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Lysine catabolism, an effective versatile regulator of lysine level in plants

Minireview

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Summary. Lysine is a nutritionally important essential amino acid, whose synthesis in plants is strongly regulated by the rate of its synthesis. Yet, lysine level in plants is also finely controlled by a super-regulated catabolic pathway that catabolizes lysine into glutamate and acetyl Co-A. The first two enzymes of lysine catabolism are synthesized from a single *LKR/SDH* gene. Expression of this gene is subject to compound developmental, hormonal and stress-associated regulation. Moreover, the *LKR/SDH* gene of different plant species encodes up to three distinct polypeptides: (i) a bifunctional enzyme containing the linked lysine-ketoglutarate (LKR) and saccharopine dehydrogenase (SDH) whose LKR activity is regulated by its linked SDH enzyme; (ii) a monofunctional SDH encoded by an internal promoter, which is a part of the coding DNA region of the *LKR/SDH* gene; and (iii) a monofunctional, highly potent LKR that is formed by polyadenylation within an intron. LKR activity in the bifunctional LKR/SDH polypeptide is also post-translationally regulated by phosphorylation by casein kinase-2 (CK2), but the consequence of this regulation is still unknown. Why is lysine metabolism super-regulated by synthesis and catabolism? A hypothesis addressing this important question is presented, suggesting that lysine may serve as a regulator of plant growth and interaction with the environment.

Keywords: Lysine – Essential amino acids – Lysine ketoglutarate reductase – Saccharopine dehydrogenase – Metabolism

Lysine catabolism is a ubiquitous pathway in plants and animals

The presence of a lysine catabolism pathway in plants (Fig. 1) was first confirmed by showing that ^{14}C-lysine, fed into barley seeds, was converted into glutamate and α-amino adipic semialdehyde (Sodek and Wilson, 1970; Brandt, 1975). Since then, bifunctional LKR/SDH enzymes, containing the first two linked enzymes of this pathway, namely, LKR and SDH, were discovered first in maize (Arruda et al., 1982; Arruda and Da Silva, 1983) and subsequently in a number other plant species. The plant bifunctional LKR/SDH enzymes possess characteristics similar to animal LKR/SDH enzymes, in which the linkage of LKR and SDH on a single polypeptide was first identified (Markovitz et al., 1984). The ubiquity of the LKR/SDH enzymes in plants, and their biochemical characteristics are discussed by Azevedo et al. (2006) in this issue.

The *LKR/SDH* gene, encoding the bifunctional LKR/SDH enzyme was first cloned from Arabidopsis plants (Epelbaum et al., 1997; Tang et al., 1997) and later was also cloned from other plant species and from mammals. It represents a relatively unique situation in which a ubiquitous gene of higher eukaryotes was first cloned from plants.

In mammals, lysine catabolism is an important pathway which apparently regulates lysine levels in many organs (Rao et al., 1992). This pathway is also highly active in brain tissues (Rao et al., 1992), where it is apparently also used to generate glutamate, which regulates nerve signal transmission via glutamate receptors (Papes et al., 2001). Defects in the lysine catabolism pathway in humans cause a severe genetic disorder called familial hyperlysinemia, which is associated in some patients with mental retardation (Woody, 1964; Markovitz et al., 1984). A mutation in the *LKR/SDH* gene causes familial hyperlysinemia (Sacksteder et al., 2000).

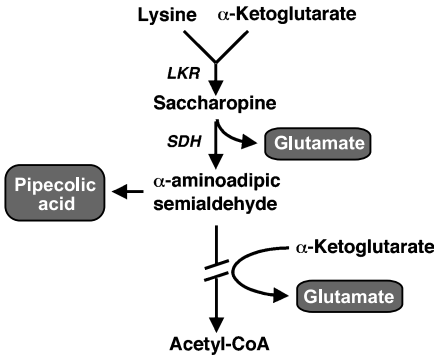

Fig. 1. The lysine catabolism pathway and metabolites derived from it. *LKR*, lysine ketoglutarate reductase; *SDH*, saccharopine dehydrogenase. Broken arrow represents several non-specified enzymatic reactions. Glutamate and pipecolic acid residues are situated inside gray boxes

Functional evidence for the regulatory role of lysine catabolism in lysine homeostasis in plants

The first functional clue for the physiological significance of lysine catabolism in regulating lysine homeostasis in plants was the demonstration that seed-specific lysine overproduction in developing tobacco seeds, expressing a bacterial feedback-insensitive dihydrodipicolinate synthase (DHPS), is associated with over 10-fold stimulated activity of LKR (Karchi et al., 1994). A bacterial DHPS was also expressed in a seed-specific manner in three additional transgenic crop plants, namely soybean, rapeseed and maize (Falco et al., 1995; Mazur et al., 1999). Seeds of these transgenic plants overproduced lysine but also contained significantly higher levels of lysine catabolic products than their wild-type parents. The first direct functional evidence for the regulatory role of lysine catabolism in balancing lysine levels in plants originated from analysis of a knockout mutant in the Arabidopsis *LKR/SDH* gene. This mutant possesses higher seed lysine levels than wild-type plants (Zhu et al., 2001). Analysis of natural high-lysine maize mutants have also confirmed a regulatory role of lysine catabolism in balancing lysine concentration in seeds (Azevedo et al., 2003, 2004a, b).

To elucidate further the potency of lysine catabolism in balancing lysine level in seeds, a bacterial feedback-insensitive DHPS was expressed in a seed-specific manner either in wild-type Arabidopsis or in the Arabidopsis *LKR/SDH* knockout mutant (Zhu and Galili, 2003). While transgenic plants expressing the bacterial DHPS, or the knockout mutant, contained respectively about 12- or about 5-fold higher moles percent levels of seed free lysine than wild-type plants, the combination of these two traits caused a synergistic about 80-fold moles percent increase in seed free lysine level (Zhu and Galili, 2003). This shows that lysine catabolism can become a very potent pathway when lysine overaccumulates.

The extreme lysine accumulation in mature seeds of the Arabidopsis plants, expressing the bacterial DHPS in the LKR/SDH knockout background, also severely reduced seed germination (Zhu and Galili, 2003). Since the *LKR/SDH* knockout eliminates lysine catabolism in all tissues, it could not be determined whether the inhibition of seedling growth was due to a negative physiological effect of excess lysine on seed maturation or to defective post-germination catabolism of lysine, which accumulated in the mature seeds. This issue was addressed by co-expressing the bacterial DHPS gene with an RNAi construct of the Arabidopsis *LKR/SDH*, both under control of the same seed-specific promoter (Zhu and Galili, 2004). In this genetic background, both the enhanced lysine synthesis and its suppressed catabolism are restricted to the developing seeds. Co-expression of these two seed-specific constructs significantly boosted seed lysine content, while seed germination was significantly improved (Zhu and Galili, 2004), implying that post-germination lysine catabolism inhibited seedling growth. The operation of lysine catabolism in the vegetative state was further demonstrated by the fact that constitutive expression of the bacterial DHPS in the *LKR/SDH* knockout mutant boosted lysine levels also in vegetative tissues (Zhu and Galili, 2004). Hence lysine catabolism is an important pathway in both vegetative and reproductive tissues.

LKR/SDH: A super-regulated gene of lysine catabolism

Although the Arabidopsis *LKR/SDH* locus contains a large open reading frame encoding the bifunctional LKR/SDH polypeptide, this is not the only production of *LKR/SDH* locus. A monofunctional SDH mRNA, which is translated into a monofunctional SDH enzyme, is also encoded by this locus from an autonomous gene that is nested inside the coding and 3′ noncoding sequence of the *LKR/SDH* gene (Tang et al., 1997, 2000). Moreover, the complexity of the composite *LKR/SDH* locus of plants does not end by encoding a bifunctional LKR/SDH and a monofunctional SDH. The *LKR/SDH* locus of cotton has been shown to encode also a monofunctional LKR mRNA via transcription termination in an intron located in the intermediate region between the LKR and SDH coding regions (Tang et al., 2002). In addition, we have also identified an

Arabidopsis expressed sequence tag (EST) encoding a monofunctional LKR, but the mechanism of formation of this mRNA is still unknown. It is though important to state that not all of the composite *LKR/SDH* loci of plants necessarily encode three distinct polypeptides. DNA sequence analysis suggests that while the composite *LKR/SDH* loci of Arabidopsis, rapeseed, cotton and tomato may possess autonomous monofunctional SDH genes nested inside them, the loci of maize and soybean may not (Kemper et al., 1998; Miron et al., 2000). Moreover, the possible differential production of monofunctional SDH in the various plant species is also associated with differential accumulation of lysine catabolic products in them (Falco et al., 1995; Mazur et al., 1999).

Why do plants need a monofunctional SDH and monofunctional LKR? The answer to this question is still speculative. The need for a monofunctional SDH may be related to the interesting properties of LKR/SDH polypeptides, whose two linked enzymes possess significantly different pH optima of activity. The maximal activity of LKR occurs at neutral pH, while the maximal activity of SDH occurs at pH 9 or above (see Azevedo et al., 2006). Since LKR/SDH is located in the cytosol (Kemper et al., 1999; Zhu et al., 2000), whose pH is relatively neutral, it is likely that SDH activity of LKR/SDH is relatively inefficient in vivo. Plants may therefore require an excess of a monofunctional SDH relative to LKR in order to maintain an efficient flux of lysine catabolism. This supposition is supported by experimental evidence showing that the Arabidopsis monofunctional SDH polypeptide is much more abundant than the LKR/SDH polypeptide (Stepansky et al., 2004). Why is a monofunctional LKR needed? LKR activity in the bifunctional LKR/SDH enzyme is regulated by functional interaction with the SDH domain, which is mediated by the intermediate linker region (Zhu et al., 2002), while the monofunctional LKR is much more efficient having significantly lower K_m than lysine (Tang et al., 2002). It is thus possible that the monofunctional LKR is extensively synthesized in cases where very efficient flux of lysine catabolism is needed, such as in cotton abscission zone (Tang et al., 2002). All in all, the data suggest that the three different products of plant *LKR/SDH* loci enable a highly regulated, and yet also efficient flux of lysine catabolism.

Lysine catabolism is regulated not only by the three protein products of the *LKR/SDH* gene, but also by its pattern of expression. Encoding a catabolic enzyme, it is expected that the *LKR/SDH* gene will be expressed primarily in senescing tissues and under conditions of sugar starvation in which amino acids are converted into sugars. However, the pattern of expression of plant *LKR/SDH* genes is much more complicated. The Arabidopsis *LKR/SDH* gene is also expressed in germinating seedlings, as well as in roots and shoots of young plants, although its expression in roots is more dominant (Stepansky and Galili, 2003; Stepansky et al., 2004). In situ mRNA hybridization also suggests that the Arabidopsis *LKR/SDH* gene is up regulated in ovarian tissues, developing embryos, as well as in the outer layers of the endosperm (Tang et al., 1997). In developing maize grains, the *LKR/SDH* gene is abundantly expressed during grain development and this expression is regulated by the Opaque2 transcription factor, which also controls the expression of some classes of the zein storage protein genes (Kemper et al., 1999). The maize LKR/SDH enzyme is localized, by in situ analysis of SDH activity, to the outer endosperm layers of the developing grain, with little detectable activity in the embryo (Kemper et al., 1999). As evident from using the *LKR/SDH* knockout of Arabidopsis (Zhu et al., 2001) and analysis of ESTs, this gene is also dominantly expressed in developing Arabidopsis seeds, primarily during the stages of reserves accumulation. Moreover, analysis of tomato ESTs shows that the *LKR/SDH* gene is also expressed in fruits.

Expression of the LKR/SDH gene is also under compound control by hormones as well as by metabolic and environmental signals. The level of the Arabidopsis LKR/SDH mRNA and protein in young plants is enhanced by abscisic acid, jasmonate, sugar starvation, salt and drought stresses as well as by excess lysine level (Stepansky and Galili, 2003; Stepansky et al., 2004). In contrast, excess sugars and nitrogen starvation reduce the LKR/SDH mRNA and protein levels (Stepansky and Galili, 2003; Stepansky et al., 2004), implying that lysine catabolism appears to fulfill multiple functions in plants.

Lysine catabolism is also regulated by posttranslational control. The lysine-mediated stimulation of LKR activity in tobacco seeds is regulated by Ca^{2+} and by protein phosphorylation (Karchi et al., 1995). It was also shown that the LKR/SDH polypeptide of soybean, maize and Arabidopsis can be phosphorylated in vitro by the catalytic α-subunit of CKII (Miron et al., 1997; Arruda et al., 2000) (A. Stepansky and G. Galili, unpubl.), but the in vivo consequence of such a phosphorylation is still unclear. Lysine has been shown to stimulate the in vitro phosphorylation of the maize LKR/SDH polypeptide with CKII-α as well as its activity (Arruda et al., 2000). In contrast, lysine does not stimulate the in vitro phos-

phorylation of the Arabidopsis LKR/SDH polypeptide by CK2-α (A. Stepansky and G. Galili, unpubl.).

Analysis by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF-MS) of a recombinant LKR domain of the Arabidopsis LKR/SDH polypeptide, expressed in yeast, identified two peptides containing a phosphorylated threonine 258 and serine 548, which are both situated inside consensus CK2 phosphorylation sites (Zhu et al., 2002). Replacement of threonine 238 with either alanine or aspartate had no significant effect on LKR activity, while replacement of serine 458 with alanine, but not with aspartate, significantly inhibited LKR activity (Zhu et al., 2002). The regulatory and functional significance of the CK2-mediated phosphorylation of LKR/SDH and the in vivo function serine 458 in this regulation awaits future studies.

LKR activity of many, but not all, plant LKR/SDH enzymes is stimulated in vitro by calcium (see Azevedo et al., 2006). Notably, a putative EF-hand-like domain, which confers regulation by calcium and calmodulin, was identified in the LKR domain of the maize LKR/SDH polypeptide (Kemper et al., 1998) and has also been hypothesized to regulate the calcium-dependent stimulation of LKR activity and its association into a homodimer (Arruda et al., 2000). Interestingly, serine 458 of the Arabidopsis LKR/SDH is located in this putative EF-hand-like domain, but it does not control a calcium-dependent assembly of Arabidopsis enzyme. Whether this EF-hand-like domain functions in the regulation of plant LKR/SDH enzymes in vivo also awaits future studies.

Presumable functions of the lysine catabolism pathway in plants

Results obtained from studies employing the Arabidopsis *LKR/SDH* knockout mutant and the RNAi-mediated suppression of the Arabidopsis *LKR/SDH* gene (Zhu et al., 2001; Zhu and Galili, 2004) imply that lysine catabolism in plants operates to balance excess lysine levels. The stimulation of *LKR/SDH* gene expression by sugar starvation (Stepansky and Galili, 2003; Stepansky et al., 2004) further implies that similar to other catabolic pathways, lysine catabolism functions in the conversion of amino acids to sugars when sugar levels become limiting. Yet, the super-regulated pattern of expression of plant *LKR/SDH* genes suggests that lysine catabolism may have also additional regulatory functions in plants whose identification is a major challenge of future research. Clues supporting such additional regulatory functions come not only from the super-regulated characteristic of the *LKR/SDH* gene but also from two different lines of evidence.

1. Expression of the *LKR/SDH* gene is enhanced in developing seeds of cereal grains (Arruda et al., 2000), which are known to contain very limited levels of lysine (Larkins and Mertz, 1997). This implies that lysine catabolism does not function solely under conditions of excess lysine accumulation. A similar case is also the up regulation of the *LKR/SDH* gene in various floral tissues of wild-type plants (Tang et al., 1997).
2. Bioinformatics analysis suggests that expression of the *LKR/SDH* gene in Arabidopsis plants is not highly coordinated with the expression of genes encoding other catabolic enzymes (H. Less and G. Galili, unpubl.). This implies that lysine catabolism may function also under conditions in which other catabolic pathways do not.

How may lysine catabolism exert its regulatory effects? Lysine is a potent feedback inhibitor of the lysine-sensitive aspartate kinase isozymes, which regulate not only lysine biosynthesis but also the biosynthesis of threonine, isoleucine and methionine (see Azevedo et al., 2006). Methionine is not only a protein building block but also a major regulator metabolite, serving as a precursor for the hormones ethylene and polyamine as well as a methyl donor for multiple cellular processes (Amir et al., 2002).

Lysine may also regulate plant growth via other mechanisms. Being a basic amino acid, lysine may participate in the regulation of cellular pH, which is known to be an important regulatory signal in plants. In addition, lysine may also serve by itself as a direct regulatory signal in plants. Although no evidence for such an effect has been demonstrated in plants, in prokaryotes, lysine regulates the production of enzymes in its biosynthetic pathway via binding to the RNAs encoding them (Rodionov et al., 2003; Sudarsan et al., 2003). Direct regulation of gene expression by metabolites by a processed called ''riboswitch'' is a recently developed hot field of research mainly in prokaryotes (Nudler and Mironov, 2004), and the possible identification of similar riboswitch mechanisms in plants is a major challenge for future research.

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