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Progress of Biotin Research in Plants

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Abstract Biotin is an essential component of living organisms and an important cofactor for enzymes involved in carboxylation, decarboxylation, and transcarboxylation reactions. Most of the current research on biotin has been focused on microorganisms and animals, and relatively few studies have been conducted in plants, whereas biotin may play an important role in responding to abiotic stresses in plants. Therefore, this paper reviews the development history of biotin and the research progress in plants, considering the research progress in China and abroad. It provides new ideas for further research on the functions of biotin in plants and lays a theoretical foundation for the in-depth interpretation of the molecular network mechanism of biotin in regulating the response to abiotic stresses.

Keywords Biotin; Synthesis pathway; *AtBIO2*; Abiotic stress

Introduction

In the face of climate change, many plants may be forced to adapt to new and potentially challenging environmental conditions (Lu et al., 2014; Fang and Xiong, 2015; Ding et al., 2019). Plants that face abiotic stresses such as low temperatures, drought, and salinity during growth and development acquire mechanisms to survive, through which they sense the stress and regulate their physiology accordingly. During this process, there must be some changes of substances in the plant body, and biotin is one of them.

Biotin is a water-soluble vitamin that is an important cofactor for several carboxylases, decarboxylases, and transcarboxylases in a variety of metabolic pathways in organisms (Knowles, 1989). Biotin is found in almost all living cells. Bacteria, plants, some fungi, and a few animals synthesize biotin, which is essential for growth and development (Prasad et al., 1998; Stolz et al., 1999). Previous studies have found that many vitamins are essential for plant growth and development. For example, thiamine (Vitamin B1) is an essential factor for several enzymes involved in central carbon metabolism (Settembre et al., 2003; Nosaka, 2006). Pyridoxol (Vitamin B6) is a potent antioxidant, especially effective in removing mono-linear oxygen and superoxide anions (Danon et al., 2005). Vitamin C can reduce stress-induced damage by eliminating reactive oxygen species (Chen and Gallie, 2006; Paciolla et al., 2019). In addition, it has been reported that adding biotin to the fermentation medium enhances the antioxidant activity of Pichia guilliermondii (Qi et al., 2015). Reactive oxygen species (ROS) are products of aerobic metabolism in plants, and environmental stresses can lead to the accumulation of large amounts of ROS in plant cells. The presence of a small amount of reactive oxygen species can be used as a signaling molecule in the plant to induce the expression of key genes in the face of adversity, thus enhancing the plant's ability to resist stress. However, when a large amount of ROS is generated in the plant under stress conditions, many normal metabolic processes will be impeded and even lead to plant death. Therefore, an effective reactive oxygen species scavenging mechanism will help plants maintain an appropriate concentration of reactive oxygen species to enhance plant stress tolerance.

Here, we review the history of biotin development and the biotin synthesis pathway in plants. The research progress of biotin in abiotic stresses in plants is described. A theoretical foundation is laid for further investigation of the function of biotin in plants against abiotic stresses.

1 Discovery and Naming of Biotin

Biotin (Vitamin B7 or Vitamin H) is a water-soluble vitamin essential for the normal metabolism of fats and proteins. In 1901, Wildiers first discovered a factor in yeast that is essential for its growth and named it "biotin". Bateman's team fed test animals an overdose of raw egg whites and found that this resulted in dermatitis and hair loss, which disappeared when the raw egg whites were heated (Bateman, 1916). Boas (1927) described an injury to the skin of rats caused by feeding them raw egg whites, and the appearance of a "protective factor X" in various foods which prevented and cured this injury. Allison's team discovered a respiratory auxin whose function was to promote the growth of rhizobial isolates and named it "auxin R" (Allison et al., 1933). At the same time, Kuhn also discovered this factor and called it Vitamin H. In 1936, Kogl and Tonnis isolated a substance in egg yolks that is essential for yeast growth and called it "biotin". In 1941, Du Vigneagud's team identified coenzyme R and biotin as the same substance, formalized the molecular formula of biotin, and isolated it from the liver (Du Vigneaud et al., 1940; György et al., 1940). The following year, Du Vigneaud's team formalized the structure of biotin (Du Vigneaud, 1942).

2 Synthesis of Biotin

Bacteria and plants can synthesize the required biotin by themselves (Prasad et al., 1998; Stolz et al., 1999). The first relevant explorations of biotin synthesis were done in bacteria. Initially, the biotin synthesis pathway starting from primeloyl CoA and alanine was elucidated in bacteria. And biotin biosynthesis in bacteria involves a four-step reaction with the products being 7-keto-8-aminopelargonic acid (KAPA), 7,8-diaminopelargonic acid (DAPA), desulfotransfer biotin (DTB), and finally biotin. In Escherichia coli, these enzymes (*bioF*, *bioA*, *bioD*, *bioB*) are encoded by four genes clustered into a single manipulator whose structure and function have been elucidated in detail (Marquet et al., 2001).

Research on biotin synthesis in plants began with the model plant *Arabidopsis thaliana*. The biotin synthesis pathway in plants is similar to that in bacteria, and the process is carried out by enzymes encoded by the *BIO4*, *BIO1-BIO3*, *BIO1-BIO3*, and *BIO2* genes, which are homologs of the bacterial *bioF*, *bioA*, *bioD*, and *bioB* genes, respectively. The first step is catalyzed by KAPA synthase (*BIO4*) in the cytosol to produce KAPA. The enzyme that catalyzes the second and third steps is composed of DAPA synthase (*BIO1*) and DTB synthase (*BIO3*), a combined enzyme gene named *BIO1-BIO3* (Muralla et al., 2008) that catalyzes KAPA to produce DTB in mitochondria. The final step is catalyzed by biotin synthase (*BIO2*) to produce biotin in mitochondria. The *BIO2*-catalysed step is considered to be the rate-limiting step in the biotin synthesis pathway. Unlike the biotin synthesis pathway in bacteria, biotin in plants is synthesized at two different sites. The initial synthesis product, KAPA, is synthesized in the cytosol while the final conversion of desulfated biotin to biotin occurs in the mitochondria (Weaver et al., 1996; Picciocchi et al., 2003; Arnal et al., 2006). Metabolic enzymes that require biotin as a cofactor are usually located in four different sites: chloroplasts, mitochondria, proteasomes, and cytoplasm (Che et al., 2003). In recent years, it has been shown that peroxisomes exhibit involvement in biotin biosynthesis in plants and fungi. In fungi, peroxisome protein-deficient mutants exhibit biotin deficiency (Tanabe et al., 2011).

3 Advances in Plant Biotin Synthesis Genes

Since the discovery of the biotin synthesis pathway in *Arabidopsis thaliana*, many efforts have been devoted to the study of biotin synthesis genes. *AtBIO4* encodes a KAPA synthase, and the *bio4-1* mutant accumulates hydrogen peroxide in large quantities and increases the expression of several genes involved in defense against reactive oxygen species signaling. genes involved in defense against reactive oxygen species signal transduction. Studies on *bio4* mutants have revealed that biotin deficiency leads to light-dependent spontaneous cell death and regulates the expression of defensive genes (Li et al., 2012). In 1998, another biotin nutrient-deficient mutant, *bio2*, was identified and it was experimentally demonstrated that the addition of biotin resulted in normal growth of the *bio2* mutant, but the addition of desulfurized biotin did not affect the mutant, thus identifying *AtBIO2* as being involved in the final step of biotin synthesis. Later studies revealed that this catalytic reaction occurs in plant mitochondria and confirmed that *AtBIO2* requires

mitochondria-targeted activity to fulfill its role in biotin synthesis (Patton et al., 1998). *AtBIO3* was earlier thought to encode the gene encoding desulfurised biotin synthase in the biotin synthesis pathway and the bio3 mutant has a phenotype similar to that of and nutrient-deficient phenotype. However, in-depth studies have revealed that *BIO3* and *BIO1* produce chimeric *BIO3-BIO1* transcripts, and this study confirms that *BIO3-BIO1* has a bifunctional site that catalyzes two sequential reactions in the same metabolic pathway (Muralla et al., 2008). In all studies of mutants of biotin synthesis genes, it was confirmed that biotin is an essential vitamin for plant growth and that plants cannot grow in the absence of biotin synthesis and without exogenous biotin additions. In 2000, a yeast mutant lacking the vht1 gene (*dvht1*) was used to identify possible plant biotin transport proteins, and after complementation of an *Arabidopsis* cDNA library was screened for a single clone capable of growth in a medium containing low concentrations of biotin. This screen identified sequences with high similarity to sucrose transporters (e.g, *AtSUC1*, *AtSUC2*). Functional analysis of the proteins showed that a member of the *Arabidopsis* family of sucrose transporter proteins (named *SUC5*; At1g71890) was radiolabelled also confirming that *SUC5* can transport biotin (Ludwig et al., 2000). In biotin biosynthesis-deficient (*bio1* and *bio2*) embryos, *SUC5* is an essential carrier for the delivery of biotin.

4 Progress in the Study of Plant Biotinases

Many enzymes in plants catalyze carboxylation, decarboxylation, and transcarboxylation reactions with biotin as an essential cofactor (Nikolau et al., 2003). Carboxylases typically use bicarbonate ions as the carboxyl donor and organic molecules as the acceptor; decarboxylases typically use organic molecules as the donor and water as the carboxyl acceptor; and transcarboxylases typically use organic molecules as the carboxyl donor and organic molecules as the carboxyl acceptor (Knowles, 1989). Four carboxylases with biotin as a cofactor have been identified, and these carboxylases catalyse the following two-step reaction, with A representing the carboxylated receptor substrate:

$$HCO^{3-} + ATP + \text{Enzyme-biotin} \rightarrow \text{Enzyme-biotin-}CO^{2-} + ADP + Pi$$
$$\text{Enzyme-biotin-}CO^{2-} + A \rightarrow \text{Enzyme-biotin} + \text{A-}CO^{2-}$$

Acetyl coenzyme A carboxylase (ACCase) first received attention as an important component of the fatty acid biosynthesis pathway, catalyzing the first rate-limiting step of fatty acid synthesis in the presence of ATP and bicarbonate with biotin as a cofactor (Salie and Thelen, 2016). In prokaryotes, green algae, and most plants, this enzyme is a heterologous complex, and its activity is dependent on four distinct subunits, biotin carboxylase (BC), biotin carboxyl carrier protein (BCCP), and α- and β-carboxyltransferases (CT) (Elborough et al., 1996). Embryo-specific overexpression of biotin carboxyl carrier protein 2 (BCCP2) in mature *Arabidopsis thaliana* seeds inhibits ACCase activity in plastids, thereby altering oil, protein, and carbohydrate composition (Chen et al., 2009). A novel family of proteins in *Arabidopsis thaliana*, named biotin/lipoic acid-binding structural domain-containing protein family (BADC), was identified in in vivo immunoprecipitation using subunit-specific antibodies. Immunoprecipitation methods demonstrated that this newly identified protein interacts with acetyl coenzyme A carboxylase. Meanwhile, the yeast two-hybrid technique demonstrated that the three protein isoforms of BADC interact with each of the two protein isoforms of BCCP, and this interaction is not biotin-dependent (Salie et al., 2016). Another carboxylase identified with biotin as a cofactor is 3-methylcrotonamide acetyl coenzyme A (MCCase) (Nikolau et al., 2003). MCCase is a complex consisting of the biotin subunit MCCA and the non-biotin subunit MCCB. It catalyzes the ATP-dependent process from 3-methylcrotonamide acetyl coenzyme A (MC-CoA) to 3-methyl glutamyl acetyl coenzyme A (MG-CoA) (McKean et al., 2000). When *Arabidopsis* was used as the study material, it was found that the catabolism of leucine in the mitochondria was inhibited in the mutant material of MCCA and MCCB, resulting in a significant increase in leucine accumulation in the plant. In addition, the mutant materials of MCCA and MCCB exhibited abnormal flower and cilia development and a significant decrease in mutant seed germination, phenotypes that were attributed to the blocked leucine metabolism (Ding et al., 2012). In the study of *Arabidopsis* MCCase, it was also found that MCCase is inhibited by exogenous carbohydrates, especially sucrose, a phenomenon that may predict that one of the major physiological roles of MCCase is the maintenance of carbon homeostasis in plants (Che et al., 2002).

5 Advances in the Study of Biotin in Abiotic Stresses in Plants

Because plants grow solidly, they cannot move to escape from adversity, so abiotic stress (such as extreme temperature, salt stress, drought or light stress, etc.) will accompany the entire development process of plants, severely stressing their distribution, growth, quality and yield, and even survival. Plants can only adapt to the environment by changing their own morphology and structure as well as physiological and biochemical reactions, or by releasing chemicals to influence the growth and development of other plants in the neighbourhood, in order to change the microenvironment and make the environment more suitable for their own growth. Biotin is a cofactor in the first reaction step of the fatty acid biosynthesis pathway and also a rate-limiting step in the fatty acid biosynthesis pathway. Previously, biotin was also found to be involved in plant response to abiotic stresses. In 1996, Patton reported that the expression of the plant *BIO2* was regulated by cellular biotin concentration (Patton et al., 1996). They also showed that *BIO2* expression changes during the light/dark cycle and that this trend is reproducible, consistent with the regulation of light or circadian rhythms (Patton et al., 1996). In 2016, Shin Kamiyama found that different cultivation conditions have an effect on biotin content in green vegetables, especially in pea sprouts (*Pisum sativum*). The biotin content was reduced under low temperature or short light conditions. The expression of *BIO2* gene also changed similarly to biotin content (Kamiyama et al., 2016). In 2020, Wang Yao found that the gene encoding biotin synthase, *AtBIO2*, was significantly up-regulated under carbonate stress, and *AtBIO2* overexpression plants had significantly higher biotin content than wild-type *Arabidopsis thaliana* and were more resistant to carbonate stress. This demonstrates that the exogenous addition of biotin can enhance the ability of *Arabidopsis thaliana* to resist carbonate stress (Wang et al., 2020).

6 Future Prospects

Previous studies on plant biotin have mainly examined fatty acid biosynthesis and accumulation (Chen et al., 2009; Jang et al., 2015). Earlier studies on biotin biosynthesis genes were related to potential bioherbicides (Hwang et al., 2010; Hahn et al., 2015). Currently, relatively few studies have been conducted on biotin's ability to protect plants from specific abiotic stresses. Therefore, in the future, it is necessary to further validate the relationship between biotin and plant resistance to abiotic stresses, and to explore the mechanism of biotin's action under specific abiotic stress conditions.

In addition, the factors that regulate biotin synthesis in plants are unknown. Biotin synthesis requires energy inputs from ATP, SAM and other reducing equivalents (e.g. nicotinamide adenine dinucleotide phosphate). To date, the source of sulfhydryl coenzyme a, the precursor of biotin synthesis, remains unclear. Plants may utilize aminobutyric acid as a carbon source for biotin, but genes associated with aminobutyric acid coenzyme a synthase have not yet been identified in plants. In bacteria, the genes involved in biotin synthesis form a cluster of genes whose transcription is regulated by a biotin manipulator that is sensitive to both intracellular biotin concentration and the level of homologous proteins that require biotin (Chakravartty and Cronan, 2012). In *Arabidopsis*, genomic loci for genes involved in biotin synthesis are dispersed, although the *bio1* and *bio3* genes have a bifunctional locus and produce a fusion protein that catalyzes two sequential reactions in the biotin synthesis pathway (Muralla et al., 2008). However, the details of elucidating how genes involved in biotin synthesis are regulated in plants have not yet been reported, so in the future, we further explored the regulatory mechanisms of biotin synthesis and metabolism under abiotic stress conditions.

Authors' Contributions

FDL drafted the manuscript and compiled the literatures. BYY was the director of the project and revised the manuscript. LSK supervised and critically revised the manuscript. All authors read and approved the final manuscript.

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