植物におけるサリチル酸生合成経路

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The Biosynthetic Pathways of Salicylic Acid in Plants

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Summary: Salicylic acid (SA) is a signaling molecule which plays an essential role in plant resistance to pathogens. Biosynthesis of SA is induced by many environmental stresses including pathogen attack. In bacteria, SA is synthesized from chorismate via isochorismate by the reactions of isochorismate synthase and isochorismate pyruvate lyase. In plants, biosynthetic pathways of SA are still not fully understood; however, two pathways have been proposed to date. The first is isochorismate pathway in which, similar to bacteria, SA is simply produced from chorismate via isochorismate. The second pathway is phenylpropanoid pathway which is initiated by phenylalanine ammonia lyase from chorismate-derived phenylalanine. In phenylpropanoid pathway, SA has been proposed to be synthesized from benzoic acid by the reaction of benzoic acid 2-hydroxylase. In this review, the advances in the understanding of SA biosynthetic pathways and their regulatory mechanisms will be summarized.

Key word: Disease resistance, salicylic acid, biosynthesis, ICS, PAL

Salicylic Acid Plays an Important Role in Plant Resistance

Plants are sessile organisms and thus are always exposed to a risk of infection by pathogenic microbes. To cope with the problem, plants have evolved sophisticated defense mechanisms which are rapidly induced by pathogen attack. In response to pathogen attack, plants produce many hormones and signaling molecules which mediate induction of defense reactions. One of such signaling molecules is salicylic acid (SA). SA is induced when plants are exposed to pathogen attack and then induces many defense responses including expression of defense genes such as pathogenesis-related proteins. The importance of SA in resistance to pathogens has been genetically confirmed. Reduction of SA levels in Arabidopsis thaliana and tobacco (Nicotiana tabaccum) by the mutation in SA biosynthetic gene or expression of SA degrading enzyme compromised resistance to fungal, bacterial and viral pathogens.

Proposed Biosynthetic Pathways of SA

Classically, the biosynthetic pathways of SA have been studied by tracer experiments using radioisotope-labeled putative precursors of SA in many plant species such as potato (Solanum tuberosum), pea (Pisum sativum) and rice (Oryza sativa). These experiments have suggested that SA is produced from trans-cinnamic acid, the first product of the phenylpropanoid pathway which is initiated by phenylalanine ammonia lyase (PAL). Subsequent analyses in tobacco suggested that the final step of SA biosynthesis is 2-hydroxylation of benzoic acid (BA) catalyzed by BA 2-hydroxylase (BA2H) activity although BA2H gene is not identified to date. The importance of PAL in SA biosynthesis has been confirmed by pharmacological and genetic experiments. In Arabidopsis, exogenous application of PAL inhibitor suppressed SA induction and compromised resistance to oomycetes pathogen. Similarly, tobacco plants, in which PAL expression is suppressed by co-suppression, showed reduced level of SA induction after tobacco mosaic virus inoculation. These results have strongly indicated that SA production is mediated...
Fig. 1 Proposed pathways of SA biosynthesis in plants.

BA2H, benzoic acid 2-hydroxylase; CM, chorismate mutate; ICS, isochorismate synthase; IPL, isochorismate pyruvate lyase; PAL, phenylalanine ammonia lyase.

by PAL.

Wildermuth et al. (2001)\(^2\), however, found that Arabidopsis SA induction deficient 2 (sid2) mutants, which produce a lower level of SA than wild-type plants following pathogen attack, have a defect in isochorismate synthase (ICS) 1. In bacteria, SA is synthesized from chorismate via isochorismate by the reactions of ICS and isochorismate pyruvate lyase (IPL)\(^9\). Subsequently, it was reported that silencing of Nicotiana benthamiana ICS also reduces SA production induced by biotic and abiotic stresses\(^11\). These lines of genetic evidence clearly showed the involvement of ICS in pathogen-induced SA production and raised the possibility that plants also produce SA by the reactions of ICS and IPL as do bacteria (Fig. 1). This hypothesis, however, contradicts the key role of PAL in SA biosynthesis which has been proposed for a long time\(^7\). Very recently, the importance of PAL in SA production was further supported by the report that quadruple knockout mutants of Arabidopsis PAL1, PAL2, PAL3 and PAL4 show substantially reduced levels of SA and display increased susceptibility to a bacterial pathogen\(^12\). Therefore SA biosynthetic pathways in plants will be not as simple as those in bacteria. In fact, there are no genes which show significant similarity to bacterial IPL in Arabidopsis genome.

Interestingly, SA levels in the healthy state of plants vary dramatically dependent on species. For example, healthy rice contains more than 50 folds SA than do Arabidopsis and tobacco\(^9\). Therefore rice and Arabidopsis might use different SA biosynthetic pathways. This hypothesis is supported by the fact that isochorismate is a precursor of not only SA, but also phylloquinone, which is required for photosynthesis\(^13\). If a large amount of SA is constitutively produced from isochorismate, plant will suffer from a decrease in the production of phylloquinone. The mechanisms that rice maintains such a high level of SA will be a subject of future analysis.

**Regulation of SA Biosynthetic Pathways**

Regulatory mechanisms of SA biosynthetic pathways have been poorly understood except for the transcriptional regulation of ICS1. Very recently, Zhang et al. (2010)\(^14\) reported that two transfectors, SARD1 and CBP60g, are required for pathogen-induced SA synthesis in Arabidopsis. They are recruited to the promoter of ICS1 in response to pathogen infections, and overexpression of SARD1 resulted in the constitutive accu-
mulation of SA. These results clearly showed that one of key mechanisms of SA induction in Arabidopsis is the transcriptional induction of ICS1.

In addition to sid2 (ICSl), genetic analysis in Arabidopsis identified eds5/sidl mutant which does not accumulate SA after pathogen inoculation\(^{3,15}\). Map-based cloning of EDS5 revealed that it is homologous with members of the MATE (multidrug and toxin extrusion) transporter family\(^{16}\). This result suggested that EDS5 might be involved in the transport of SA or its precursors, but biochemical function of EDS5 remains unclear.

Several lines of evidence have indicated the involvement of mitogen-activated protein kinases (MAPKs) in the negative regulation of SA biosynthesis. In Arabidopsis, loss-of-function mutant of MPK4 constitutively accumulates a large amount of SA and induces defense reactions which are inducible by SA\(^{17}\). Recently, we found that SA is abnormally induced by wounding in the tobacco plants silenced with WIPK and SIPK, two pathogen- and wound-induced MAPKs\(^{18}\). Future identification of target proteins of these MAPKs will help our understanding in the negative regulation of SA biosynthesis.

**Concluding remarks**

As described above, the biosynthetic pathways of SA and its regulatory mechanisms remain still unclear despite its importance in plant resistance. Although two SA biosynthetic pathways have been proposed to date, enzymes which catalyze the final step of SA biosynthesis have not been identified. Future identification of BA2H and/or IPL will help us understand the SA biosynthetic pathways.

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植物におけるサリチル酸生合成経路

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要 約

サリチル酸（salicylic acid；SA）は植物の病害抵抗性に不可欠のシグナル物質である。SA の生合成は病原体ストレスをはじめとして様々な環境ストレスにより誘導される。細菌において、SA はイソコリスミン酸合成酵素とイソコリスミン酸ピルビン酸リアーゼの反応により、コリスミン酸からイソコリスミン酸を介して合成される。植物における SA 生合成経路はまだ完全には明らかになっていないが、一つの合成経路を提唱されている。一つのバイオルミン酸経路であり、細菌と同様に SA はコリスミン酸からイソコリスミン酸を介して合成される。二つ目のコリスミン酸由来のフェニルアラニンスルホンフニルアラニンアミノリアーゼの働きにより開始されるフェニルプロパノイド経路である。フェニルプロパノイド経路においては、SA は安息香酸より安息香酸 2-水酸化酵素の反応により合成されると考えられている。本報では、SA 生合成経路とその制御機構について現在までに得られた知見を総括する。