Regenerative Medicine

By Megha Agrawal, PhD

Executive Editor

Treating Genetic Disease by Antigen-Specific Induction of Immune Tolerance in Humans

Antigen-Specific Induction

The therapeutic efforts over the past several years for the prevention or reversing of autoimmune, allergic or anti-protein drug responses and transplant rejection saw the development of monoclonal antibodies, fusion proteins, and regulatory T cell therapies. These biological drugs helped expand substantially the toolkit of suppression immunotherapy and enabled more targeted treatments than traditional immune suppressive drugs [1]. However, these drugs are limited for their wide-scale use in the consumer sector due to the reason that they are very expensive in the first place. In addition, to perform the manipulations, specialized centers are often required for patient care. Antigen-specific induction of immune tolerance in humans has been suggested a viable alternative therapeutics. It is believed that antigen-specific regimens could significantly benefit the treatment of autoimmune diseases, where some of the target antigens are known [1]. For example, in the treatment of genetic diseases using protein replacement therapies, the widespread problem encountered is the formation of anti-drug antibodies (ADA). Antigen-specific tolerance induction could overcome this problem and would be far more desirable than general immune suppression. This is due to the fact that antigen-specific induction could enable avoiding risks of infection and side effects of immune suppressive drugs. Researchers have shown potential pathway toward such a protocol that involves the introduction of the target antigen via a route, which leads to tolerogenic antigen presentation [1]. To this end, the available pre-clinical data, have shown that oral delivery of protein antigens may induce immune tolerance [2-4]. This approach was recently successfully demonstrated in the prevention of peanut allergy through regular ingestion of peanut-containing foods in infants [5].

Oral Immunotherapy Offers Hope to Prevent Life-Threatening Food Allergies: A New Concept of Antigens in Plant Cells

Oral immunotherapy (OIT) has been employed to prevent life-threatening food

allergies [1]. The clinical application of OTT has been demonstrated with high rates of success in desensitization of the allergic response. OIT also showed effectiveness in some cases that involved long lasting tolerance and termed sustained unresponsiveness [6]. A plant based product is currently considered the front-runner for first FDA approval for an orally delivered for peanut allergy [7]. Advanced pre-clinical development of this next generation of drugs is underway to develop the ability to orally administer specific auto-, allo-, and therapeutic antigens that are based on transgenic plants (Figure 1) [1].

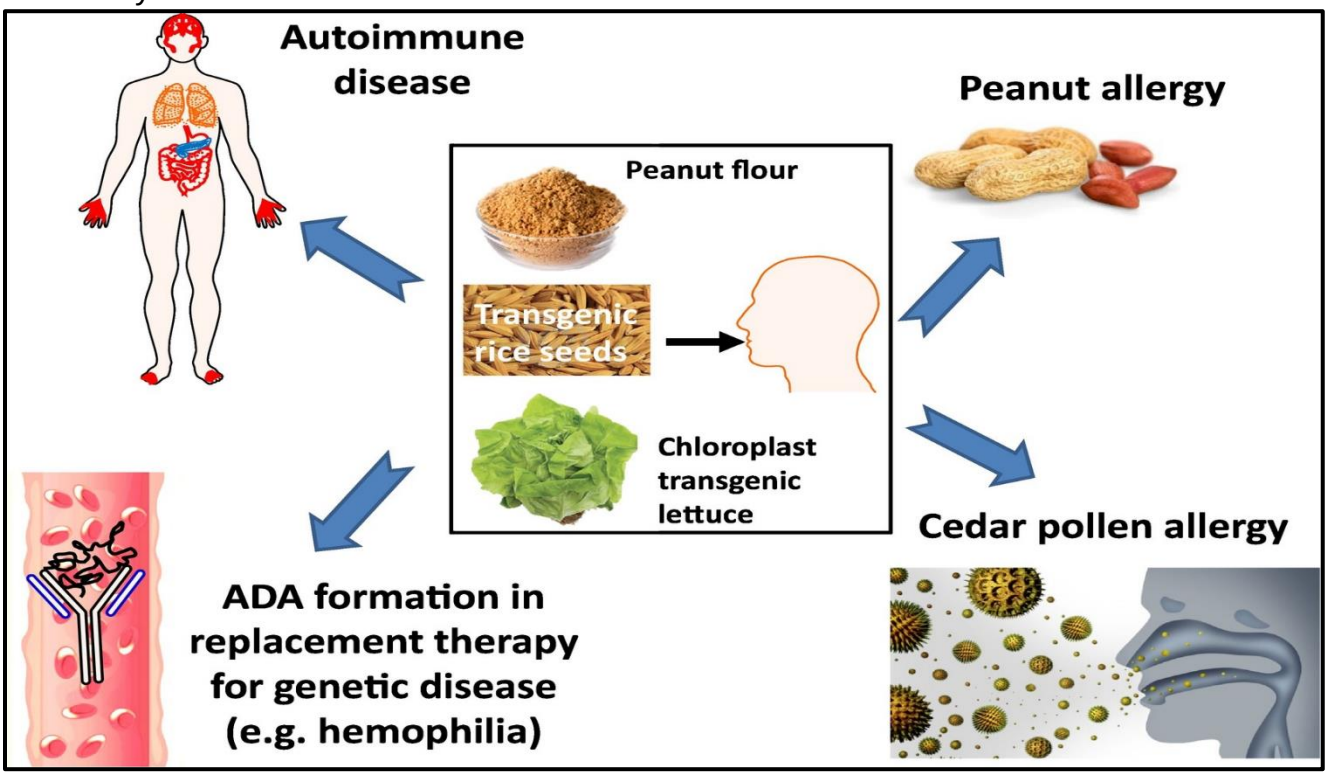

*Figure 1: Schematic illustrations showing specific examples of oral immune modulatory therapy using plant cells. Antigens bioencapsulated in plant cells are derived from leaves, nuts, or seeds that can be orally delivered to promote tolerance to autoantigens, allergens, and therapeutic proteins. These antigens can be expressed in transgenic plants and can be employed to treat genetic disease [**Source:** Biotechnology Advances 37 (2019)].*

The major clinical advantage of the oral tolerance method is that it does not require custom design of antigens for specific major histocompatibility complex (MHC) molecules unlike in the case of peptide-based methods. It also does not require genetic manipulations of host cells that are required for example, in gene therapy. However, the current state-of-the-art of translation of this method poses technological limitation due to the reason that it involves substantial costs of production of large amounts of antigen for oral delivery. Another reason is the inefficiency of delivery to the gut immune system due to antigen digestion in the stomach by acids/enzymes that create blockage of antigen absorption by gut epithelium [1].

Researchers have shown some recent breakthrough inventions that have addressed these limitations by expression of antigens or protein drugs in plant cells. These expressed antigens in plant cells can be protected from stomach acids or enzymes through bioencapsulation. The process involve commensal bacteria that degrades plant cell wall and releases antigens in the gut lumen [1]. Subsequently, transmucosal carriers are fused to antigens that deliver them across the gut epithelium and to the immune system through ubiquitous binding sites [8-10].

Oral Tolerance Induction Using Plant Cells

The process involving use of plant cells is often termed as green bioreactors, which is now rapidly becoming a promising approach for production and delivery of biopharmaceutical proteins [1]. Researchers have shown this approach very successful in the case of treatment for genetic disease, where oral tolerance induction to the therapeutic protein has been shown to suppress formation of anti-drug antibodies. This enables the administration of replacement therapy that can correct the genetic disease [1]. Current ongoing research suggests that several other protein antigens made in plant cells are in clinical development. These plant cell-made proteins are advantageous as they are protected in the stomach from acids and enzymes after their oral delivery because of bioencapsulation within the plant cell wall. They are eventually released to the immune system upon digestion by gut microbes [1].

Researchers have also shown that the utilization of fusion protein technologies can facilitate delivery to the immune system. In such a process, the oral tolerance induction done at low antigen doses can result in efficient induction of FoxP3+ and latency-associated peptide (LAP)+ regulatory T cells, which enables to express immune suppressive cytokines such as IL-10. LAP and IL-10 expression. They all represent potential biomarkers for plant-based oral tolerance (Figure 2) [1].

Concluding Remarks

Oral tolerance by antigen-specific induction from plant cells is an emerging immunotherapy that can potentially prevent or reverse autoimmune, allergic, or anti-protein drug responses. This approach is shown to be advantageous over other biological drugs due to the fact that it offers non-invasive and antigen-specific therapeutics. To this end, a number of successes have recently been demonstrated by researchers that have shown the applicability of this approach for food allergies employing crude forms of peanut antigens in pre-clinical trials. We anticipate further research and developments happening in this field in the near future that would enable transition of oral tolerance to the successful practical applications in the treatment of autoimmune diseases. The future strategies could combine with other immune modulatory strategies, such as monoclonal antibody therapy. The plant-based method offers distinct advantages including substantially more cost effective and also blocking antibody formation in replacement therapies for inherited protein deficiencies.

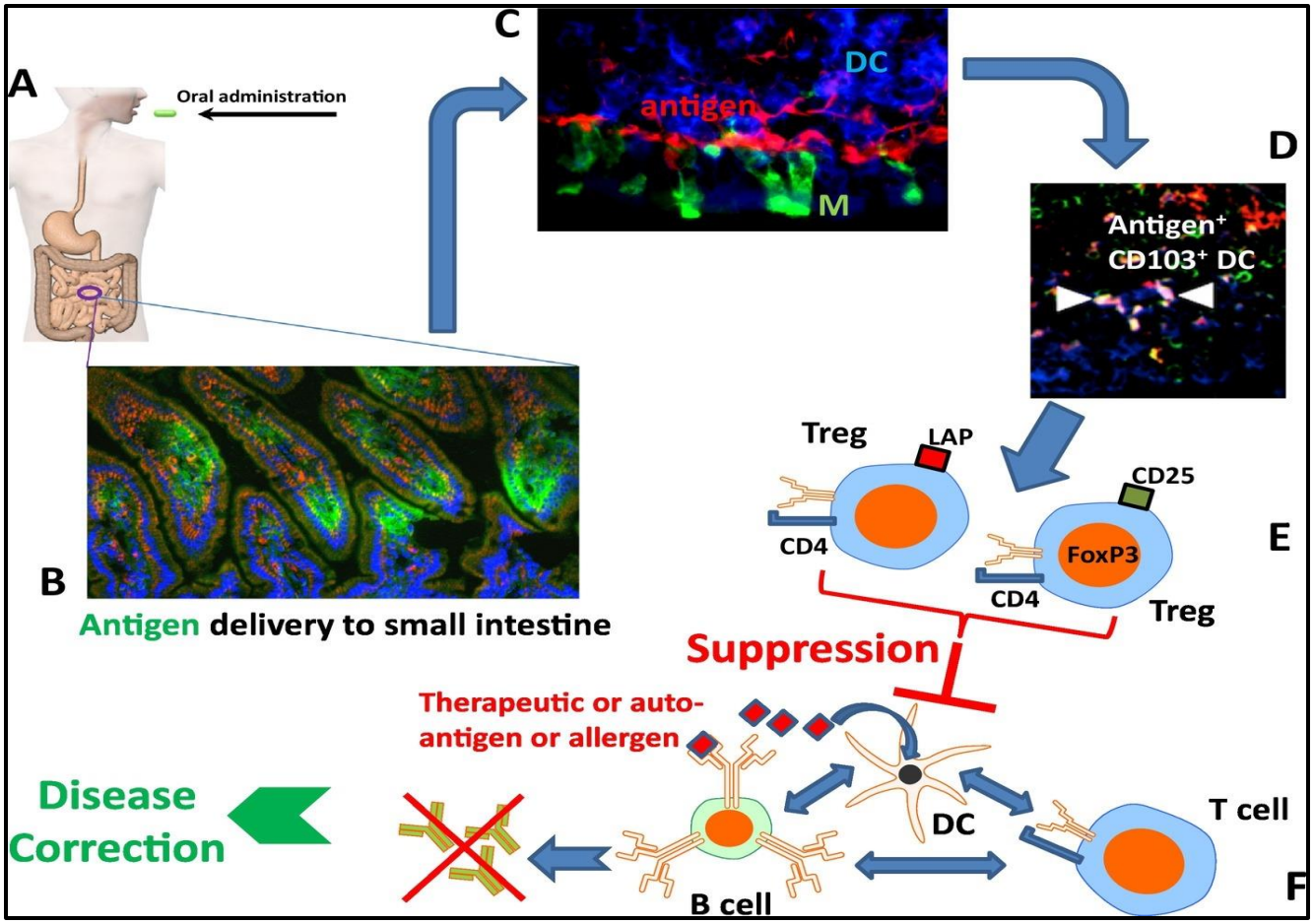

*Figure 2: A schematic representation showing the concept of oral tolerance induction using plant cells. (A) Transgenic plant cells are shown expressing the specific antigen that are orally delivered. (B) Subsequently, the antigen (shown in green) is translocated to the gut-associated immune system upon release in the small intestine. (C) Antigen (shown in red) then accumulates in areas rich in to dendritic cells (DCs, blue). M cells are also shown (green) in the picture. (D) Some of the antigen is used by tolerogenic CD103+ DCs. (E) Antigen-specific regulatory T cells (CD4+CD25+FoxP3+ and CD4+CD25−FoxP3−LAP+ T cells) are induced. (F) Induced Treg suppress B and T cell responses against the antigen that result in elimination of autoimmune or allergic responses. Further, oral tolerance induction to the therapeutic protein can suppress formation of anti-drug antibodies that allows the administration of replacement therapy, which can correct the genetic disease [**Source:** Biotechnology Advances 37 (2019)].*

References for Further Reading

1. Henry Daniell, Michael Kulis, Roland W.Herzog, Plant cell-made protein antigens for induction of Oral tolerance, Biotechnology Advances 37, 107413 (2019).
2. C. Kuhn, H.L. Weiner, Immunology. How does the immune system tolerate food? Science, 351, 810 (2016).
3. A.M. Mowat, To respond or not to respond - a personal perspective of intestinal tolerance, Nat. Rev. Immunol., 18, 405 (2018).

4. R.M. Rezende, H.L. Weiner, History and mechanisms of oral tolerance Semin. Immunol., 30, 3 (2017).

5. G. Du Toit, G. Roberts, P.H. Sayre, H.T. Bahnson, S. Radulovic, A.F. Santos, H.A. Brough, D. Phippard, M. Basting, M. Feeney, V. Turcanu, M.L. Sever, M. Gomez Lorenzo, M. Plaut, G. Lack, L.S. Team, Randomized trial of peanut consumption in infants at risk for peanut allergy, N. Engl. J. Med., 372, 803 (2015).

6. B.P. Vickery, J.P. Berglund, C.M. Burk, J.P. Fine, E.H. Kim, J.I. Kim, C.A. Keet, M. Kulis, K.G. Orgel, R. Guo, P.H. Steele, Y.V. Virkud, P. Ye, B.L. Wright, R.A. Wood, A.W. Burks, Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective, J. Allergy Clin. Immunol., 139, 173 (2017).

7. S.A. Tilles, D. Petroni, FDA-approved peanut allergy treatment - the first wave is about to crest, Ann. Allergy Asthma Immunol., 121, 145 (2018).

8. H. Daniell, H.-T. Chan, E.K. Pasoreck, Vaccination via chloroplast genetics: affordable protein drugs for the prevention and treatment of inherited or infectious human diseases, Annu. Rev. Genet., 50, 595 (2016).

9. H. Daniell, C.-S. Lin, M. Yu, W.-J. Chang, Chloroplast genomes: diversity, evolution, and applications in genetic engineering, Genome Biol., 17, 134 (2016).

10. K.C. Kwon, H. Daniell, Oral delivery of protein drugs bioencapsulated in plant cells, Mol. Ther., 24, 1342 (2016).