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Promise and issues of genetically modified crops

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The growing area of genetically modified (GM) crops has substantially expanded since they were first commercialized in 1996. Correspondingly, the adoption of GM crops has brought huge economic and environmental benefits. All these achievements have been primarily supported by two simple traits of herbicide tolerance and insect resistance in the past 17 years. However, this situation will change soon. Recently, the advance of new products, technologies and safety assessment approaches has provided new opportunities for development of GM crops. In this review, we focus on the developmental trend in various aspects of GM crops including new products, technical innovation and risk assessment approaches, as well as potential challenges that GM crops are currently encountering.

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Introduction

Since genetically modified (GM) crops were first commercially grown in 1996, their application has achieved remarkable success in terms of both economic and environmental effects. The grown area of GM crops increased 94-fold, from 1.7 million hectares in 1996 to 160 million hectares in 2011. The number of countries growing GM crops also increased from 6 in 1996 to 29 in 2011. The estimated seed market of GM crops reached 13.2 billion US dollars in 2011 [1••]. In line with the rapid increase of grown area, the adoption of GM crops has brought substantial economic and environmental benefits. The direct global farm income benefit from GM crops was 14 billion US dollars in 2010, which is equivalent to conferring 4.3% of additional value to global production for the four main crops of soybean, maize, canola and cotton. The cumulative increase in farm incomes has reached 78.4 billion US dollar during 1996–2010. Since 1996, the use of pesticides (counted as active ingredients) on the GM crop area was reduced by 448 million kg (9% reduction), and the environmental impact quotient — an indicator measuring the environmental impact associated with herbicide and insecticide use on these crops — fell by 17.9%. In 2010, the total carbon dioxide emission savings associated with GM crop adoption were equal to the removal from the roads of 8.6 million cars due to reduced fuel use and additional soil carbon sequestration [2••]. In this review, we are mainly concerned with the developmental trend in the future for various aspects of GM crops including new products, technical innovation, risk assessment approaches and potential challenges. However, we only focus on GM crops with agronomic trait improvements, and issues concerning GM crops for biopharming or bioenergy are not discussed.

Next generation of GM crops for human health benefits

GM crops have been commercially grown for 17 years, but it is still hard to say that they have acquired wide acceptance and support from the public, especially in Europe. For many consumers, it is possibly simply because consuming GM products has no direct benefit for them, as both herbicide tolerance (HT) and insect resistance (IR), which are two primarily targeted traits in GM crops, which only benefit the growers [3]. Consumer preference studies confirmed that GM food would be more desirable for consumers if they provide additional health benefits [3]. The coming of the next generation of GM crops that benefit consumers will soon change the situation. The main target traits of the next generation of GM crops so far include: micronutrients (vitamin A, iron, folate, and ascorbate), fatty acid composition (oleic acid, omega-3 fatty acid), resistant starch, and antioxidants (anthocyanins), etc. (Table 1). Table 1 summarizes some important examples of the next generation of GM crops that have been developed recently. In general, one or several key genes in metabolic pathways are introduced or knocked down by genetic modification to promote the accumulation of healthy metabolites. Some of the next generation of GM crops have been well developed and are almost ready to release. One famous example is golden rice, which contains a high content of β-carotenoid by introduction of a previously absent biosynthetic pathway into rice endosperm [4]. Consuming golden rice can prevent vitamin A deficiency that prevails in poor populations. Release of golden rice in the Philippines is planned for 2013 [1••]. However, golden rice helps eliminate malnutrition that generally exists in poor populations in some developing countries, and has no obvious

Table 1

The next generation of GM crops developed recently

Nutrient/trait	Crop	Base level	Max level in GM crop	Main benefits	Reference
β-Carotene	Rice	0 μg/g	37 μg/g	Vitamin A deficiency causes blindness and increased child mortal	[4]
Iron	Rice	–	Increase > 6 fold	Iron malnutrition causes anaemia or impaired mental development	[5]
Folate	Rice	<1 μg/g	17 μg/g	To prevent neural tube defects	[6]
Ascorbate	Maize	18 μg/g	107 μg/g	Ascorbate deficiency causes scurvy in human	[7]
Oleic acid	Soybean	~20%	~80%	To hinder the progression of adrenoleukodystrophy, and reduce blood pressure	[8,9]
Omega-3	Canola	12%	50%	To reduce coronary heart disease and maintain heart health	[10]
Amylose	Wheat	28%	75%	Benefit for some health issues associated with some chronic diseases	[11,12]
Anthocyanin	Tomato	0 μg/g	2.83 μg/g	To extend the life of cancer-prone mice	[13]

attraction for people living in developed countries where malnutrition is uncommon. Therefore, another type of the next generation of GM crops, which can reduce risks of major chronic diseases including obesity, heart disease, type 2 diabetes and many cancers threatening all populations, would be more influential. There are at least two GM soybean varieties with high level of oleic acid that benefit cardiovascular health: Plenish™ developed by Hi-Bred International and Vistive® Gold developed by Monsanto are almost ready to enter the market. The U.S. Department of Agriculture (USDA) has deregulated Plenish™ (http://www.aphis.usda.gov/newsroom/content/2010/06/ge_soybeans.shtml) in 2010 and Vistive® Gold (http://www.vistivegold.com/Pages/Home.aspx) in 2011. Moreover, Plenish™ has also acquired a Chinese safety certificate of importation in 2011 (http://www.moa.gov.cn/ztzl/zjyqwgz/spxx/201202/P020120203380940533480.pdf). GM soybean variety Soymega™ containing omega-3 fatty acid is also under research and development by Monsanto (http://www.soymega.com/). It can be expected that the commercialization of the next generation of GM crops will greatly improve the public perception of GM products and increase the market of GM crops and products in the next 5–10 years.

New biotechnologies for risk mitigation of GM crops

In line with the development of new GM products, novel technologies in genetic engineering have been developed as well. Recently, the concept of 'new biotechnologies' was proposed by Lusser *et al.* [14••]. In their article, seven methods are listed as new biotechnologies: that is, zinc-finger nuclease (ZFN), oligonucleotide-directed mutagenesis (ODM), cisgenesis/intragenesis, RNA-dependent DNA methylation (RdDM), grafting (on GM rootstock), reverse breeding and agro-infiltration [14••]. Although most of these new biotechnologies are not really new, they share a 'new' core principle: to produce non-GM products based on a genetic modification process. Differing from traditional genetic modification, these new biotechnologies avoid the introduction of novel genetic elements or proteins in the final products, and therefore they take advantage of transgenic process with the reduction of potential risks and the increase of public acceptance.

We believe that the recently developed genome editing technologies would be one of the most representative new biotechnologies. There are at least three methods to realize site-specific genome editing with high efficiency: ZFN [15,16], transcription activator like (TAL) effector nuclease (TALEN) [17,18,19••,20•] and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) system [21••,22••]. The key step of all three methods is similar: to generate double stranded breaks (DSBs) at a specific site of the host genome (Figure 1a and b). Once DSBs have been created, three types of site-specific genome editing: gene disruption, point mutation and gene addition can be realized with high efficiency depending on the situation of donor DNA templates (Figure 1c), which has enormous application potential in plant breeding, gene function study and gene therapy. ZFN, TALEN, and CRISPR/Cas are different from each other in the mechanism of introducing DSBs. Both ZFN and TALEN are artificial nucleases that can recognize and cleave specific DNA sequences with similar enzyme structure and mode of action, except that their DNA recognition and binding mechanism is different (Figure 1a) [23]. Whereas the mechanism of CRISPR/Cas to create DSBs is completely different from ZFN or TALEN (Figure 1b). CRISPR/Cas is the immune defense system existing in bacteria and archaea that use short RNA to direct degradation of foreign nucleic acids. Two recent reports proved that bacterial CRISPR/Cas can be modified to cleave the host genome at specific sites and be used as genome editing tools in human and mouse cells [21••,22••]. ZFN has been developed for over 10 years, and TALEN has been adopted for few years since the DNA recognition mechanism of TAL effectors was deciphered in 2009 [24,25]. The use of CRISPR/Cas as genome editing tools has just been reported in 2013 [21••,22••]. TALEN has exhibited advantages in comparison with ZFN in terms of specificity, ease of design, context dependence, off-target effects and toxicity [26•]. While comparing with TALEN, CRISPR/Cas appears more facile with much higher efficiency [21••,22••]. The rapid development of genome