such costs fall into several categories: first, the costs of crop breeding approximately double for each independently segregating locus which must be maintained in the breeding population; second, any yield penalty associated with the transgene must add to the cost of the end product; third, identity preservation of a transgenic crop adds to storage, transport and processing costs; and fourth, perhaps most importantly, the cost of special extraction or processing of a new plant product can dramatically increase the price of an end product. For example, much biological production of chemicals is now done through fermentations. Perhaps a useful comparison can be made of how extraction costs impact the cost of two biologically produced and biodegradable plastics. PHB (polyhydroxybutyrate) plastic (biopol) can be produced in *E. coli* at a level of 70% of its dry weight. Polyactic acid plastic (PLA) can be produced by polymerization from lactic acid produced in *E. coli*. PHB sells for $4–5/kg whereas PLA can be produced for $1–2/kg. This substantial difference is in large part due to the extraction, and purification costs associated with recovery of PHB from *E. coli* cells whereas the precursor of PLA is soluble and can be recovered from the fermentor at low cost. The obvious lesson is that plant metabolic engineering schemes will be most successful if the products can be recovered at low cost and high yield.

In summary, there are a number of fundamental economic trends and technical advances which have converged to propel us toward phase two of plant metabolic engineering. The articles in this section provide some details on what needs to be done to realize the full potential of plants as chemical factories.

**References**

