Nutritional enhancement of plants

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Plants can provide most of the nutrients required in the human diet; however, the major staple crops are often deficient in some of these nutrients. Thus, malnutrition, with respect to micronutrients like vitamin A, iron and zinc, affects >40% of the world's population. Advances in molecular biology are being exploited to produce crops enhanced in these key nutrients. Other nutritional targets include the modification of fatty acid composition and the enhancement of antioxidant levels, particularly carotenoids, such as lycopene, and flavonoids. However, the benefit of these 'biofortified' crops to human nutrition remains to be elucidated.

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Abbreviations

CVD	cardiovascular disease
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
GLA	γ-linoleic acid
PUFA	polyunsaturated fatty acids
QTL	quantitative trait loci

Introduction

The advent of molecular biology and a recent increase in consumer awareness of nutrition have provided the means and incentive to enhance the nutritional value of plant material [1,2]. This nutritional enhancement of plants is being tackled using a variety of approaches [3]. Conventional breeding is one such approach, exemplified by the production of broccoli with enhanced glucosinolate content [4]. Glucosinolates are thought to have a role in the prevention of cancer by acting as inducers of the anti-carcinogenic marker enzyme quinone reductase. The new hybrid varieties show a 100-fold increase in the ability to induce this enzyme [4]. The other major approach to nutritional enhancement is via genetic modification, an example of which is the production of so-called 'golden rice', which has enhanced levels of the carotenoid β-carotene in its grains [5,6]. β-Carotene acts as a precursor to vitamin A in the human diet. In this case, the introduction of three genes encoding key enzymes in the carotenoid biosynthetic pathway resulted in the synthesis of β-carotene in the rice grain. The use of this genetic modification approach, however, has met with considerable consumer resistance amid concerns for its safety [7]; stringent controls and the provision of more public information are necessary to assure and encourage public acceptance [8].

Although the ability to manipulate plant metabolism is becoming well established, identifying which target nutrients are suitable for such 'biofortification' is problematic. For example, it has been suggested from epidemiological studies that increased consumption of fruit and vegetables is correlated with a reduced risk of several diseases, including cancer [9] and cardiovascular disease (CVD). However, it has proved difficult to attribute this effect to any particular nutrients within these foods. To date, targets for 'biofortification' have included macronutrients such as proteins (e.g. it may be desirable to increase levels of essential amino acids such as methionine) and fatty acids. Micronutrients such as vitamins A and E, carotenoids such as lycopene, flavonoids and minerals like iron and zinc have also been targeted. The 'bioavailability' of these nutrients is another area where there is a need for better information. The form in which nutrients are absorbed or how they may be metabolised within the body is often unclear. Over the past year several advances have been made in the application of molecular biology to produce nutritional enhancement in plants. Here, we discuss some recent achievements, especially in the enhancement of antioxidants, minerals and fatty acids.

Antioxidants

Several studies have found inverse relationships between the intake of fruit and vegetables and the incidence of cancer [9]. A similar link has been suggested with CVD and a recent paper has provided support for this by demonstrating a correlation between fruit and vegetable intake and CVD in the general US population [10•]. This protective ability is thought to reside in the antioxidants found in fruit and vegetables. The consumption of fruit and vegetables has been shown to increase plasma antioxidant levels in human subjects and this has been associated with reduced blood pressure, which in turn could be a preventative factor in CVD [11•]. Fruit and vegetables contain a wide range of antioxidants including carotenoids such as lycopene and β-carotene, vitamins C and E, and polyphenolics such as quercetin.

Lycopene

The major carotenoid pigment found in tomato — lycopene — has aroused considerable interest, especially as a

potential cancer chemopreventative. Intake has been particularly associated with protection from prostate cancer [12,13], although these epidemiological studies have produced some inconsistent results. The inconsistencies may be partly explained by problems with the bioavailabilty of lycopene from different sources [14]. Fruit and vegetable intake has also been linked with protection from breast [15] and colorectal [16] cancers, although in both cases a link with lycopene, or any other dietary carotenoid, has not been conclusively established. The mode of action of lycopene has been tested in a few animal models, but although several of these studies have confirmed a protective response its mechanism of action is not clear [17]. Although lycopene is a potent antioxidant there is some evidence that it, like other dietary carotenoids, may act in other ways to protect from cancer [18].

Several approaches have been used to enhance lycopene levels in plants. Natural mutants of tomato are available, such as high pigment, and these may be employed in breeding strategies. A recent study using crosses between carrot varieties identified one quantitative trait locus (QTL) for lycopene and three for β-carotene [19•]. A similar study using recombinant inbred lines of tomato has identified 130 QTL for 38 different traits including lycopene and carotene levels [20•]. The characterisation of these QTL may assist conventional breeding for enhanced carotenoid levels by providing molecular markers.

Lycopene levels in tomato fruit have also been enhanced through genetic modification. Expression of a gene for phytoene synthase — a key enzyme in the carotenoid pathway — from the bacteria *Erwinia uredovora* in tomato plants resulted in a twofold to fourfold increase in total carotenoid levels and an enrichment of 1.8-fold and 2.2-fold for lycopene and β-carotene, respectively, in the fruit [21••]. The expression of a yeast *S*-adenosyl methionine decarboxylase in tomato fruit also resulted in an enhancement of lycopene levels [22•]. In this instance, however, the aim of the genetic modification was the manipulation of polyamine biosynthesis; we know this was achieved as these fruit also exhibited increased levels of spermine and spermidine. The effect on lycopene levels was unexpected and is difficult to explain.

It is a matter of some debate whether raising the levels of lycopene in tomato fruit will have any major influence on its bioavailability. Lycopene is a fat-soluble compound and as such is poorly absorbed by the body from fresh fruit. Absorption is much greater from processed tomato products, such as pastes, especially if this involves mixing with fats. A recent report has described an artificial formulation in which the lycopene is entrapped within whey proteins. This 'lactolycopene' has similar bioavailability to lycopene in tomato paste [23]. On the basis of absorption from ketchup or oleoresin capsules, it has been suggested that an intake of 5–10 mg a day would be required to provide a reasonable plasma level of lycopene [24]. The state of current research is such that although there may be a general link to prevention of prostate cancer, there is no official clinical recommendation for any supplementation [25].

Another potential problem with lycopene relates to which form of the carotenoid is actually absorbed. It has been shown that in the fruit and tomato products such as paste and lactolycopene >90% of lycopene is in the all-*trans* form. However, the lycopene appearing in the plasma and accumulating in the body tissues is predominantly in the *cis* form [26]. The *cis* form is more soluble in the bile micelles and this might account for any preferential absorption of this isomer. The effect, if any, of this on the efficacy of lycopene either as an antioxidant or as a chemopreventative agent is unclear.

Vitamin E

Tocopherol, or vitamin E, is another important dietary antioxidant and has been the target of genetic modification. It occurs in plants in several isomeric forms, with α- and γ-tocopherol being the most abundant. It is thought that α-tocopherol is the most beneficial dietary form, but in many foods it is γ-tocopherol that predominates. The over-expression of γ-tocopherol methyl transferase in *Arabidopsis* enhanced production of the α form of this vitamin [27]. Similar genetic modification is being used in attempts to modify the α-tocopherol:γ-tocopherol ratio in corn [28] and to identify molecular markers to assist breeders. However, it has recently been proposed that γ-tocopherol, or compounds metabolised from it, may also be important for health and as such the total levels of both isoforms should be increased. The recent characterisation of a tocopherol cyclase [29], which is a key enzyme in the biosynthesis of all tocopherols, may prove beneficial in the future, as may the discovery of a new biosynthetic pathway [30].

Other antioxidants

Other important antioxidants in fruit include polyphenolics such as flavonols. Tomato has been a useful model for studying methods that we might use to enhance levels of these antioxidants. In the normal fruit, flavonoids are at a low level and are localised in the skin. The induction of flavonoid synthesis in the flesh of the tomato fruit has been demonstrated [31••]. This was achieved by expression of two transcription factors, LC and C1, from maize, which resulted in the production of high levels of the flavonol kaempherol in a tissue that would normally be devoid of this compound.

Minerals

A lack of minerals, especially iron, is a major cause of malnutrition in many countries. It has been estimated that iron deficiency affects ~30% of the world's population [32••]. Thus, the 'biofortification' of plants with

minerals is another major target for nutritional enhancement. Again, this is being addressed by the application of conventional breeding and genetic modification. Genetic variation in mineral accumulation has been observed in several staple crops and this is being exploited in breeding programmes. However, the inheritance of this trait is likely to be complex [33]. The identification of QTL may assist these breeding programmes, and as more information on the biochemistry of mineral accumulation becomes available genetic modification can be applied [34]. A particular target for genetic modification is the increased accumulation of iron in rice [32••]. A twofold enhancement of iron concentration was achieved by the expression of a gene for ferritin in rice. In addition to enhancing mineral levels, factors that influence bioavailability, either positively or negatively, may also be manipulated [35]. In rice the bioavailability of iron has been targeted by introducing a gene for a phytase; this resulted in a 130-fold increase in the expression of this enzyme. As cysteine-rich peptides are thought to enhance bioavailability of iron, the expression of a gene encoding a cysteine-rich metallothionein-like protein in the rice may also assist absorption of this mineral [32••].

The manipulation of phytase activity is an important approach to enhancing mineral bioavailability. Phytic acid, a storage form of phosphorous in plant tissue, binds several minerals, including iron and zinc, very strongly. As it is poorly digested and thus prevents absorption of these minerals, phytic acid may represent the most important factor restricting the uptake of these minerals [36]. The expression of phytase in crops enhances the breakdown of phytic acid and releases minerals. This enzyme may also help to increase the bioavailability of phosphorus [36]. The reduction of phytic acid levels is an alternative approach and breeding strategies are being used to develop low-phytate varieties of maize, barley, rice and soybean [37].

Fatty acids

The fatty acid composition of seed oils was an early target for manipulation via the application of genetic modification. Early achievements included the production of oils high in either oleic or stearic acid, which gives stability during cooking and solidity at room temperature, respectively. This has been achieved through a combination of breeding, natural mutations and genetic modification [38], the latter also being exemplified by the recent manipulation of cotton seed oil [39]. These modifications may have nutritional benefits in that they reduce the need for saturated, hydrogenated or *trans* fatty acids, which may favour the development of CVD.

Another target would be the production of polyunsaturated fatty acids (PUFAs) whose enhancement in the diet, although not 'essential', might be highly beneficial to human health [40]. PUFAs include γ-linoleic acid (GLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). GLA is synthesised from linoleic acid by the action of a Δ-6 desaturase enzyme found in a restricted range of higher plants. The incorporation of a borage gene encoding Δ-6 desaturase into tobacco has been shown to confer the ability to synthesise GLA [41]. More recently, this has been carried out in tomato and the resulting transgenic fruit shown to have 10% of their total fatty acids as GLA [42]. A Δ-6 desaturase gene isolated from a fungal source has been used to transform Brassica to give a seed oil containing ~40% GLA [43]. A more challenging target is the production of ω-3 PUFAs, especially EPA and DHA. These are normally associated in the diet with fish oils and are synthesised by microorganisms such as marine algae. These fatty acids contain 20 and 22 carbons, respectively, and therefore their production would require the introduction of specific elongases, as well as desaturases, into target crops. The classic aerobic biosynthetic pathway for these fatty acids is well known, but more recently it has been shown that a novel anaerobic pathway, analogous to the polyketide biosynthetic pathway, exists in some microorganisms [44•]. Genes encoding enzymes in these pathways may be useful in directing the synthesis of these long-chain fatty acids in heterologous hosts. The first steps along this route have been taken with the characterisation of keto-reductase genes from *Saccharomyces cerevisiae* [45,46], which are enzymes involved in the microsomal elongase. A putative elongase has also been characterised from *Isochrysis galbana*, marine algae rich in DHA. When expressed in transgenic yeast, this gene conferred the ability to elongate linoleic acid and α-linoleic acid to their 20-carbon equivalents [47••].

Conclusions

Rapid advances in conventional breeding, assisted by QTL identification and genetic modification, are providing a range of novel crops with enhanced concentrations of key nutrients. However, the actual potential for these to benefit human health remains to be established. Clear targets for enhancement need to be set. These may include long-chain PUFA, vitamins such as A, C, E and folate, carotenoids such as lycopene, polyphenolics such as flavonoids, steroids, and minerals. There is also likely to be a much wider range of nutritionally beneficial phytochemicals awaiting discovery. In some instances the desirability of nutritional enhancement seems clear, as with iron and vitamin A in rice. However, in other cases the potential is more vague. Also, the bioavailability of nutrients from, and efficacy of, these nutritionally enhanced crops needs to be carefully assessed. In some cases manipulation of this bioavailability, either alone or in combination with nutrient enhancement, may be more beneficial. Finally, resistance from the public to the introduction of genetically modified foods may well seriously inhibit the introduction of potentially beneficial crops. It is therefore clear that more studies need to be

carried out to assure the public of the safety and benefits of these foods.

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