Crop pharming

The idea of adapting plants to produce vaccines is almost as old as the genetic engineering of plants itself. Recent clinical trials suggest that it is an approach whose time may finally have come.

We are used to seeing plants as the suppliers of a huge variety of natural products that are used for food, clothing, building materials, dyestuffs, pharmaceutical agents and so on, but this is not the limit of their synthetic usefulness. With a bit of tweaking, plants can also be induced to make 'unnatural products' — complex chemicals that do not normally fall within their repertoire. One use for such plant biotechnologies is the production of vaccines, which has taken a major step forward recently with the approval by Health Canada, the government department responsible for Canada's national health policy, of a human vaccine against COVID-19 whose major component is produced in plants.

The concept of plant-produced pharmaceutical agents is far from new. As long ago as 1989, techniques were developed to produce monoclonal antibodies in tobacco leaf segments by transient transfection[1]. Several mammalian proteins, such as trypsin, lysozyme and lactoferrin, have been produced commercially from rice and maize since the early 2000s, and large-scale production of human collagen has more recently been achieved in tobacco plants[2]. There are a number of advantages to using plants as production systems for therapeutic proteins, such as ease of growth and compatible post-translation modifications. Also, transgenic products accumulated in seeds can remain stable over long periods of time, even without refrigeration.

The production of vaccines in plants has shown slower progress, despite considerable research in the area. The first plant-derived vaccine to be approved by the US Department of Agriculture (USDA) was against Newcastle disease, a highly infectious and devastating viral disease that affects poultry. This received a market licence in 2006 but was not widely deployed commercially, owing — amongst other things — to public concerns over genetically modified organisms. The approach has been revisited recently, with groups looking to produce vaccines against Newcastle disease in maize[3] and tobacco[4].

The development of plant-produced vaccines against human diseases has been given a substantial boost by the emergence of COVID-19. Medicago, the Quebec-based pharmaceutical company whose vaccine has recently received approval, were already working on influenza vaccines before the onset of the pandemic. Indeed, a human influenza vaccine has successfully completed phase 3 clinical trials[5]. Their approach is to transiently transfect *Nicotiana benthamiana* plants using *Agrobacterium tumefaciens* that contains instructions for the synthesis of virus-like particles (VLPs); essentially empty viral coats displaying important viral antigens, such as haemagglutinin in the case of influenza viruses or the spike protein in the case of SARS-CoV-2. After a few days, the plants, now containing high yields of VLPs, are harvested, and the VLPs are purified and mixed with adjuvant to form an injectable vaccine. One advantage of this approach is that the genetic sequence carried by the *Agrobacterium* vector can be quickly adapted to accommodate alterations found in newly emerging variants.

Injection is not the only method of delivery for vaccines, and perhaps the more important use of plants in vaccination may turn out to be as edible vaccines. It is an appealing idea to engineer a food plant to produce antigens for a given disease, so that eating its fruits or seeds will provide protection. This should be particularly effective against diseases that chiefly affect the gastrointestinal tract. In the late 1990s and early 2000s, this approach was used to create vaccines against enterotoxic *Escherichia coli*, norovirus, hepatitis B and even rabies, using such crops as potatoes, maize, lettuce and spinach. These reached phase 1 clinical trials but did not progress further. One problem encountered was the difficulty of controlling the dosage of antigen given, and of course there were concerns over the public acceptance of the consumption of genetically modified material.

Nevertheless, the idea of edible vaccines has not been abandoned: only last year the results of phase 1 trials on 'MucoRice-CTB' were published[6]. This is a rice variety, originally developed in 2007, that expresses the cholera toxin B (CTB) subunit[7] and so is hoped to provide protection against *Vibrio cholera*, which affects some 1.3 million or so people each year and causes between 21,000 and 143,000 deaths. A rice-based vaccine would be particularly helpful against this diarrhoeal disease as it does not need to be refrigerated to remain active, and is so easily administered. In recent human trials participants had increased antibodies against CTB without serious side effects.

The COVID-19 pandemic has spread, and continues to spread, a disastrous cloud over much of the world's population. If it has any silver lining, a renewed interest in the use of plants as vaccines just might be it. ❐

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