Genetic discovery uncovers key tool for morphine production in poppies

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Opium poppy (Papaver somniferum) Credit: Public Domain

Scientists at the University of York and GlaxoSmithKline (GSK) Australia have made a key genetic discovery in poppies, paving the way for more effective painkillers.

The discovery, published in the latest issue of *Science*, reveals the long sought after gene that is seen as a critical gateway step in the synthesis of the morphinan class of alkaloids, which include the painkiller drugs morphine and codeine.

The gene, called STORR, is only found in poppy species that produce morphinans. The STORR gene evolved when two other genes encoding oxidase and reductase enzymes came together millions of years ago. The resulting gene fusion plays a key role in production of morphine.

Scientists hope this will enable the breeding of bespoke poppy varieties, including those that produce the anti-cancer compound noscapine. Discovery of the STORR gene completes the set of genes needed for genetic engineering of morphine production in microbes such as yeast. Whether or not this can compete commercially with plant based production remains to be seen.

The breakthrough came when scientists identified poppy plants that were not able to produce morphine or codeine but instead accumulated another compound called (S)-reticuline. These plants were found to carry mutations in the STORR gene. These mutations cause a roadblock in the pathway to morphine production in poppy plants. The scientists were able to show that the non-mutated wild type gene can overcome the roadblock, by expressing it in yeast cells.

Professor Ian Graham, who led the research in the Centre for Novel Agricultural Products, based in the Department of Biology at the University of York, said: "Plants produce an amazing array of natural chemicals. Discovery of this STORR gene fusion provides us with new insight into how poppy plants have evolved to produce the most effective painkillers known to man".

The naturally occurring opiates of the morphinan class of alkaloids

include morphine, codeine and thebaine. Morphine and codeine can be directly used as analgesic painkillers. Thebaine is widely used as the starting point for synthesis of a number of semi-synthetic opiates including hydrocodone, hydromorphone, oxycodone, and oxymorphone. Thebaine is also used to synthesise the opioid antagonist naloxone, which is used to counter the effects of opiate overdose.

Dr Thilo Winzer, lead author on the *Science* publication, said: "Opium poppy is one of the most important medicinal plants. The formation of the fusion protein was probably a key evolutionary event in its ability to synthesise pharmaceutically important morphinan alkaloids."

The discovery of the STORR gene completes the suite of genes thought to be required for production of morphinans in microbial systems. Plants remain a proven and efficient production system delivering Kg amounts per hectare of active pharmaceutical ingredients (API) at relatively low cost. Discovery of the STORR gene may enable an alternative supply route to be evaluated.

Tim Bowser, Head of R&D for GSK Australia's Opiates Division, said: "The discovery of the STORR gene provides us with a new tool for molecular plant breeding, making it faster and easier. GSK are using this discovery to develop bespoke commercial poppy varieties."

More information: "Morphinan biosynthesis in opium poppy requires a P450-oxidoreductase fusion protein" by Thilo Winzer et al. will be published by *Science* within the *Science Express* web site on Thursday, 25 June 2015. www.sciencemag.org/lookup/doi/ … 1126/science.aab1852

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