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Systems biology and metabolic engineering of microalgae for the production of pharmaceutical *Amaryllidaceae* alkaloids

Several *Amarylllidaceae* plant alkaloids (AAs) possess powerful pharmaceutical and biotechnological properties. Thus, AA metabolism and its fascinating molecules, including anti-acetylcholinesterase galantamine, anti-microbial lycorine and anti-cancer narciclasine, have attracted the attention of both the industry and researchers involved in plant science, chemical bioengineering and medicine. Currently, access and availability of high-value AAs [commercialized (e.g. galantamine) or not (e.g. narciclasine)] is limited by low concentration in nature, seasonal production and time-consuming low-yield extraction methods. Nevertheless, commercial AA galantamine is still extracted from plant sources. Efforts to improve the production of AA have largely been impaired by the lack of knowledge on AA metabolism. The purpose of this study was to use recent development and integration of next-generation sequencing technologies and metabolomics analyses to unravel metabolic pathways allowing the use of metabolic engineering and synthetic biology approaches to increase production of valuable AAs. Novel genes encoding AA biosynthetic enzymes were identified from our transcriptome databases using bioinformatics tools. The genes were characterized, and their activities were studied through classical biochemistry experiment such as cloning into expression vectors, heterologous expression, recombinant protein purification and specific enzyme assays. In addition, AA precursor pathway was introduced into microalgae cells to validate the function of the biosynthetic genes and to produce AA metabolites (precursors and intermediates). Next, the final steps of the AA biosynthetic pathway will be added to reach galantamine or other AA synthesis in microalgae. Metabolic engineering provides opportunity to overcome issues related to restricted availability, diversification and productivity of plant alkaloids. Engineered cells can act as biofactories by offering their metabolic machinery for the purpose of optimizing the conditions and increasing the productivity of a specific alkaloid.

Recent Publications:

1. Hotchandani T and Desgagne-Penix (2017) Heterocyclic *Amaryllidaceae* Alkaloids: Biosynthesis and Pharmacological Applications. Current topics in medicinal chemistry. 17: 418-427.
2. Singh A and Desgagne-Penix (2014) Biosynthesis of the *Amaryllidaceae* alkaloids. Plant Science Today. doi. org/10.14719/pst.2014.1.3.41.
3. Kilgore M and Kutchan T (2015) The *Amaryllidaceae* alkaloids: biosynthesis and methods for enzyme discovery. Phytochemistry Reviews. doi:10.1007/s11101-015-9451-z.
4. Diamond A and Desgagne-Penix (2016) Metabolic engineering for the production of plant isoquinoline alkaloids. Plant biotechnology journal. doi:10.1111/pbi.12494.

Biography

Isabel Desgagné-Penix has her expertise in Plant Biochemistry and specialized metabolism. Her research program is aimed at understanding the Molecular Biology and Biochemistry of isoquinoline alkaloid metabolism in *Amaryllidaceae* plants. Narcisses and snowdrops remains the only commercial source for the anti-cholinesterase galantamine and several potential alkaloid pharmaceuticals. The recent availability of some *Amaryllidaceae* alkaloid biosynthetic genes creates metabolic engineering opportunities in plants and microorganisms. Her innovative and creative new ways to attempt production of valuable plant metabolites are of interest.

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