【Grant-in-Aid for Scientific Research (S)】
Biological Sciences (Agricultural Sciences)

Title of Project : Characterization of Molecular Evolution of Plant Isoquinoline Alkaloid Biosynthesis and its Application To Metabolic Engineering

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Research Project Number : 26221201 Researcher Number : 10127087
Research Area : Agricultural chemistry, Applied biological chemistry
Keyword : Metabolic engineering, Synthetic biology, Isoquinoline alkaloid production

【Purpose and Background of the Research】

Higher plants produce diverse low-molecular-weight chemicals such as alkaloids, terpenoids and phenylpropanoid compounds. Among these chemicals, alkaloids are particularly important in medicine due to their high biological activities. However, the low yield of metabolites, especially alkaloids, in plants limits large-scale development of the plant natural product industry. In this research, we characterize the molecular evolution of isoquinoline alkaloid (IQA) biosynthesis in higher plants and develop metabolically engineered plant cells and microbes that produce useful secondary metabolites in high yield and of high quality, using the latest techniques in metabolic engineering and synthetic biology.

【Research Methods】

Based on the molecular characterization of the genome structure of *Eschscholzia californica*, in which the IQA biosynthetic pathway has been intensively studied at the molecular level, all of the IQA biosynthetic enzyme genes and the entire enzyme network will be characterized to design more advanced metabolically engineered plant cells.

The biosynthetic pathways in other plants that produce IQAs, such as emetine in *Carapichea ipecacuanha*, galantamine in *Lycoris radiata*, aristolochic acid in *Aristolochia debilis* and so on, are characterized using RNA sequencing, metabolomic analysis and metabolic engineering.

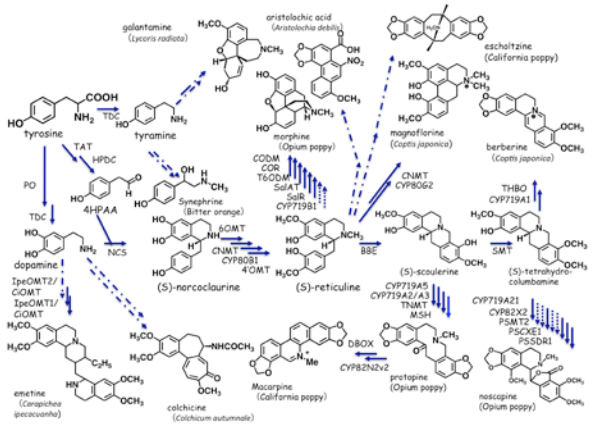

Figure 1 Biosynthetic pathway of isoquinoline alkaloids characterized in this study

With the use of this molecular information on IQA biosynthesis, IQA biosynthetic pathways are re-constructed in plant cells and/or microbial cells to produce the desired novel IQAs in high yield and with high quality. The functionalities of IQA products are also investigated using model animal cell systems.

【Expected Research Achievements and Scientific Significance】

Full characterization of isoquinoline alkaloid biosynthetic pathways at the molecular level should contribute to studies on the secondary metabolism in higher plants.

Furthermore, full information about the biosynthetic enzyme genes for IQAs should help us prepare molecular tools for re-constructing biosynthetic pathways to produce desired known and also novel IQAs.

Advanced metabolic engineering and synthetic biology should contribute to the development of plant and microbial cells that can produce useful IQAs in high yield and of high quality. These materials and the screening of biological activity performed in this study should provide useful information for the development of new medicines.

【Publications Relevant to the Project】

・Sato F, Kumagai H. (2013) Microbial Production of Isoquinoline Alkaloids as Plant Secondary Metabolites Based on Metabolic Engineering Research. **Proc. Jpn. Acad., Ser. B**, 89, 165-182.
・Nakagawa A, Minami H, Kim JS, Koyanagi T, Katayama T, Sato F, Kumagai H. (2011) A bacterial platform for fermentative production of plant alkaloids. ・**Natre Comm.** 2, Article number: 326.

【Term of Project】 FY2014-2017

【Budget Allocation】 143,100 Thousand Yen

【Homepage Address and Other Contact Information】

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