

Plant Molecular Farming: Future Prospects and Biosafety Challenges

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Plant Molecular Farming (PMF), using genetically engineered plants as platforms for production of recombinant pharmaceutical or industrial compounds, offers attractive perspectives to produce recombinant pharmaceuticals or industrially important proteins on a large scale at low costs [1-3]. The feasibility of precise plant genetic manipulation, high-scale expression of recombinant proteins, rapid and easy scaling up, convenient storage of raw material and less concern of contamination with human or animal pathogens during downstream processing have attracted biotechnologists to PMF, especially plastid and chloroplast engineering for this purpose [2,4,5]. During the last two decades a diverse upstream (production) and downstream (purification) technologies, such as table nuclear transformation, stable plastid transformation, plant cell-suspension cultures and transient expression systems (Agro infiltration method, gene gun technology, virus infection method and magnification technology)were developed in PMF, and thousands of plant-derived biopharmaceutical proteins including antibodies, vaccines, human blood products, hormones and growth regulators were produced at laboratory and pilot levels, and some of them reached the late stages of commercial and are expected to be marketed soon [6-11]. Also some of them, such as Caro RX previously have been commercialized [11].

After about two decades production of recombinant proteins in plants, only recently the focus has shifted away from technical and principle studies to a serious consideration of the requirements for sustainable productivity and the biosafety regulatory approval of pharmaceutical products [3]. The manufacturing and clinical development of the plant-derived pharmaceutical proteins fall under the same safety and good manufacturing practice (GMP) regulations covering drugs from all other sources. Only recombinant proteins produced by plant cell suspensions in the bioreactor systems may practically observe the GMP guidelines, so for other plant systems are needed to improve new GMP and biosafety standards and regulations [7].

Plants genetic engineering is a new departure from conventional breeding to modern technology, so it raises some safety concerns. Genetically modified plants are generally evaluated critically to ensure that they do not possess any harmful characteristics for environment and human health before field trials or commercialization and release. This risk assessment is a fascinating and challenging work involving many disciplines such as ecology, agronomy, and molecular biology which mainly focus on food and environmental safety [6,12]. The objective of risk assessment is to identify and evaluate on a case-by-case basis potential adverse effects of a GM plant on the environment(s) and human health. Through this approach, the GM plant is compared with its non-GM parent (substantial equivalence) having safe use history and familiarity for the environment, in order to identify differences. Risk assessment is performed principally according to the following steps, including problem formulation and hazard identification, hazard characterization, exposure assessment, risk characterization, identification of risk management and communication strategies, and finally, overall risk evaluation and conclusions. The risk assessment finally leads to a conclusion as to whether the overall health and environmental impact of the GM plant can be accepted or not [2,13,14]. Similar to all genetically modified plants, those intended for molecular farming must go through a complete risk assessment before they can be used in the field. However, in addition to the risk assessment framework of GM plants used as food/feed or processing (FFPs), PMF raises new questions and concerns that might trigger a need for specific biosafety considerations due to the nature of the used recombinant genes [3,8].

The public concern about the potential health and environmental risks associated with the transgenic plants used as molecular farming sources, include the possible risks of very high concentration of recombinant proteins on the morphology and physiology of host plants, possible physiological responses in humans and in animals caused by the plant biologically active products, economic risks to farmers and food industry as result of co-mingling and contamination of MF plants with food/feed chain, possible vertical transgene flow and spread by pollen, seed or fruit dispersal, unintended effects on non-target organisms, particularly birds, insects and soil microorganisms, and horizontal gene transfer by asexual means [10,15,16].

The risk of co-mingling and contamination of transgenic plants used as source of PMF with other agriculturally important crops could be reduced by use of non-food/feed crops as source of PMF, production of recombinant proteins by cell suspension cultures in bioreactors, strict physical agronomic confinement and containment strategies for food/feed crops, post-harvest field monitoring and cleaning, use of late maturing or early maturing cultivars or planting at different periods to ensure harvesting at different periods from other crops intended for food/feed and processing (FFPs) [10,16]. Vertical gene flow or gene flow by plant sexual reproduction is the most important form of transgene pollution and occurs commonly via the dispersal of transgenic pollen. Plants for molecular farming should be chosen with the minimum possible gene flow and minimum seed production [8]. The biosafety strategies to prevent vertical gene flow include the use of closed isolated physical containment facilities (greenhouses, glasshouses, hydroponics and plant cell suspension cultures), biological containment (self pollinating species (cleistogamous lines), chloroplast transformation, cytoplasmic male-sterile transgenic plants, sexually incompatible crop with wild relatives, non-germinating seeds or nonsprouting tubers/bulbs, engineered parthenocarpy and apomixes, transgene excision, tissue-specific expression of the transgene and use of inducible promoters) [8,10,14,17].

Horizontal gene transfer commonly is known as exchange of genetic material between sexually incompatible species belonging to different

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taxonomic groups and is often observed between bacteria [8]. The risk of horizontal gene transfer (especially, antibiotic resistance genes) from plants to microbes is generally believed to be extremely low, as there has been no report of such incidence to date, and in addition, it is important to note that loads of microorganisms, such as symbiotic, pathogenic, endophytic and ectophytic bacteria and fungi with antibiotic resistant genes, are naturally harbored by plants [10].

In conclusion, recently technical advances have improved the technologies of gene transfer, recombinant protein production and purification in order to engineer plants and use them as bioreactor for mass production different pharmaceuticals. Like for GM plants, different biosafety risks have been considered for MF plants. So, to facilitate commercialization of PMF, it is necessary to develop scientific and regulatory risk assessment and risk management strategies and standards.

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