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Review Article

Genetically Modified Plants: Think Twice before Saying "No"

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Abstract

Since manipulation of DNA sequences was feasible, it has also become feasible to insert such sequences into distinct genomes. The possibility of creating plants with completely new characteristics conferred by one or more genetic sequences is undoubtedly an exciting platform to be explored, and for sure, a point of divergence between to accept or to deny such new variations created. Currently, several products present new traits ranging from insects resistance to vaccine synthesis, and the technique is still a subject of great criticism. Different nomenclatures are adopted for plants that had their genome altered and in this work they will be named genetically modified plants, which encloses plants presenting traits from non-related organisms such as viruses and bacteria, as well as plants belonging to the new concepts of cisgenic and intragenic. These concepts were created due to the possibility of obtaining isolated genes containing their own regulatory elements or genetic combinations between plant regulatory sequences and target genes, allowing the cisgenic technique to be partially considered an improvement on the classical reproduction technique. In this review we will discuss the three generations of GMs developed, as well as the recent questions about the concept of cisgenic and intragenic, and how these new approaches on genome engineered plants can collaborate to overcome public acceptance of an increasing in availability of GM foods for consumers.

ABBREVIATIONS

GM: Genetically Modified

INTRODUCTION

Historically, the release of genetically modified plants (GMs) for cultivation and commercialization generates divergences of public opinion that guides the elaboration of favorable or unfavorable policies to the subject. Certainly, cultural issues are central to determine the behavior of acceptance or refusal to the presence of GM foods on the market. Clearly there are two market poles when the subject is GM: a more favorable, like the North American, and a more unfavorable, like the European. However, the development and release of GM foods grow not only in developed countries, but in developing countries, where consumer behavior is largely defined by food shortages or reduced purchasing power. Currently, genetically modified plants of first, second and third generation are a reality around the world and the formation of a public opinion on the subject needs to consider different proposals of development of such plants.

GENETICALLY MODIFIED PLANTS OF FIRST, SECOND AND THIRD GENERATION

Genetically modified plants (GM) plants are divided into three groups, depending on the purpose of its generation. GM plants of first generation are those with input traits basically related to increase insect and herbicide resistance. GM plants of second generation present output traits related direct to benefit the consumer, aiming mainly to add value to the final product through nutritional improvement or better storage conservation. GM plants of third generation can be so called "green factories" and be used in the production of novel products, like pharmaceuticals and biofuels in an environmentally sustainable manner [1].

GM plants of first generation are the most widespread cultivated crops and have been commercialized since the mid-1990s. GM crops with resistance traits to herbicide and insect attack were used on about 12 percent of the world's cultivated area by 2015. Among them, soybean is the most cultivated, followed by cotton, maize and canola [2]. Basically, these crops are present in all of the global territory, representing 179.7 million hectares of cultivated area in 2015 [3]. This massive growth of GM crops is directly linked to the economic benefits provided, such as reduction in herbicide application and increasing in yields.

Genes commonly used to confer insect resistance traits are those isolated from the soil bacterium *Baccilusturingiensis* (*Bt*) encoding Cry or Vip proteins, used against lepidopteron and coleopteran pests. Herbicide resistance traits are given from genes like *bar*, *pat*, *gox*, EPSPS, also isolated from bacteria [4]. These new traits are responsible for increasing in production and reduction of insecticides in such crops. For example, in India the cultivation of *Bt* GM cotton, a pest-resistant crop, started in 2002 and since then increasing in yields have been observed reaching $18.3 billion in 2014 in farm income gains [3].

Meanwhile, poisoning due the use of insecticide decreased among Chinese farmers who adopted *Bt* rice. Results showed a reduction of 50–60% in pesticide spraying in such crops from Wuhan producers and physical examinations showed improved health through the adoption of *Bt* rice [4,5]. In addition, a reduction of approximately 41% in insecticide use through *Bt* technology in cotton farms has also been reported over three growing seasons in India, improving producer's health [6].

Moreover, comparisons between yields of crop varieties with *Bt* to yields of varieties without *Bt* showed that *Bt* in maize and cotton contributed to a reduction in the gap between actual yield and potential yield, from 1996 to 2015 when targeted pests could not be controlled by synthetic chemicals and caused substantial damage to non-GM varieties. In Brazil, the second biggest GM grower, the most cultivated biotech crop is soybean, with 32.2 million hectares in 2015. Both herbicide tolerant and insect resistant cultivars are present. Maize is the second most biotech crop cultivated and is estimated that during the crop period of 1996/97 to the 2012/13, benefits for users of this technology have reached US$24.8 billion [2]. According to recent data, due to GM crops Brazil gained US$2.5 billion for 2014 alone [3].

Lately, cultivation of crops with stacked traits has been increasing, corresponding to almost 33% of the total GM area in 2015 [2]. This increase fits perfectly to the higher potential of such crops. One of them is the delay in the evolution of pest resistance to the inputted trait. Since two or more genes against insect-pests are introduced to a same variety, the speed of generation of resistant insects can be slowed, allowing growers to reduce the refuge area recommended. As an example, recently, two companies received approval for the cultivation of a hybrid corn with eight different genes for herbicide tolerance and insect-protection. This product was created by breeding crosses of previously approved GM events presenting genes like Cry1Fa, Cry34Ab, Cry35Ab, Cry3Bb/RR2, Cry1A.105 and Cry2Ab for pest control, and two genes related to weed control - RR2 and EPSPS. The approval was given by the Environmental Protection Agency (EPA) from United States and allowed growers to reduce the refuge area for this culture from 20 to 5% in the US Corn Belt [7].

In 2013 studies associated a reduction of 18.3% in the environmental impact in areas cultivated with GM and an 8.9% reduction in the use of herbicides and pesticides [8]. This reduction reflects on the survey of non-target insects in GM areas and around. Probably, the biggest worry concerning insect resistant GM crops are related to honey bees, once they represent a species of high economic and environmental importance. Due to its world occurrence, honey bees have been used as surrogate species for studies of non target insect effects of GM crops. Recent results showed that different classes of Cry proteins do not promote changes in their hypo pharyngeal gland, a very important gland for this insect, and are not harmful for adult bees or larvae, in comparison to insecticides commonly used [9-11].

The second-generation of GM plants enclose those products with traits that will benefit final consumers directly, such as improved nutritional qualities. Possibly they will face less market resistance than first generation GM crops due to their direct advantages. The first GM food released for consumption, the tomato Flavr Savr by Calgene company failed the marked due to high production and distribution costs [12]. This fact, however, did not discourage companies from developing new genetically modified foods based on consumer needs. The new wave of GM foods launched have Artic Apples® and Innate® Potatoes as examples of products that focus on benefits to the consumer with traits related to low bruise and non browning, higher resistance to blight and higher nutritional quality. Artic Apples®, developed by Okanagan Specialty Fruits®, present two approved varieties of apples called Artic® Golden and Artic® Granny. These products do not turn brown due to the silencing of four genes from the polyphenol oxidase (PPO) family. Even though consumers and market claim for GM food free of selection genes or sequences unrelated to eukaryotes, the Artic Apples® contain genes of Cauliflower Mosaic Virus and *Escherichia coli* but its safety was ensured by scientists of Health Canada who also allowed commercialization [13]. On the other hand, Innate® Potatoes developed by J. R. Simplot© have traits conferred by genes exclusively isolated from cultivars of potatoes, providing reduced bruise and black spots, late blight resistance, higher nutritional quality and enhanced cold storage capability [14]. The most recently products approved for consumption that are under spotlight are the pink pineapple from Del Monte Fresh Produce, containing lycopene due to the silencing of the enzyme and Purple Tomato, from Norfolk Plant Science, that produces high levels of anthocyanins, an antioxidant known for its benefits for human health. Studies showed extension of life span of cancer-susceptible mice fed with high-anthocyanin tomatoes, suggesting that the accumulation of anthocyanin present in tomatoes was efficient for improving the health of the animals tested [15]. The market success of such products is still to be watched. Older than Artic Apples® and Innate® Potatoes, Golden Rice and Banana 21 projects aim to biofortify staple foods by adding new nutritional traits like pro vitamin A and iron. Although results have demonstrated that the pro vitamin A from Golden Rice is indeed absorbed by human intestine [16], this product is not yet approved for commerce.

The third generation of GM crops is heading towards a new era of technology through the application of synthetic biology to engineer plants with new input and output traits. The use of synthetic biology is beyond additions of transgenes, but aims the direct design of new metabolic pathways, physiological traits, and developmental control strategies, exploiting the potential of generation of plant varieties, or even species, for the production of chemicals and biomaterials, creating a class of plants destined for processing and not for food [17]. The creation of plants with biorefining, bioremediator, biosensors and other purposes with the construction of synthetic signaling pathways, engineering metabolism through compartmentalization, improvement of polysaccharide composition and diversification of secondary metabolism is becoming a reality [18]. It has already been demonstrated that GM plants are capable of remediate persistent organic pollutants like 2,4,6-trinitrotoluene (TNT), hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), trichloroethylene (TCE), and polychlorinated biphenyls (PCBs). Genetically engineered model plants as *Arabidopsisthaliana* and *Nicotianatabacum* showed the ability to degrade such chemicals, and other plants like poplar, switch grass and hybrid aspen are being used to the same goal [19]. A recent demonstration that the use of plants as green factories for the synthesis of drugs and vaccines is possible occurred in the last outbreak of Ebola virus when the treatment of some infected patients was authorized even without previous clinical trials. The patients were treated with three monoclonal antibodies obtained by transient expression in *Nicotianabenthamiana* [20]. The success of such treatment excited continuous studies for development of vaccines against Ebola using different virus targets and immunization purposes [21].

CISGENIC AND INTRAGENIC: A NEW APPROACH ON GM AIMING BETTER ACCEPTANCE

Probably, the popular acceptance of GM first-generation crops has been hampered due to a lack of information and mainly a lack of sense of direct benefits that such products provide to the final consumer. Coupled to the resistance and distrust that all new technology generates, the popularization of GM foods is still a hindrance. Perhaps this scenario tends to be altered by a new concept of GM that aims to produce plants with traits closer to the conventional breeding.

A "cisgenic plant" refers to "a crop plant that has been genetically modified with one or more genes containing intron and flanking regions such as native promoter and terminator regions in a sense orientation) isolated from a crossable donor plant" [22]. Basically, it means that the cisgenic crop is created by the introduction of a native complete copy of the natural gene with all its regulatory elements, maintaining their natural genetic composition. The source of a cisgenic is the same plant species or a sexually compatible species, and different from the traditional breeding, cisgenic crops contain only the desired gene or genes and no other genetic elements [23]. Indeed cisgenesis can overcome a major bottleneck in traditional breeding due to the possibility of monitoring the trait or traits that are being transferred without linkage drag issues that slow down breeding [24]. The other concept, an intragenic crop is a GM where the transformed intragene is obligatory isolated from the same species or a crossable species, but its regulatory elements like promoter and termination regions can be originated from different genes and loci. Due to the possibility of new combinations, intragenes can be considered hybrid genes [25]. Such combinations allow novel gene expression patterns and GM with innovative properties [23].

According to recent studies, cisgenic and intragenic plants are tending to alter consumers point of view about GM foods [26,27]. Although deep studies have demonstrated that long-term feeding with GM foods is safe [28], a large part of the population refuses to accept their commercialization. Due to considering that cisgenic are more natural products, their acceptance is greater among Europeans consumers, once GM foods are seen as "unnatural" [26]. Although better, this acceptance is still low when compared to Indian consumers. Recent studies about commercialization of a GM rice showed that survey respondents were willing to pay for cisgenic or 'GM' rice since both or some of them had the "no fungicide" attribute. Among consumers, 73% willingness-to-consume cisgenic rice and 76% answered the same to GM rice. Interestingly, 88% agreed about labeling cisgenic rice as GM, and this seems to be less important for the purchase than price or fungicide usage [27]. These data suggests that the opinion of consumers may have been changing in relation to acquisition of GM foods available in the marketing. Recently, it has been proposing a labelling scheme according to the category in which the product fits: Pest Resistance (PR), Enhanced Nutrition (EN), Environmental Stress Resistance (SR), and Improved Yield (IY). Product labels are asked to contain a "Quick Response" code that after scanned links the consumer to a USDA website with additional information about the GM. Labeling GMs properly will possibly allow consumers to re-evaluate their opinion and increase their knowledge about the theme [29].

FINAL CONSIDERATIONS

The first generation of GM plants brought a very innovative approach that proposed reduction or extinction of the use of pesticides and herbicides, thus generating greater production gains. First-generation plants have genetic characteristics that confer advantages, making their cultivation preferred over unmodified plants. Although benefits brought by GM crops are scientific certified, the cultivation of such plants is still an object of great social refusal. The reasons for such refusal range from fear to criticism to the monopoly of the GM seed market by some companies. Indeed, the absence of perception of direct benefits to the final consumer brought by first-generation GM plants, helped to make the popular refusal even greater. However, second-generation of GM plants are increasingly gaining the fresh market consumption with products that bring better nutritional value and are more durable, directly benefiting consumers. Differences in the genetic origins of the sequences introduced in some of these products can contribute to a change of behavior in relation to GM plants. Finally, it is still necessary to get used to an idea of plants produced for processing and not for consumption, as the case of GM plants of third generation. The potential for development of such biofactories is enormous and tends to be increasingly explored.

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