Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

Editorial overview: Biofortification of crops: achievements, future challenges, socio-economic, health and ethical aspects

Dominique Van Der Straeten, Teresa B Fitzpatrick and Hans De Steur

Current Opinion in Biotechnology 2017, **44**:vii–x

For a complete overview see the Issue

Available online 22nd March 2017

http://dx.doi.org/10.1016/j.copbio.2017.03.007

Dominique Van Der Straeten

Laboratory of Functional Plant Biology, Department of Biology, Ghent University, K.L. Ledeganckstraat 35, B-9000 Ghent, Belgium
e-mail: Dominique.VanDerStraeten@UGent.be

Dominique Van Der Straeten is a full professor in Plant Physiology at Ghent University and is the Research Director of the Laboratory of Functional Plant Biology. Her PhD studies on ethylene metabolism in plants were conducted at Harvard University in Boston and at Ghent University. Her research interests encompass micronutrient biofortification, plant hormone biology and bio-imaging. She has authored over 170 Web-of-Science indexed publications and received several scientific awards.

Teresa B Fitzpatrick

Department of Botany and Plant Biology, University of Geneva, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland
e-mail: Theresa.Fitzpatrick@unige.ch

One of the biggest challenges humankind is facing in the 21st century is to sustainably feed the ever-growing population on the globe, estimated to exceed 11 billion by 2100 [1]. In 2015, chronic undernourishment decreased from over 1 billion to below 800 million for the first time in 25 years [2]. However, while caloric malnutrition (acute hunger) has decreased, micronutrient malnutrition, the so-called “hidden hunger” caused by a lack of vitamins and minerals, still affects 2 billion people and hence represents the most common form of malnutrition. Paradoxically, being overweight from food overconsumption affects another 1.9 billion people (although these may also suffer from hidden hunger) [3].

In April 2016, the United Nations (UN) declared the start of an “International Decade on Nutrition” to meet the nutrition-related targets of the Sustainable Development Goals (SDGs) adopted by its member nations last year [4]. As part of the SDGs, a major aim is to end all forms of malnutrition by 2030, overarching the objectives of ensuring both food and nutritional security. Ending hunger, achieving food security and improving nutritional quality of crop products will require a profound change of the food and agricultural system, as well as a major investment in nutrition education, both of which should foster diversity. Though this will empower farmers to grow – and consumers to choose – healthier crop products, there is not only a need to address the production and processing but also the marketing and advertisement of food products, which should collectively aim at healthy diets.

While not being limited to the developing world, micronutrient malnutrition has by far the most profound impact thereon. Micronutrient malnutrition has long-term effects on human health, learning ability and productivity and thus poses a major impediment to socioeconomic development and contributes to a vicious circle of underdevelopment [5]. Micronutrients are particularly low in the 5 major staple crops (rice, corn, wheat, cassava and potato), on which more than half of the world population relies for its daily caloric intake. Micronutrient content is further decreased due to post-harvest and processing losses [6,7].

Several strategies exist to fight micronutrient malnutrition, including supplementation (*e.g.* in the form of pills) and industrial fortification. Unfortunately, the latter have their limitations in practice. Supplements are not always taken on a regular basis, while food fortification requires quality

Teresa B Fitzpatrick is a full Professor at the University of Geneva in Plant Biochemistry and Physiology and is the Director of the Department of Botany and Plant Biology. She obtained her PhD from the University of Dublin and started her own research group at the Swiss Federal Institute of Technology in Zurich before moving to Geneva. Her research is strongly focused on vitamin metabolism in plants, particularly the B vitamins and their association with general metabolism and stress responses in plants. A variety of molecular approaches are used ranging from protein chemistry to genetics.

Hans De Steur

Department of Agricultural Economics, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium
e-mail: hansdesteur@hotmail.com

Hans De Steur is a post-doctoral assistant at the Department of Agricultural Economics, Faculty of Bioscience Engineering at Ghent University, Belgium. He obtained his M.S. degrees in Sociology and Complementary Studies in Economics and Business Administration from Ghent University. In 2011, he successfully finished his PhD in Applied Biological Sciences, entitled "Market potential of folate biofortified rice in China". His research foci include socio-economic analysis of biofortified and GM crops.

control, imposing the need for specialized techniques and infrastructure, which usually are very restricted in developing countries. Fortified foods and supplements are often only available in cities and hence, cannot be benefited from by poor rural populations. Biofortification of staple crops is a complementary, cost-effective method to alleviate the global burden of micronutrient malnutrition [8]. Biofortification can be defined as the process by which the nutritional quality of food crops is improved through agricultural technologies, including conventional and molecular plant breeding, metabolic engineering through modern biotechnology such as genetic modification, fertilization techniques or, in the case of minerals, by biostimulants improving their bioavailability. Several efforts to biofortify staples have been undertaken, with vitamin A enhancement of rice and sweet potato as prime successful examples of metabolic engineering and breeding, respectively (Golden Rice, [9,10]; Orange Fleshed Sweet Potato, [11]. The growing recognition of biofortification as a means to fight micronutrient deficiencies was illustrated by the 2016 World Food Prize honoring Maria Andrade, Robert Mwanga, Jan Low, and Howarth Bouis for the development and implementation of biofortification by breeding critical micronutrients into staple crops, reducing 'hidden hunger' for millions (https://www.worldfoodprize.org). Despite a few attempts and the fact that there are no examples of multi-biofortification where the target levels of all enhanced micronutrients has been reached, the content of a series of single micronutrients has been successfully enhanced in several target crops, and their bio-availability has been proven.

This issue of *Current Opinion in Biotechnology* highlights metabolic engineering and breeding techniques towards biofortification of crop plants. Different reviews focus on carotenoid-derived vitamin A, vitamin B_1, B_6, B_9, C and E as well as two mineral micronutrients, iron and iodine.

Giuliano discusses the enhancement of carotenoids in crop products, with provitamin A being a major target. Worldwide an estimated 250 million preschool children are vitamin A deficient and between 250,000 to 500,000 vitamin A-deficient children become blind every year, half of them dying within 12 months of losing their sight. Since the development of first generation Golden Rice, enhancement of both provitamin A and non-provitamin A carotenoids has been obtained in a series of crops.

The efforts on B vitamin enhancement indicate the importance of balancing different vitamers, in particular for vitamin B_1 and B_6.

Thiamin (vitamin B_1) deficiency is common in populations whose diets are mostly based on high carbohydrate staples like white rice. Goyer summarizes the current knowledge about thiamin biosynthesis in plants and efforts that have been made to increase its content by genetic engineering. Together with the discovery of regulatory elements, the characterization of biosynthesis, transport and salvage genes has laid the foundation for the first successful thiamin engineering strategies. Yet many aspects of thiamin metabolism remain poorly understood, hindering further improvement in biofortification of this vitamin. Fudge et al. present a rationale for vitamin B_6 biofortification and the most recent advances in achieving this. Three of the world's top five staple crops (rice, wheat and cassava) do not meet the recommended dietary intake for vitamin B_6, when consumed as a major proportion of the diet. In contrast to vitamin B_1, vitamin B_6 enhancement up to target levels has been achieved in cassava by genetic engineering. In addition, controlled enhancement of the appropriate B_6 vitamer in crops has the potential to confer stress resistance, as well as enhance bioavailability.

Strobbe and Van Der Straeten report on vitamin B_9 (folates), the deficiency of which is still very common. They summarize how the biosynthesis pathway has led to successful engineering for biofortification purposes in rice, tomato, Mexican common bean and lettuce, and present strategies to enable adequate biofortification in potato and other staple crops. They also report on the essentiality of ensuring stability of the vitamin, which has been achieved in rice, and justify the need to successfully biofortify other staple crops with folate.

Macknight et al. highlight that in addition to the renowned antioxidant function of vitamin C, it is also required as a cofactor for enzymes involved in epigenetic reprogramming and as a regulator of cellular iron uptake. Vitamin C is also important in the response to many environmentally induced stresses in plants, therefore its enhancement can potentially combat both the latter stress responses as well as improving nutritional content. Interestingly, some ‘super-fruits’ accumulate vitamin C at levels orders of magnitude above other tissues or crops. Deciphering the mechanism behind this accumulation could provide efficient ways to enhance vitamin C levels in the edible parts of staple crop plants to positively impact human health.

Mène-Saffrané and Pellaud present the case for biofortification of vitamin E, a potent antioxidant. Surprisingly, large portions of Western populations are reported to exhibit chronic symptoms of vitamin E deficiency. However, the long-term effects of chronic deficiency in humans are yet to be established. The biosynthesis pathway is outlined and breeding as well as engineering approaches to enhance vitamin E content in plants are summarized. The authors conclude that the γ-/α-tocopherol conversion is one of the most effective ways to enhance active vitamin E content in crop plants and propose that elucidation of chlorophyll turnover will likely open new avenues for vitamin E biofortification.

Though for several micronutrients only poor statistics of deficiency prevalence are available, iron and iodine deficiency are considered the most important amongst mineral deficiencies. Iron deficiency anemia affects around two billion people globally. Women and children are the most vulnerable. Vasconcelos et al. highlight achievements on iron biofortification through conventional breeding and genetic modification. Enhancing the level of minerals in target tissues requires proper understanding of the complex process of bioavailability, uptake, transport, and sequestration mechanisms in plants. Through conventional breeding, bean and pearl millet varieties with a high iron content have been developed and were shown to improve the iron status in young women in Rwanda and in school children in India. Achieving the target levels of iron in polished rice grains however, was only possible by genetic engineering. This represents another good example of how the available genetic tools can be successfully employed on a species-specific basis. Iodine deficiency is the world’s most prevalent, yet easily preventable, cause of brain damage. Gonzali et al. evaluate the case of iodine biofortification. Commercial iodine-biofortified vegetables with positive nutritional impact have been developed. Dietary inclusion of iodine-enriched plant food, together with the use of iodized salt, may thus successfully contribute to improving the iodine status of a population. However, none of the staple crops have been successfully biofortified with iodine so far. Identification of the genetic traits regulating iodine uptake, mobilization and retention in the plant and suitable manipulation thereof are therefore necessary.

Despite the efforts on the individual micronutrient cases outlined above, most staples are deficient in a considerable number of micronutrients, implying the urgent need to invest in multi-biofortification approaches to create nutritionally complete crops. Moreover, in several cases conventional breeding approaches alone cannot increase the micronutrient content in crops to nutritionally relevant levels because of the lack of natural variation. The use of metabolic engineering, either by genetic modification or novel genome editing and epigenetic methods, is the most valuable option to complement breeding technology or to obtain an increase of multiple nutrients conferred by a single overexpression cassette, carrying the different traits. In addition to simultaneous enhancement of the level of multiple micronutrients, it is imperative to consider the issue of long-term stability of micronutrients in stored crop products. This is of particular importance for grain crops, as poor subsistence farmers store the seeds until the next harvest, which can be up to a year. Moreover, bio-accessibility and bioavailability, both depending on the biochemical nature of the nutrient, can promote or delay uptake, and determine how efficiently different nutrients are transported through the blood, stored, and utilized. Díaz-Gómez et al. reflect on how nutrients are presented, which affects their processing in the human body. The latest studies on the effects of the food matrix, processing and storage on nutrient transfer from biofortified crops are reviewed, as well as current knowledge about nutrient absorption and utilization. Hence, several new challenges lie ahead. Sustainable eradication of micronutrient deficiencies can however not be reached unless biofortification approaches go hand in hand with diversification, nutrition education, and promotion of locally produced nutritious crops, with the additional advantage to contribute to a lower carbon footprint.

With the proof-of-concept of various biofortified crops by genetic engineering being illustrated, research on social and economic impacts (cost-effectiveness, willingness-to-pay and trade issues), health aspects (potential effects on micronutrient intake gap) and ethical issues is crucial for informing policy makers and other stakeholders, and ensuring a successful scale-up and effective delivery. De Steur et al. highlight socio-economic studies which demonstrate that biofortification by genetic engineering as a health policy intervention is not only well accepted by the majority of its key beneficiaries, with consumers' premium levels generally above 20%, but also offers good value for money, especially when several micronutrients are targeted in one single crop (multi-biofortification). While trade issues are considered less relevant when targeting domestic markets, local supply chains need to be upgraded to further exploit the potential and ensure a successful delivery. De Steur et al. summarize findings from an absorption study on Golden Rice and describe estimates of the potential effects of various genetically modified (GM) biofortified crops on closing the micronutrient gap. The clinical trial reports a high bio-conversion rate of β-carotene in Golden Rice, while potential effects of GM biofortified crop consumption on nutritional outcomes are promising, with daily servings sometimes reaching daily estimated average requirements. By using a public health ethical framework, Glass and Fanzo discuss public health goals, the potential burdens of GM technology, and areas to consider for minimizing burdens and ensuring beneficence, autonomy, and low infringements on justice. When GM foods are considered relevant in addressing these goals, governments should take into account the local food and agricultural environments and the specific context of each community when preparing effective and transparent communication and implementation strategies.

References

1. UN, Department of Economic and Social Affairs: *Population Division. World Population Prospects: The 2015 Revision*. United Nations: New York; 2015.
2. FAO, UNDP, WPF: *The State of Food Insecurity in the World*. 2015:. Online publication http://www.fao.org/3/a-i4646e.pdf.
3. IPES-Food: *From Uniformity to Diversity: A Paradigm Shift from Industrial Agriculture to Diversified Agroecological Systems*. International Panel of Experts on Sustainable Food systems; 2016.
4. UN General Assembly 28 March. United Nations Decade of Action on Nutrition (2016–2025). 2016, A/70/L.42.
5. FAO: *Combating Micronutrient Deficiencies: Food-based Approaches*. Edited by Thompson in, Amoroso si.CAB International and FAO; 2011. ISBN 978-1-84593-714-0.
6. Fitzpatrick TB, Basset GJC, Borel P, Carrari F, DellaPenna D, Fraser PD, Hellmann H, Osorio S, Rothan C, Valpuesta V, Caris-Veyrat C, Fernie AR: **Vitamin deficiencies in humans: can plant science help?** *Plant Cell* 2012, **24**:395-414.
7. Blancquaert D, De Steur H, Gellynck X, Van Der Straeten D: **Metabolic engineering of micronutrients in crop plants**. *Ann N Y Acad Sci* 2017, **1390**:59-73.
8. Garcia-Casal MN, Peña-Rosas JP, Giyose B, consultation working groups: **Staple crops biofortified with increased vitamins and minerals: considerations for a public health strategy**. *Ann N Y Acad Sci* 2017, **1390**:1749-6632.
9. Ye XD, Al-Babili S, Kloti A, Zhang J, Lucca P, Beyer P, Potrykus I: **Engineering the provitamin A (beta-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm**. *Science* 2000, **287**:303-305.
10. Schaub P, Al-Babili S, Drake R, Beyer P: **Why is Golden Rice golden (yellow) instead of red?** *Plant Physiol* 2005, **138**:441-450.
11. Low JW, Arimond M, Osman N, Cunguara B, Zano F, Tschirley D: **A food-based approach introducing orange-fleshed sweet potatoes increased vitamin A intake and serum retinol concentrations in young children in rural Mozambique**. *J Nutr* 2007, **137**:1320-1327.