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Short Communication

Synthesis of human haemoglobin by plants

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Haemoglobin, Hb is the red, protein pigment in blood that transports oxygen round the body. Decreased quantity could lead to anaemia, and when the anaemic condition turns severe, blood transfusion becomes inevitable. However, the safety of human source has become questionable in recent times, and this has aroused the interest of scientists to search for alternative source(s). Interestingly, Agrobacterium tumefaciens, a soil bone, gram-negative bacterium has been discovered to integrate a segment of its Ti plasmid into plant chromosome through wounds. Workers thus, exploited this natural genetic engineering process to transfer Hb gene into plants. Evidence suggests that initial trials recorded some measure of success. Although, the nascent technology is still being refined, when fully developed it would reduce the fear and risk associated with the human source of blood for transfusion.

Key words: Haemoglobin, Agrobacterium tumefaciens, Ti-plasmid, anaemia.

INTRODUCTION

Haemoglobin, Hb, a conjugated protein, consists of a red pigment moiety, haem and a colourless globin molecule. Globin is a complex protein containing four polypeptide chains and haem is a cyclic tetrapyrrole compound (protoporphyrin) with a centrally located ferrous ion, Fe^{2+}. In the Hb unit, one haem moiety attaches to each polypeptide chain of the globin molecule through the N-group of histidine. The Hb molecule is roughly spherical with a molecular weight of about 68,000, and is made up of 96% globin and 4% haem.

Hb, like any other protein is synthesized according to the inherited genetic information, and so, its genetic code dictates the type and quantity of globin chain. Therefore, alterations in such coding assignment results in the production of aberrant Hb. In fact, more than 500 genetic variants of Hb are known to occur in the human population and each form could result in either mild or severe clinical symptoms.

Hb is the blood component that carries oxygen, O_2, round the body. Therefore, decreased Hb content would reduce the oxygen-carrying capacity of the red blood cells, and could also lead to anaemia. Decrease in Hb quantity has wide array of causes, and when severe, it might necessitate blood transfusion. Blood transfusions are now a prime tool in medicine, and have been regarded as “the gift of life” since millions have donated blood or have accepted it. However, each year hundreds of thousands have adverse reactions to blood, and many die. Speculations indicate that the mortality from blood transfusion is high. As such, the safety of human source has raised doubts in the minds of so many people.

The present screening tests performed to certify blood safe is therefore, inadequate as there are so many diseases transmitted through blood. Again, recent report shows that just as you have individual fingerprints, so also you have individual’s unique blood, and that when one is transfused to the other, reactions are bound to occur (Dixon, 1988). Thus, a negative screening test cannot be read as a clean bill of health. If the “safety” approval hinges on the screening tests performed, then the approach could be questionable. This disturbing trend has aroused the concern of the scientific community to explore for alternative safe source. The advent of biotechnology appears to offer a ray of hope in this context. Today, tobacco plants are being coaxed to synthesize human Hb, and the techniques involved have reached an advanced stage.

Currently, the most famous plant cell vectors are the Ti plasmids of Agrobacterium tumefaciens, a soil-borne, gram-negative bacterium, which invade plants at the site

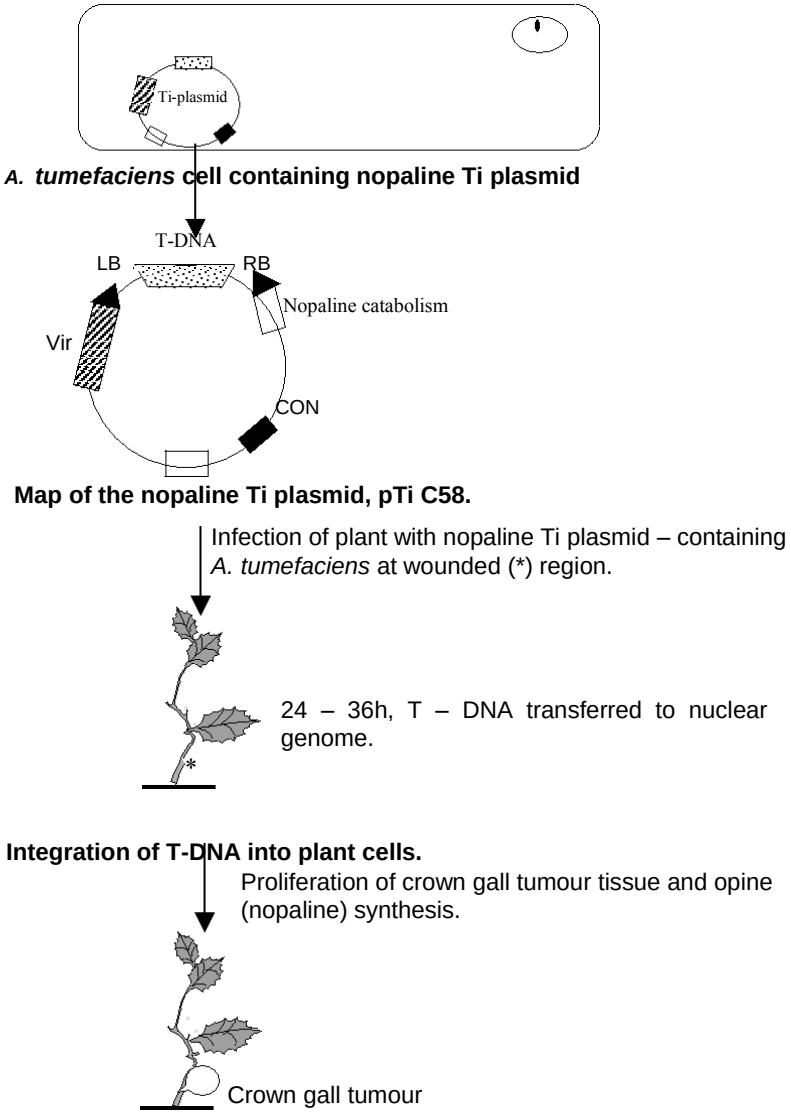

Figure 1. Transfer of genes into plant nuclear genome Sources**:** Brown et al. (1987) and Nicholl (1996).

of wound in the stem, transforming plant cells near the wound and inducing them to develop a tumour of cancerous tissue at the crown of the plant. The agent responsible for the formation of the crown gall tumour is not the bacterium itself, but the Ti plasmid it habours (Figure 1). Ti plasmids are large, ranging from 140 to 235 kb.

When the bacterium contacts a plant cell, a segment of the Ti plasmid called T-DNA is transferred from the plasmid to the plant cell nucleus and is integrated at a random position in one of the plant's chromosomes during transformation (Das, 1998). This is a rare example of DNA transfer from a prokaryote to a eukaryote, and it represents a natural genetic engineering process. The transfer of T-DNA from A. tumefaciens to the plant cell nucleus is mediated by 25 bp repeat sequences, the left and right boarder, LB and RB, that flank the T-DNA, and by the products of several genes on the virulence (Vir) region (Ream et al., 1998) located at another portion in the Ti plasmid. The vir genes are transcriptionally activated by specific signal molecules that are produced by wounded but not intact plant cells. For tobacco plant, these signal molecules are phenolic compounds, and examples include: acetosyringone and α-hydroxyacetosyringone. The T-DNA codes for enzymes that convert plant metabolites into two classes of compounds import ant to the bacterium. The first is the plant growth hormones, auxins and cytokinins, which stimulate growth

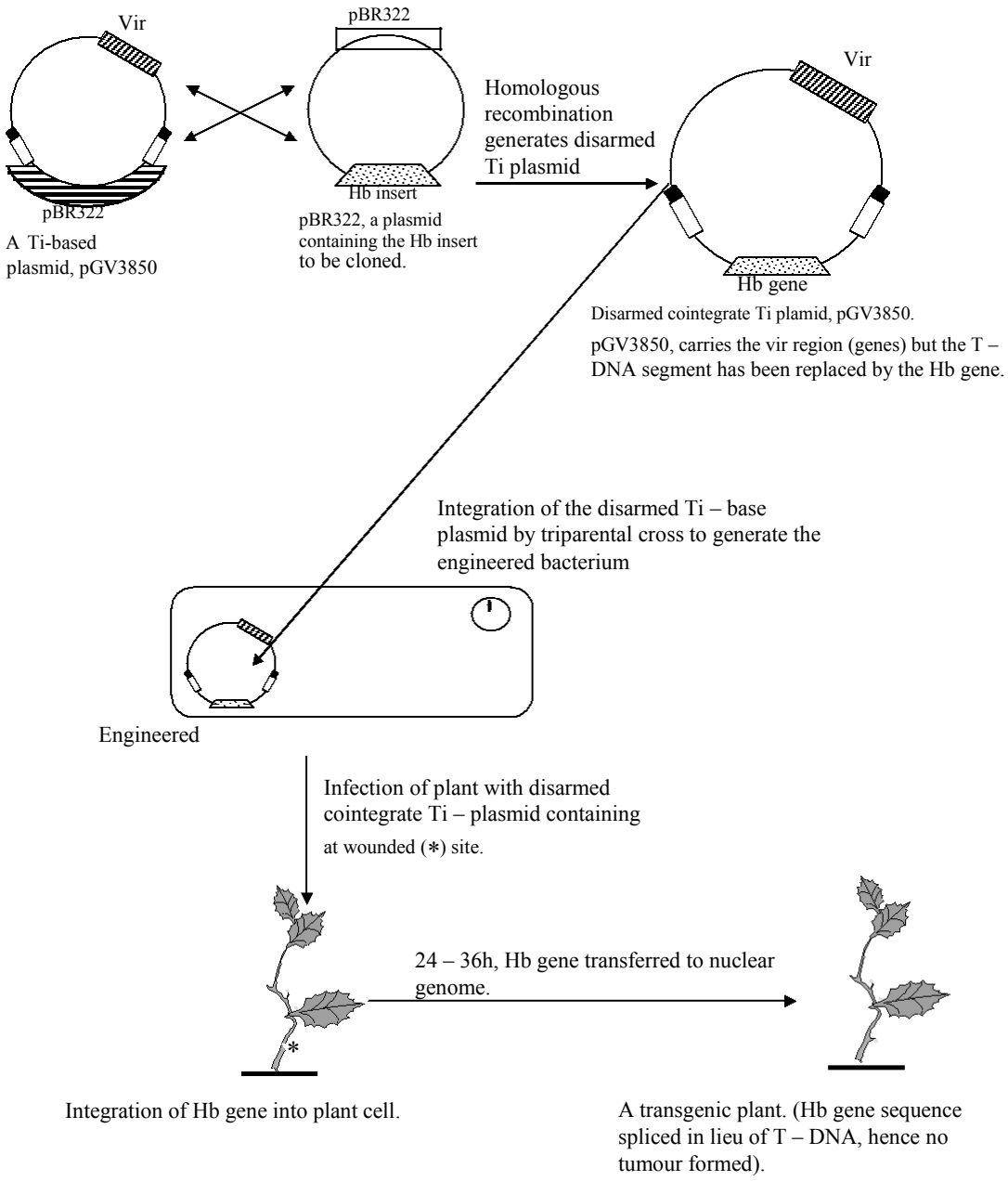

Figure 2. Making transgenic plants. Sources: Watson et al. (1983) and Nicholl (1996).

ant to the bacterium. The first is the plant growth hormones, auxins and cytokinins, which stimulate growth of the transformed plant cells to form the crown gall tumour, and the second, is a series of unusual amino acids called opines, a food source for the bacterium. There are two main types of opines produced, octopine and nopaline and Ti plasmids are classified on this basis into either octopine or nopaline- containing Ti plasmid. A. tumefaciens cells harbour only one sort of Ti plasmid. Thus, the integration of the T-DNA into plant chromosomes provides the vehicle necessary to introduce foreign genes into plants, and once introduced, it is transmitted to progeny through seed in successive generation.

There are two approaches in the used of Ti based plasmid to make transgenic plants: i) cointegration and ii) the binary vector system. In the cointegrate method, a plasmid, based on pBR322 is used to clone the gene of interest. This plasmid is then integrated by tripartite or triparental cross with a Ti- based vector and a conjugation-proficient plasmid in A. tumefaciens that can now facilitate integration of the cloned Hb DNA sequence to plant genome on infection (Figure 2). Once spliced, plant genome expresses such alien Hb gene. Disarmed

Ti-based plasmids lack tumorigenic functions, since the T-DNA has been replaced by the cloned Hb gene of interest, hence no tumour developed. The binary vector system is complex, and the procedure is yet to be fully developed. However, the hypothesis involved the use of complement plasmids as transfer vehicle.

Although, the technology is still being refined, when fully developed it would reduce the risk and fear associated with the human source of blood for transfusion. This breakthrough would also be of interest, particularly now that people are no longer keen to donate blood for fear of being discovered to be HIV-positive.

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