Plant Cell Rep (2013) 32:807–813
DOI 10.1007/s00299-013-1396-3

REVIEW

ABA homeostasis and signaling involving multiple subcellular compartments and multiple receptors

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Received: 2 January 2013 / Revised: 30 January 2013 / Accepted: 8 February 2013 / Published online: 21 February 2013

Abstract The plant hormone abscisic acid (ABA) plays pivotal roles in many important physiological processes including stomatal closure, seed dormancy, growth and various environmental stresses. In these responses, ABA action is under the control of complex regulatory mechanisms involving homeostasis, perception and signaling. Recent studies provide new insights into these processes, which are of great importance in understanding the mechanisms underlying the evolutionary principle of how plants can survive as a sessile organism under ever-changing environmental conditions. They also form the basis for designing plants that have an enhanced resistance to various stresses in particular abiotic stress.

Keywords Abscisic acid (ABA) · Biosynthetic pathways · Catabolic pathways · ABA transport · ABA perception and signaling

Introduction

Plants are sessile organisms and have to rely on the flexibility of growth and development to allow them to adapt to constantly changing living conditions at their fixed locations. The phytohormone abscisic acid (ABA) is one of the most important stress hormones which play pivotal roles in various plant physiological processes like seed dormancy, stomatal movement and responses to abiotic stress (Wilkinson and Davies 2002; Zeevaart and Creelman 1998; Zhu 2002). In these responses, the fluctuation of cellular ABA levels plays an essential part. Thus, the mechanism that regulates cellular ABA levels is of great importance in understanding ABA perception and ABA-mediated signaling in these responses. Such information is also critical to facilitate production of genetically engineered plants that have enhanced resistance to abiotic stresses. Conceptually, cellular ABA levels are perceived by ABA receptors, which in turn results in the initiation of ABA signaling (Ma et al. 2009; Pandy et al. 2009; Park et al. 2009; Shen et al. 2006). However, recent studies have provided evidence that ABA production occurs in multiple compartments (Cheng et al. 2002; Dietz et al. 2000; Endo et al. 2008; Lee et al. 2006; Xu et al. 2012). Moreover, ABA and its metabolites are transported between subcellular compartments within a cell as well as between cells (Hartung et al. 2002; Jiang and Hartung 2008; Nambara and Marion-Poll 2005; Sauter et al. 2002; Seo and Koshiba 2011). These findings have raised an intriguing question as to which pool of ABA in a cell is perceived by the ABA receptors. It is possible that perception of ABA in different subcellular compartments may exert different physiological outputs. ABA biosynthesis, catabolism as well as movement within plants have been intensively studied (Hubbard et al. 2010). However, it remains unclear how ABA homeostasis is regulated and how the different subcellular ABA pools contribute to ABA signaling in plant cells. In this review, we discuss the mechanisms of ABA biosynthesis, catabolism and transport in relation to the homeostasis of cellular

Communicated by P. Kumar.

A contribution to the Special Issue: Plant Hormone Signaling.

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ABA levels and also the possible perception of different subcellular ABA pools that may lead to different physiological outputs.

Biosynthesis, catabolism and transport of ABA

ABA synthesis

The main pathway of de novo ABA biosynthesis is the production of ABA from carotenoids (Nambara and Marion-Poll 2005). Most of the genes involved in ABA de novo biosynthetic pathways have been identified. *AtABA1* encodes Zeaxanthin epoxidase that catalyzes the epoxidation of zeaxanthin via antheraxanthin to produce all-trans-violaxanthin (Nambara and Marion-Poll 2005). AtABA4 is involved in the conversion of violaxanthin to neoxanthin (North et al. 2007). The cleavage process from cis-isomers of violaxanthin and neoxanthin to a C15 compound xanthoxin is carried out by nine-cis-epoxycarotenoid dioxygenase (NCED) enzymes. This step is the rate limiting process in the de novo ABA biosynthesis in plants. All the steps of the de novo biosynthetic pathway except the last two steps occur in plastids. Consistent with this notion, AtABA1, AtABA4 and AtNCED localize to plastids (Iuchi et al. 2000; Qin and Zeevaart 1999; Tan et al. 2001, 2003). The final two steps occur in the cytosol. Thus, xanthoxin has to be transported out from the plastids into the cytosol by an unknown mechanism. The conversion of xanthoxin to abscisic aldehyde is catalyzed by AtABA2 which belongs to the SDR family (Cheng et al. 2002; Gonzalez-Guzman et al. 2002). The final step, the oxidation of abscisic aldehyde to ABA, is catalyzed by abscisic aldehyde oxidase (Seo et al. 2004). Numerous mutants have been identified at every step in the biosynthesis pathway in *Arabidopsis*, tomato and maize, which have been instrumental in revealing the biochemical reactions involved in ABA production (Burbidge et al. 1999; Nambara and Marion-Poll 2005; Tan et al. 2001).

Another pathway for ABA synthesis is to produce ABA from ABA-GE. Intracellular glucosyl esters of ABA can be hydrolyzed by the β-glucosidase homologs, AtBG1 and AtBG2, which localize to the ER and vacuole, respectively (Lee et al. 2006; Xu et al. 2012). Compared to the lengthy de novo biosynthetic pathway, hydrolysis of ABA-GE to ABA by β-glucosidase is a single step process and, thus, can rapidly increase ABA levels. In fact, under abiotic stress conditions, it would be a challenging task for plants to increase the levels of many proteins involved in the lengthy de novo ABA biosynthetic pathway through transcription and translation. The physiological role of ABA produced by AtBG1 and AtBG2 has been addressed by loss-of-function and gain-of-function mutants. Intriguingly, the *atbg1* loss-of-function mutant exhibits a severe ABA-deficient phenotype whereas the *atbg2* mutant shows a mild phenotype, raising the possibility that ABA produced by these two β-glucosidase homologs exerts different physiological responses. Thus, this raises an intriguing possibility that ABA produced in different compartments may have different roles. Indeed, these new findings raise many interesting questions including how ABA produced in different compartments contributes to the homeostasis of cellular ABA levels and how the ABA production pathways in different compartments are coordinated to achieve certain levels of cellular ABA levels depending on changing environmental conditions (Table 1).

ABA catabolism

The catabolic process of ABA is divided into two pathways, hydroxylation and glucose conjugation. Among three different methyl groups, the C-8′ position is the predominant position for the hydroxylation reaction, which is mediated by the proteins encoded by the *AtCYP707A* gene family (*AtCYP707A1*, *2*, *3* and *4*) in *Arabidopsis* (Saito et al. 2004). In the conjugation pathway, ABA is conjugated with glucose by ABA-glucosyltransferase (ABA-GTase). ABA-GE has been thought to be a physiologically inactive by-product stored in the lytic vacuole (Zeevaart 1983). However, it is now clear that ABA-GE is the stored form of ABA (Fig. 1).

Long distance transport of ABA

ABA is thought to be produced in most tissues including leaves and roots. However, the expression of ABA production-related genes at high levels in vascular parenchyma cells of plants raises an intriguing possibility that they are transported from one tissue to another through the vascular system of plants. In fact, it has been shown that ABA produced in root tissues is transported to the leaf tissues via long distance transport and ABA produced in xylem cells is transported to the guard cells for stomatal closing. Given the fact that the pKa of ABA is 4.7 and the protonated form of ABA is able to penetrate lipid bilayers, it has been postulated that ABA synthesized in root tissues could be transported to the apoplastic space of the leaf tissue by long distance transport and then enter into the cytoplasm of leaf cells by simple diffusion without any particular transporters (Wilkinson 1999; Wilkinson and Davies 2002; Seo and Koshiba 2011). However, under stress conditions, the apoplastic pH increases substantially, which may be an unfavorable condition for the simple diffusion of ABA from the apoplast to the cytoplasm, thus, raising the possibility that an ABA transporter is necessary for the transport of ABA across cellular membranes. Indeed, the recent identification of an ABA exporter and

Table 1 Characteristics of ABA synthetic and catabolic enzymes

Enzyme	Reaction	Localization	Gene Expression	Post-translational regulation	Reference
AtABA1	Conversion of zeaxanthin to violaxanthin	Chloroplast	Induced by stress conditions	Unknown	Rock and Zeevaart (1991); Xiong et al. (2002)
AtABA2	Oxidation of xanthoxin	Cytosol	Induced by sugar but not by stress conditions	Unknown	Cheng et al. (2002); Gonzalez-Guzman et al. (2002)
AtABA3	Sulfurylation of dioxo form of Moco to mono-oxo form	Cytosol	Induced by stress conditions	Unknown	Bittner et al. (2001); Xiong et al. (2001)
AtABA4	Conversion of violaxanthin to neoxanthin	Chloroplast	Induced by stress conditions	Unknown	North et al. (2007)
AtNCEDs	Oxidative cleavage of 9-cis-epoxycarotenoid	Chloroplast	Induced by stress conditions	Unknown	Tan et al. (1997); Iuchi et al. (2001); Endo et al. (2008)
AtAAO3	Oxidation of abscisic aldehyde	Cytosol	Induced by stress conditions	Unknown mechanism regulates the protein abundance in dehydration stress	Seo et al. (2000), (2004); Seo and Koshiba (2002, 2011)
AtCYP707As	ABA C-8′ position hydroxylation	Unknown	Induced by high-humidity	Unknown	Saito et al. (2004); Okamoto et al. (2006, 2009)
AtBG1	Hydrolysis of ABA-GE to ABA	Endoplasmic reticulum	Induced by stress conditions	Rapid oligomerization in dehydration stress	Lee et al. (2006)
AtBG2	Hydrolysis of ABA-GE to ABA	Lytic vacuole	Induced by stress conditions	Stabilization in dehydration stress	Xu et al. (2012)

importer at the plasma membrane supports this hypothesis (Fig. 2).

Three different ABA transporters have been identified by genetic and functional screening (Kang et al. 2010; Kanno et al. 2012; Kuromori et al. 2010). AtABCG25, an ATP-binding cassette (ABC) transporter, harbors the ATP dependent ABA-efflux activity. Consistent with this proposed activity, the *atabcg25* mutants displayed hypersensitive phenotypes in different developmental stages (Kuromori et al. 2010). In contrast, AtABCG40/AtPDR12 is responsible for ABA uptake, which is consistent with the phenotype of *atabcg40/atpdr12* that showed a defect in stomatal closure and enhanced water loss (Kang et al. 2010). In addition, the low-affinity nitrate transporter, AtNRT1.2, also functions as an ABA transporter (Kanno et al. 2012); the *atait1/atnrt1.2* plants show less sensitivity to exogenously applied ABA during seed germination and post-germination growth, and enhanced sensitivity to dehydration stress.

ABA-GE is also involved in long distance transport (Hartung et al. 2002; Wilkinson and Davies 2002; Sauter et al. 2002). Indeed, in contrast to ABA, ABA-GE has very limited ability to diffuse across cellular membranes, thus, being an ideal compound to be transported to long distances (Jiang and Hartung 2008). Under stress conditions, the concentration of ABA-GE in xylem sap rises substantially, suggesting such transport activity.

Regulation of biosynthetic and catabolic pathways

High levels of ABA are critical to initiate the ABA-mediated signaling. Therefore, dehydration and salt stress should have some influence on the cellular ABA content. Indeed, with the exception of *AtABA2*, most of the genes involved in the de novo biosynthesis of ABA are up-regulated by dehydration and salt stress (Cheng et al. 2002; Iuchi et al. 2001; Seo et al. 2000; Xiong et al. 2001, 2002). In contrast, *AtABA2* is expressed constitutively at a relatively low level and is not induced by dehydration stress (Cheng et al. 2002; Gonzalez-Guzman et al. 2002). Similarly, *AtBG1* and *AtBG2* are also induced by dehydration stress. In addition, expression of genes involved in ABA production is regulated spatially. At the tissue level, not only genes for de novo pathway proteins such as *AtNCED3*, *AtABA2* and *AtAAO3* but also *AtBG1* and *AtBG2* are predominantly expressed in the vascular parenchyma cells (Lee et al. 2006; Endo et al. 2008; Xu et al. 2012), suggesting that xylem parenchyma cells are the major location for ABA synthesis.

Another level of regulation for the proteins involved in ABA production is posttranslational. The expression of *AtAAO3* is rapidly induced under dehydration stress. However, protein abundance or activity is not affected,

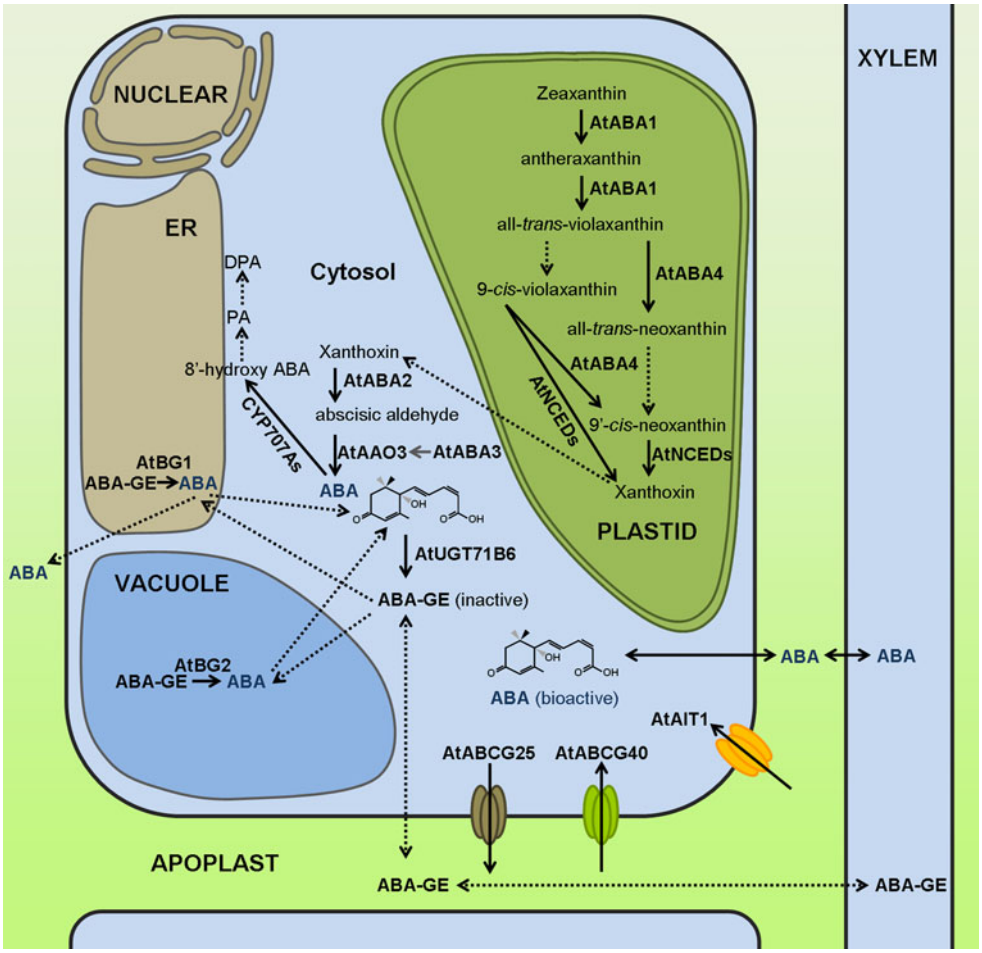

Fig. 1 ABA biosynthesis and catabolism pathways in *Arabidopsis*. The steps from zeaxanthin to xanthoxin in de novo ABA synthesis that occur in plastids are shown. Xanthoxin moves from the plastids to the cytoplasm and is converted to ABA. In the catabolic pathways, ABA is inactivated through either oxidation or conjugation. Hydroxylation as well as hydrolysis of ABA-GE is shown with the corresponding enzymes. Postulated pathways are shown by *broken lines* and the confirmed pathways are shown as *solid lines*. *ER* endoplasmic reticulum, *PA* phaseic acid, *DPA* dihydrophaseic acid, *ABA-GE* ABA glucosyl ester

raising the possibility that post-translational regulation is involved in controlling AtAAO3 activity (Seo et al. 2000; Seo and Koshiba 2002). In addition, polymerization of AtBG1 monomers into the high molecular weight form also contributes to increasing its activity. Interestingly, dehydration stress causes polymerization of AtBG1. In contrast, AtBG2 exists as a high molecular complex and its level is dramatically increased by an unknown mechanism under osmotic stress conditions.

Catabolism of ABA also plays an important role in regulating cellular ABA levels. Under rehydration conditions, expression of *AtCYP707A1, 2, 3,* and 4 is induced to reduce the cellular ABA levels, whereas the expression of *AtNCED3* is decreased, suggesting the existence of coordination between biosynthetic and catabolic pathways to control the cellular ABA levels in plants (Endo et al. 2008; Okamoto et al. 2006, 2009). Among four *AtCYP707* isoforms, *AtCYP707A1* is expressed predominantly in embryos during mid-maturation and is down-regulated during late maturation, whereas *AtCYP707A2* transcript levels increase from late-maturation to maturation stages in both the embryo and endosperm. In vegetative tissues, expression of *AtCYP707A1* and *AtCYP707A3* was induced in guard cells and vascular tissues at high-humidity conditions (Okamoto et al. 2009). These results suggest a different physiological role among these hydroxylases (Okamoto et al. 2006).

ABA perception and initiation of signaling

The ABA-mediated signaling cascade is initiated by perception of ABA by ABA receptors. One of them is the pyrabactin resistance (PYR)/regulatory component of ABA receptor (RCAR)-type ABA receptors that localize in the cytosol as well as the nucleus. Indeed, the most prevailing model for ABA perception and signal initiation is based on the interaction of PYR/RCAR-type ABA receptors together with protein phosphatase 2Cs and SNF1-related protein kinase 2 (SnRK2) kinases. The PP2C-SnRK2 complex is regarded as the "shut-off" mode of ABA signaling. However, once activated by perception of physiologically active ABA, PYR/RCAR recruits PP2C from SnRK2, leading to an inhibition of phosphatase activity, thereby allowing activation of SnRK2s whose targets include ABF/AREB/ABI5-type basic region leucine zipper (bZIP) transcription factors, ion channels as well as NADPH oxidases

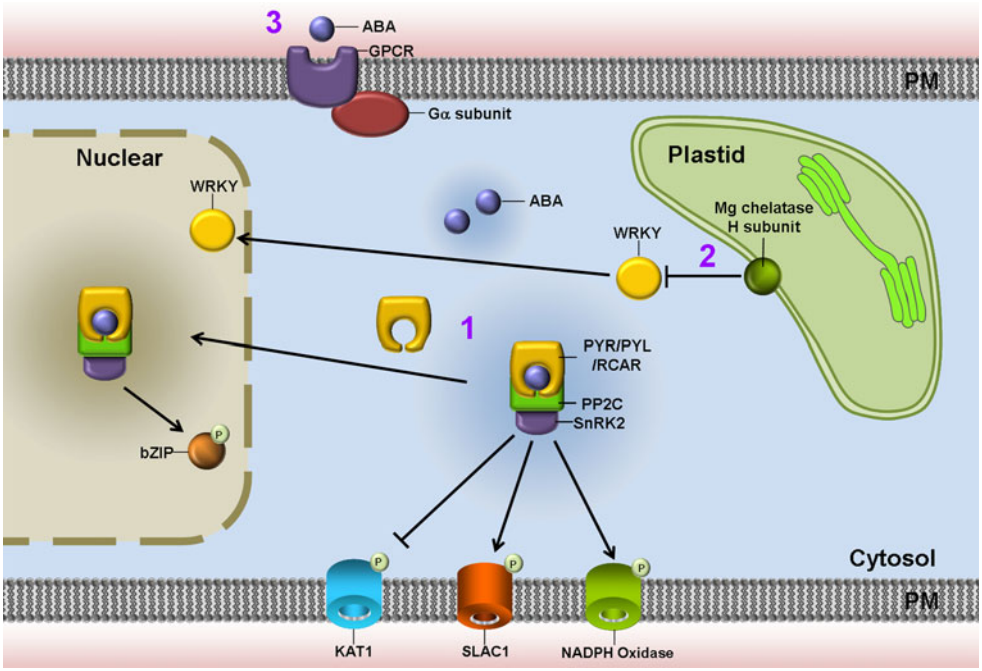

Fig. 2 Conceptual presentation of ABA perception and signaling. The ABA signaling components which are described in this review are summarized. (1) The cytosolic receptor, PYR/PYL/RCAR, forms a core complex with PP2C and SnRK2. In the nucleus, it directly phosphorylates bZIP transcription factors. Meanwhile, in the cytoplasm, it can phosphorylate potassium channels (KAT1), anion channels (SLAC1) or NADPH oxidases at the plasma membrane. (2) The chloroplast-localized receptor, magnesium-protoporphyrin IX chelatase H subunit (CHLH/ABAR), interacts with a group of WRKY transcription factors that function as negative regulators of ABA signaling. (3) Plasma membrane-localized receptors, GPCR-type G proteins (GTG1 and GTG2) interact with Gα subunit, GPA1

(Hubbard et al. 2010). Multiple homologs of PYR/RCAR exist in *Arabidopsis*, suggesting that there is functional redundancy in the cytosolic receptors. Consistent with this hypothesis, genetic analysis has revealed that although *atpyr1* single mutants display the normal response to ABA, *atpyr1 atpyl1 atpyl4* triple and *atpyr1 atpyl1 atpyl2 atpyl4* quadruple mutants display strong ABA hyposensitivity in terms of seed germination, root growth, stomatal closure as well as transcriptional regulation of ABA-responsive genes (Park et al. 2009).

CHLH (Mg-chelatase H subunit), which was originally identified as a chloroplast protein involved in chlorophyll biosynthesis and also functions in plastid-to-nucleus retrograde signaling, has been proposed to be another type of ABA receptor (Mochizuki et al. 2001). CHLH also specifically binds to physiologically active (+)-ABA but not to (-)-ABA. Moreover, ectopic expression and RNAi knock-down of *CHLH* cause the ABA-hypersensitive and hyposensitive phenotypes, respectively (Shen et al. 2006), which leads to the proposal that CHLH functions as an ABA receptor. This is consistent with the proposed role of CHLH, WRKY (WRKYGQK-containing) transcription factors (WRKY40, WRKY18 and WRKY60) which interact with the cytosolic C-terminus of the ChIH/ABAR, thereby regulating downstream ABA-responsive genes (Shang et al. 2010). As the chloroplast is the source of ABA de novo synthesis, it is possible that one branch of ABA perception exists in this compartment to assess the level of ABA production.

The third type of ABA receptor proposed is the novel GPCR-type G proteins, AtGTG1 and AtGTG2, that localize to the plasma membrane (Pandy et al. 2009). These proteins have nine transmembrane domains with a GTP binding ability. The intrinsic GTPase activity of these proteins is regulated by AtGPA1, the α-subunit of trimeric GTPase. Both of them specifically bind to the natural (+)-ABA stereoisomer in a saturable manner. Moreover, the *atgtg1 atgtg2* double knock-out mutants display ABA hyposensitivity, leading to the proposal that these proteins function as the ABA receptor. However, the activity of these proteins would lead to an unexpected model of G-protein signaling, where the GTP-bound Gα turns off the signaling, whereas the GDP-bound form initiates the signaling, which is just opposite to conventional G-protein-mediated signaling.

The presence of multiple ABA receptors, if all of them are confirmed to be true ABA receptors, raises the intriguing question as to why plant cells contain multiple ABA receptors that localize to different subcellular compartments: the cytosol, chloroplasts and plasma membrane. Recent findings, in which ABA is produced at multiple subcellular compartments, may be an important clue to

answering this question. ABA in different subcellular compartments may require different ABA receptors to initiate ABA-mediated signaling. According to this scenario, it is possible that the different physiological responses can be induced by ABA receptors that perceive different subcellular pools of ABA.

Conclusions and prospects

The existence of multiple ABA metabolic pathways in different subcellular compartments together with ABA transporters suggests that a complex regulatory mechanism is involved in the regulation of cellular ABA homeostasis during plant development and/or under abiotic stress conditions at the cellular level. At the whole plant level, the vascular tissue is the primary site of ABA production. This aspect raises another important question of how ABA production is coordinated in the plant as a whole. Plants must have a mechanism to coordinate these multiple biosynthetic and catabolic pathways as well as to regulate long distance transport to achieve the desired cellular ABA levels under constantly changing environmental conditions. Moreover, multiple ABA receptors may allow plants to have multiple ABA signaling circuits to regulate ABA-mediated signaling in more sensitive and flexible ways to respond to various developmental and environmental responses. Details of the mechanisms concerning these aspects will be crucial to our understanding of how ABA plays a role in numerous cellular responses.

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