Opinion

The plastidial MEP pathway: unified nomenclature and resources

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In plants, the plastid-localized 2-*C*-methyl-D-erythritol 4-phosphate (MEP) pathway provides the precursors for the synthesis of isoprenoid hormones, monoterpenes, carotenoids and the side chain of chlorophylls, tocopherols and prenylquinones. As a result of the fast progress in the elucidation and characterization of the pathway (mainly by genetic approaches in *Escherichia coli* and *Arabidopsis thaliana*), different names have been used in the literature to designate the orthologous bacterial and plant genes and the corresponding null and partial loss-of-function mutants. This has led to a confusing variety of naming conventions in this field. Here, we propose a reorganization of the various naming systems with the aim of facilitating the dissemination and sharing of genetic resources and tools central to plant isoprenoid research.

Plant isoprenoids

Isoprenoids, also known as terpenoids, are the most functionally and structurally diverse group of plant metabolites reported to date. They participate in essential processes such as respiration (ubiquinone), photosynthesis (carotenoids, chlorophylls, plastoquinone) and regulation of growth and development (cytokinins, brassinosteroids, gibberellins, abscisic acid). Most plant isoprenoids, however, are secondary metabolites that function in protecting plants against herbivores and pathogens, in attracting pollinators and seed-dispersing animals and as allelochemicals that influence competition among plant species [1]. A large number of secondary isoprenoid metabolites have commercial value as flavors, pigments, polymers or drugs, but in most cases only a limited supply of these compounds is available from natural sources. Although metabolic engineering has great potential to direct the production of both primary and secondary isoprenoid products in plants, only a partial knowledge of the pathways involved in the biosynthesis of their precursors was available until recently.

Two distinct pathways have evolved in nature for the synthesis of the universal precursors of all isoprenoid products, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). In plant cells, the mevalonate (MVA) pathway, known for over 50 years, produces cytosolic IPP, which is then isomerized to DMAPP by the activity of IPP isomerase. Mitochondrial isoprenoids, such as ubiquinone, are also produced from MVA-derived prenyl diphosphates that are imported from the cytosol. However, plastidial IPP and DMAPP are synthesized by the unrelated 2-*C*-methyl-D-erythritol 4-phosphate (MEP) pathway, which was not described until the mid 1990s [2,3]. The MEP pathway is also present in apicomplexan protozoa (including the malaria parasites) and in most eubacteria (including *Escherichia coli* and many pathogenic bacteria), but it is absent from animals and fungi. This phylogenetic distribution makes the MEP pathway a promising target for the development of new herbicides and antimalarial and antimicrobial drugs with broad-spectrum activity and no toxic effects in humans [4–6]. Moreover, metabolic engineering of the MEP pathway in plants has successfully increased the production of some plastidial isoprenoids of nutritional and economic relevance, including carotenoids, tocopherols and monoterpenes [7–9]. Thus, the importance of the MEP pathway goes far beyond its essential role for plant life.

A plethora of names for MEP pathway genes and mutants in bacteria and plants

After the identification of the first enzymatic step of the MEP pathway, the remaining steps (Figure 1) were solved in a relatively short time thanks to the powerful genomics tools emerging over that period [1,6,10,11]. The genes encoding the enzymes involved in the biosynthetic route were first identified in *E. coli* (Table 1). A combination of bioinformatics approaches together with different forward and reverse genetics approaches were next implemented by various research groups to identify the plant homologs. As a result, a variety of names for each of the genes and enzymes of the pathway appeared in the literature. In *Arabidopsis thaliana*, some of these names refer to the phenotypic alterations observed in their corresponding mutants. This is the case for '*cloroplastos alterados 1*' (*cla1),* a null mutant for *1-deoxy-D-xylulose 5-phosphate synthase* (*DXS*) that was so named because of the alterations it produces in chloroplast morphology [12]. Other names were based on the biochemical activity of the

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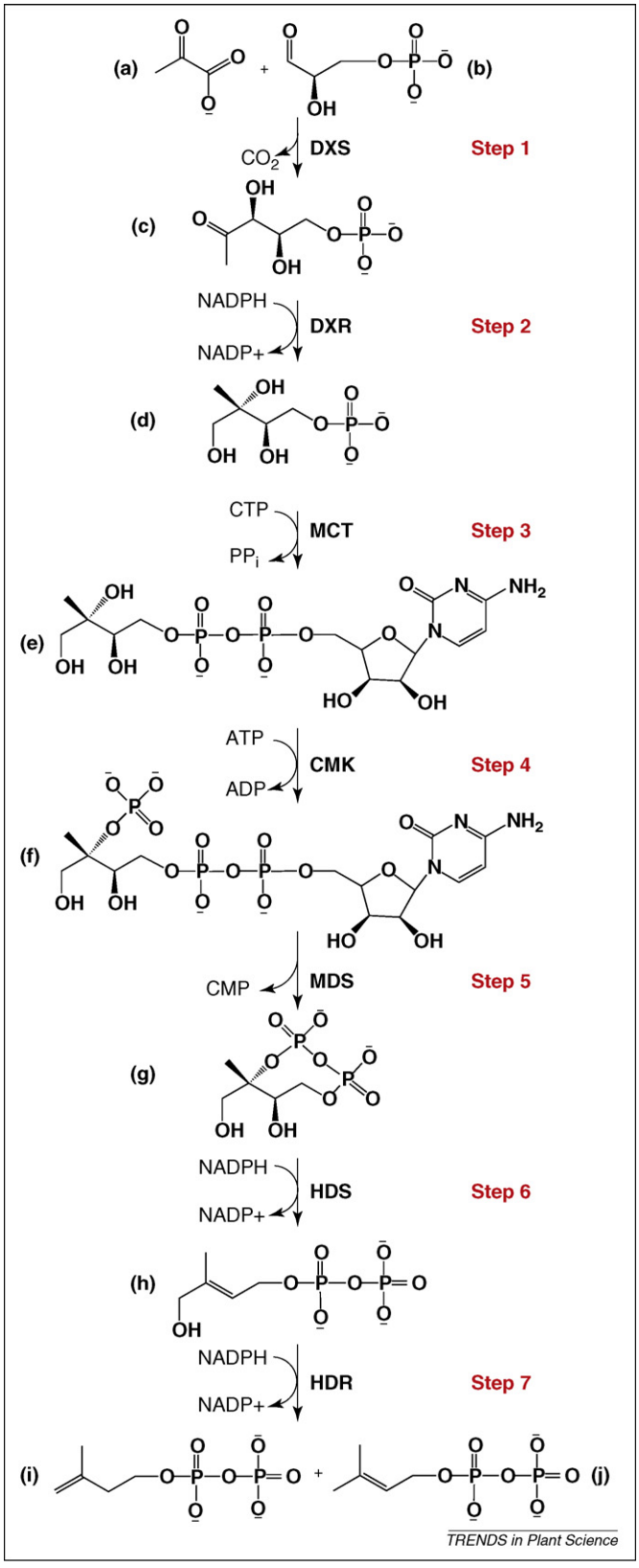

Figure 1. The steps of the MEP pathway leading to the formation of IPP and DMAPP. The biosynthetic route begins with the initial condensation of pyruvate **(a)** and D-glyceraldehyde 3-phosphate **(b)** catalyzed by 1-deoxy-D-xylulose 5-phosphate synthase (DXS) to form 1-deoxy-D-xylulose 5-phosphate **(c)**. The second step involves a reductive isomerization by 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR) that yields MEP **(d)**. In the next step, a cytidyl moiety is introduced via a diphospho bridge **(e)** by 2-*C*-methyl-D-erythritol 4-phosphate cytidylyltransferase (MCT) to produce 4-(cytidine 5′-diphospho)-2-*C*-methyl-D-erythritol. This intermediate is phosphorylated **(f)** by 4-(cytidine 5′-diphospho)-2-*C*-methyl-D-erythritol kinase (CMK) and then cyclized after loss of the cytidyl group to yield 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate **(g)** in a reaction catalyzed by 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate synthase (MDS). In two final steps catalyzed by (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate **(h)** synthase (HDS) and reductase (HDR), IPP **(i)** and DMAPP **(j)** are formed.

corresponding enzyme (such as *1-deoxy-D-xylulose 5-phosphate reductoisomerase* [*DXR*] [13]) or on the various nomenclatures of the *E. coli* homolog gene (such as *GCPE* [14] and *IspH* [15]). Unfortunately, this plethora of terminology has the danger of causing confusion rather than clarifying the exciting recent advances in the field. For example, the *Arabidopsis* gene encoding 4-hydroxy-3-methylbut-2-enyl diphosphate synthase (HDS) (Figure 1) has been reported as *HDS* [16], *GCPE* [14], *ISPG* [15], *CHLOROPLAST BIOGENESIS4* (*CLB4*) [17] and *CONSTITUTIVE SUBTILISIN3* (*CSB3*) [18]. Thus, to make the available resources in the literature related to the MEP pathway more accessible and maintain consistency in research reports and databases, we propose a reform of the various names previously used to identify plant genes and mutants of the MEP pathway. The advantages of establishing and following nomenclature standards for plant genes have been previously discussed [19].

A unified nomenclature system: the case of *Arabidopsis*

The problems with nomenclature of the MEP pathway started with the pathway's name itself [10]. Soon after its discovery, the pathway was simultaneously referred to as the non-mevalonate pathway and the Rohmer pathway. When the first steps were elucidated, the name of the pathway was changed to indicate the initial substrates (pyruvate/glyceraldehyde 3-phosphate pathway) or the first intermediate (1-deoxy-D-xylulose 5-phosphate or DOXP pathway). However, it is now accepted to name the pathway after what seems to be its first committed precursor in *E. coli* (MEP), thus following the same rule that was used to name the MVA pathway [10], even though DOXP instead of MEP might be the first committed precursor of the pathway in other organisms, including plants [20].

Here, we propose taking a further step: the standardization of the names of the enzymes, genes and mutants involved in the pathway in plants. Although we focus primarily on the most widely used model system – *Arabidopsis* – the rules we propose can be extended to other plant species. The names for MEP pathway enzymes have been adopted according to the recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (http://www.iubmb.org/). Based on these names, a three-letter acronym has been assigned to each plant enzyme, avoiding redundancy with pre-existing *Arabidopsis* names (The *Arabidopsis* Information Resource, http://www.arabidopsis.org/). As a consequence, some of the names that have been used in the literature for MEP pathway enzymes have been changed (Table 1). Following the nomenclature standards adopted by the *Arabidopsis* community [19], we propose that the same acronym codes used to describe the biochemical function of the enzyme should be used to describe the corresponding genes (written in upper case and italics) and mutants (written in lower case and italics) (Table 1). In plants with gene families encoding paralogous proteins

Table 1. The biochemical steps of the MEP pathway and the standardized names for *Arabidopsis* genes and mutant lines proposed herein

Step	Enzyme[a]	Proposed acronym	Other acronyms	*E. coli* gene	*Arabidopsis* gene	*Arabidopsis* mutants[b]	Unified name
1	1-Deoxy-D-xylulose 5-phosphate synthase (EC 2.2.1.7)	DXS		*dxs*	*DXS* (At4g15560)	*cla1* [12] Line 1055 [38] *chs5* [27] *lvr111* [28]	*dxs-1* *dxs-2* *dxs-3* *dxs-4*
2	1-Deoxy-D-xylylose 5-phosphate reductoisomerase (EC 1.1.1.267)	DXR		*ispC* (also known as *yaeM* or *dxr*)	*DXR* (At5g62790)	Line 4036 [38]	*dxr-1*
3	2-*C*-Methyl-D-erythritol 4-phosphate cytidylyltransferase (EC 2.7.7.60)	MCT	MECT, CMS	*ispD* (also known as *ygbP*)	*MCT* (At2g02500)	*ispD-1* [26] *ispD-2* [26] Line GT0946 [38]	*mct-1* *mct-2* *mct-3*
4	4-(Cytidine 5′-diphospho)-2-*C*-methyl-D-erythritol kinase (EC 2.7.1.148)	CMK	CMEK	*ispE* (also known as *ychB*)	*CMK* (At2g26930)	*ispE-1* [26]	*cmk-1*
5	2-*C*-Methyl-D-erythritol 2,4-cyclodiphosphate synthase (EC 4.6.1.12)	MDS	MECPS, MECS, MCS	*ispF* (also known as *ygbB*)	*MDS* (At1g63970)	*ispF-1* [39]	*mds-1*
6	4-Hydroxy-3-methylbut-2-enyl diphosphate synthase (EC 1.17.4.3)	HDS		*ispG* (also known as *gcpE*)	*HDS* (At5g60600)	*clb4-1* [17] *clb4-2* [17] *csb3* [18]	*hds-1* *hds-2* *hds-3*
7	4-Hydroxy-3-methylbut-2-enyl diphosphate reductase (EC 1.17.1.2)	HDR	IDS	*ispH* (also known as *lytB*)	*HDR* (At4g34350)	*ispH-1* [15] *clb6* [30]	*hdr-1* *hdr-2*

[a]Named according to the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB).
[b]Original literature reference in brackets.

with similar enzymatic activity, consecutive numbers should be added after the three letter name of the gene. When multiple complete or partial loss-of-function mutant alleles are described, a hyphen followed by a number is appended.

Table 1 lists the characterized *Arabidopsis* MEP pathway genes and mutants along with the names used for the *E. coli* homologs, the original nomenclature of the plant mutants as reported in the literature and the corresponding standardized names that we propose. The implementation of enzymatic activity as the basis for the three letter terminology has the advantage that it provides more information and is more parsimonious than names based on the corresponding *E. coli* orthologs, names derived from forward genetics approaches or other names that emerged during the effort to define the pathway. Thus, it is appropriate to emphasize the metabolic nature of the route, whose chemical steps are now well established. This nomenclature simplifies and aims to organize the somewhat confusing terminology previously employed for this pathway.

The study and description of the MEP pathway is simplified in *Arabidopsis* because it is likely that there is just a single gene for each of the enzymes that catalyze transformations between the central metabolic precursors (Figure 1a,b) and the final pathway products (Figure 1i,j). A family of two or more genes encoding DXS, usually belonging to two different classes (I and II), exists in most plants [21–23]. In *Arabidopsis*, only the At4g15560 gene, originally named as *CLA1* [12], has been demonstrated to encode a functional DXS enzyme [24]. Two additional genes with homology to DXS sequences exist in the *Arabidopsis* genome [10], At3g21500 (tentatively named *DXS2*) and At5g11380 (tentatively named *DXS3*). However, experimental evidence in the case of *DXS2* (L. Carretero-Paulet *et al.*, unpublished results) and sequence features in the case of *DXS3* [10,25] indicate that neither of them encode functional DXS enzymes. Therefore, in the proposed new nomenclature scheme, *CLA1* is renamed as *DXS*, whereas the other two DXS-like (DXL) genes, *DXS2* and *DXS3*, are renamed as *DXL1* and *DXL2*, respectively. If one of these two genes is eventually demonstrated to encode for DXS activity, its name should be changed to *DXS2* (and *DXS* to *DXS1*).

Currently available genetic and pharmacological resources for isoprenoid research in *Arabidopsis*

Because many of the isoprenoid products derived from the MEP pathway are essential for plant development and survival, a complete block of any of the MEP pathway steps results in a lethal phenotype of albino seedlings that are unable to develop after germination [10]. Knockout mutants are available for all the MEP pathway genes in *Arabidopsis* (all those listed in Table 1 except *dxs-3*, *dxs-4*, and *hds-3*). All these null mutants show a very similar albino phenotype (Figure 2a) even under low light conditions, demonstrating that this phenotype is caused by the lack of isoprenoid building blocks. Electron microscopy analyses have shown that chloroplast development is arrested at early stages in these mutants, resulting in organelles with incipient internal appressed membrane and vesicle structures but no organized thylakoid membranes or grana [15,24,26]. The fact that the loss-of-function *cla1*/*dxs-1* mutant displays this phenotype [12,24] further demonstrates that the two additional DXS-like genes found in *Arabidopsis* are not redundant with *DXS*.

The identification of partial loss-of-function mutants resulting from single mutations in two of the MEP pathway genes, *DXS* [27,28] and *HDS* [18], has allowed the identification of important regions for the enzymatic activity of the corresponding enzymes and, most interestingly, has uncovered new regulatory aspects of the MEP pathway. For example, reduced HDS activity in the *csb3* mutant (here renamed *hds-3*) causes a pale phenotype and a developmental delay (Figure 2b) due to a lower production of MEP-derived isoprenoids, such as chlorophylls and carotenoids [16], but it also causes a strong resistance to biotrophic pathogens [18], unveiling an unexpected link between the

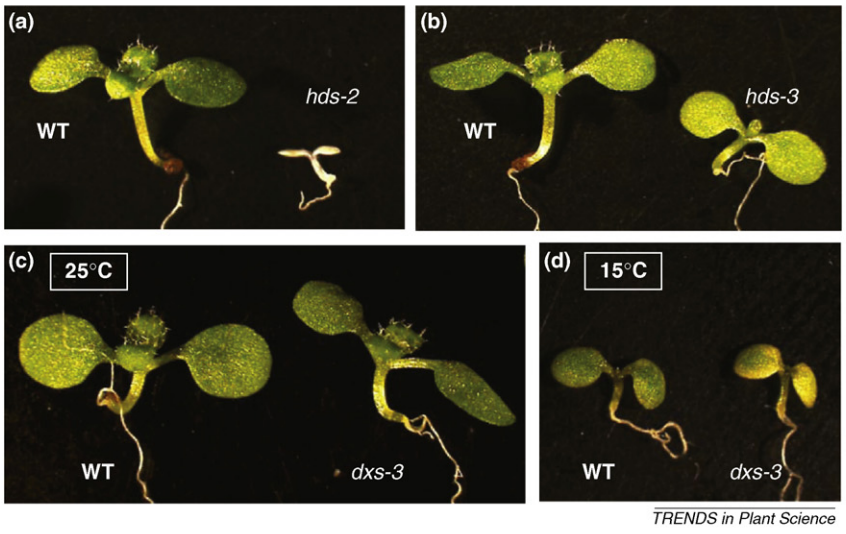

Figure 2. Representative phenotypes of *Arabidopsis* mutants of the MEP pathway. The generally pallid color of these mutants is caused by a block in one of the seven steps in this pathway needed to produce IPP and DMAPP, which are early precursors in chlorophyll and carotenoid biosynthesis. **(a)** An albino phenotype and severely stunted growth is typical of loss-of-function mutants of the pathway, such as *hds-2*. **(b)** A less severe phenotype of the partial loss-of-function allele *hds-3*. **(c)** The temperature-sensitive *dxs-3* mutant grows normally at 25 °C but displays a pale phenotype at 15 °C **(d)**. The *hds-2* mutant was previously referred to as *clb4-2* [17], *hds-3* as *csb3* [18], and *dxs-3* as *chs5* [27]. Abbreviation: WT, wild type.

MEP pathway and plant defense responses. Furthermore, crosstalk between the isoprenoid biosynthetic pathways in plant cells was uncovered when a mutant line resistant to the pharmacological block of the MVA pathway was shown to be a new *DXS* allele [28]. This mutant, *lvr111* (here renamed *dxs-4*), shows a semi-dominant variegated phenotype under normal growth conditions and can therefore be useful for addressing various aspects of the participation of the MEP pathway in chloroplast development. Another convenient tool for studying the MEP pathway is the *chs5* mutant (renamed *dxs-3*). These plants display a phenotype similar to wild type when grown at normal temperature (Figure 2c) but are much paler and even albino when grown at lower, restrictive temperatures (Figure 2d), suggesting that the activity of the mutated DXS protein in the *dxs-3* mutant is temperature-sensitive [27].

The characteristic pale/albino phenotype and developmental delay of *Arabidopsis* MEP pathway mutants (Figure 2) can be phenocopied by the use of specific chemical inhibitors of the pathway, such as ketoclomazone (an inhibitor of DXS) and fosmidomycin (an inhibitor of DXR). Such inhibitors are increasingly used as tools for better understanding the control and flux of the MEP pathway and its crosstalk with the MVA pathway [29–34]. In particular, screening for resistant mutants has led to the identification of previously unsuspected mechanisms for the regulation of the MEP pathway in *Arabidopsis*, such as the involvement of plastome-encoded proteins and the Clp protease complex in the homeostasis of DXS and DXR levels in plastids [35–37]. Finally, the ability to attenuate the activity of individual steps of the MEP pathway through the use of RNA interference or antisense expression has great potential to reveal additional information about the regulatory mechanisms that control the flux through this pathway. We anticipate that it will be possible to name subsequent partial-loss-of-function *Arabidopsis* transgenic lines derived from such analyses by following the standardized naming convention described here.

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