

Subsystem: Isoprenoid Biosynthesis

Olga Zagnitko, Fellowship for Interpretation of Genomes

Introduction

Major terpenoid building blocks, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), are produced via two different biosynthetic routes: the so-called *mevalonate* pathway in some species, and *non-mevalonate*, or DOXP pathway in others. Both pathways produce the same key building blocks (IPP and DMAPP), essential in all forms of cellular life. They have apparently involved completely independently, and share only one enzyme – isopentenyl-diphosphate delta-isomerase (IPDDI). Historically the mevalonate pathway and its enzymes have been thoroughly studied in eukaryotes. This pathway also occurs in some bacterial species, where all of the corresponding genes were identified based on homology with their eukaryotic counterparts [Ref.2,3]. Although the majority of bacteria possess only one of the two pathways, there are exceptions: both pathways can be asserted in *Listeria*. Plants also have both routes, one of them (DOXP) - of plastid (bacterial) origin. All other eukaryotes and archaea appear to have exclusively mevalonate pathway. Reconstruction of the mevalonate pathway in archaea including gene candidate predictions for some locally missing genes was described in [Ref.4]. The alternative DOXP pathway characteristic for most bacteria has not recognized until recently (for a review see [Ref.5]), and some aspects of it remained obscure until very recently [Ref.6,7]. Notably, gene encoding 1-deoxy-D-xylulose 5-phosphate reductoisomerase (ISPC) seems to be “missing” in *Brucella sp.*

Ref.1: **Osterman, A. & Overbeek R. (2003)** “Missing genes in metabolic pathways: A comparative genomics approach.” *Current Opin. Chem. Biol.* **7**, 1-14.

Ref.2: Wilding EI, Brown JR, Bryant AP, Chalker AF, Holmes DJ, Ingraham KA, Iordanescu S, So CY, Rosenberg M, Gwynn MN: **Identification, evolution, and essentiality of the mevalonate pathway for isopentenyl diphosphate biosynthesis in gram-positive cocci.** *J Bacteriol* 2000, **182**:4319-4327.

Ref.3: Humbelin M, Thomas A, Lin J, Li J, Jore J, Berry A: **Genetics of isoprenoid biosynthesis in *Paracoccus zeaxanthinifaciens*.** *Gene* 2002, **297**:129-139.

Ref.4 Smit A, Mushegian A: **Biosynthesis of isoprenoids via mevalonate in Archaea: the lost pathway.** *Genome Res* 2000, **10**:1468-1484.

Ref. 5. Eisenreich W, Rohdich F, Bacher A: **Deoxyxylulose phosphate pathway to terpenoids.** *Trends Plant Sci* 2001, **6**:78-84.

Ref. 6. Seemann M, Bui BT, Wolff M, Tritsch D, Campos N, Boronat A, Marquet A, Rohmer M: **Isoprenoid Biosynthesis through the Methylerythritol Phosphate Pathway: The (E)-4-Hydroxy-3-methylbut-2-enyl Diphosphate Synthase (GcpE) is a [4Fe-4S] Protein.** *Angew Chem Int Ed Engl* 2002, **41**:4337-4339.

Ref. 7 Adam P, Hecht S, Eisenreich W, Kaiser J, Grawert T, Arigoni D, Bacher A, Rohdich F: **Biosynthesis of terpenes: studies on 1-hydroxy-2-methyl-2-(E)-butenyl 4-diphosphate reductase.** *Proc Natl Acad Sci U S A* 2002, **99**:12108-12113

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Functional roles (A) and a Spreadsheet (B) for selected species representing functional variants

(A)

No	Abbrev	Functional Role
1	ACAT	Acetyl-CoA acetyltransferase (EC 2.3.1.9)
2	HMGCS	Hydroxymethylglutaryl-CoA synthase (EC 2.3.3.10)
3	HMGCR	Hydroxymethylglutaryl-CoA reductase (EC 1.1.1.34)
4	MEVK	Mevalonate kinase (EC 2.7.1.36)
5	PMEVK	Phosphomevalonate kinase (EC 2.7.4.2)
6	DPMVD	Diphosphomevalonate decarboxylase (EC 4.1.1.33)
7	IPDDI	Isopentenyl-diphosphate delta-isomerase (EC 5.3.3.2)
8	IPDDIf	Isopentenyl-diphosphate delta-isomerase, FMN-dependent (EC 5.3.3.2)
9	DXS	1-deoxy-D-xylulose 5-phosphate synthase (EC 2.2.1.7)
10	ISPC	1-deoxy-D-xylulose 5-phosphate reductoisomerase (EC 1.1.1.267)
11	ISPD	2-C-methyl-D-erythritol 4-phosphate cytidyltransferase (EC 2.7.7.60)
12	ISPE	4-diphosphocytidyl-2-C-methyl-D-erythritol kinase (EC 2.7.1.148)
13	ISPF	2-C-methyl-D-erythritol 2,4-cyclodiphosphate synthase (EC 4.6.1.12)
14	ISPG	1-hydroxy-2-methyl-2-(E)-butenyl 4-diphosphate synthase (EC 1.17.4.3)
15	ISPH	4-hydroxy-3-methylbut-2-enyl diphosphate reductase (EC 1.17.1.2)
16	GTT	Geranyltranstransferase (EC 2.5.1.10)

Mevalonate Pathway (rows 1-8)

Nonmevalonate Pathway (rows 9-16)

(B)

Organism	Var. Code	ACAT	HMGCS	HMGCR	MEVK	PMEVK	DPMVD	*IPDDI	DXS	ISPC	ISPD	ISPE	ISPF	ISPG	ISPH	GTT
<i>Streptococcus pyogenes</i> M1 GAS [B]	1	uni Q99YM2, more	uni Q9A093	uni Q9A094	uni Q9A098	uni Q9A096	uni Q9A097	uni Q9A095-8								uni Q95
<i>Saccharomyces cerevisiae</i> [E]	1	uni P41338	uni P54839	uni P12684, uni P12683	uni P07277	uni P24521	uni P32377	uni P15496-7, uni Q04311-7								uni P08, uni Q12
<i>Homo sapiens</i> [E]	1	uni P24752, more	uni P54868, gi 39930537	uni P04035	uni Q03426	uni Q15126	uni P53602	uni Q13907-7			gi 42657936, gi 42657936					uni P14, gi 4118, uni P22
<i>Escherichia coli</i> K12 [B]	2	uni Q46939, uni P76461						uni Q46822-7	uni P77488	uni P45568	uni Q46893	uni P24209	uni P36663	uni P27433	uni P22565	uni P19, uni P22
<i>Thermotoga maritima</i> MSB8 [B]	2								uni Q9X291	uni Q9WZZ1	uni Q9X1B3	uni Q9X1A3	uni Q9WZB5	uni Q9WZZ3	uni Q9X1F7	uni Q9V
<i>Listeria monocytogenes</i> str. 1/2a F6854 [B]	3	uni Q8Y782	gi 47095366	uni Q8Y8R9	uni Q8YAV3	uni Q8YAV1	uni Q8YAV2	gi 47095967-8	uni Q8Y7C1	gi 47096942	uni Q8Y832	uni Q8YAE1	gi 47097427	gi 47095392	gi 47095402	gi 47095, gi 4709

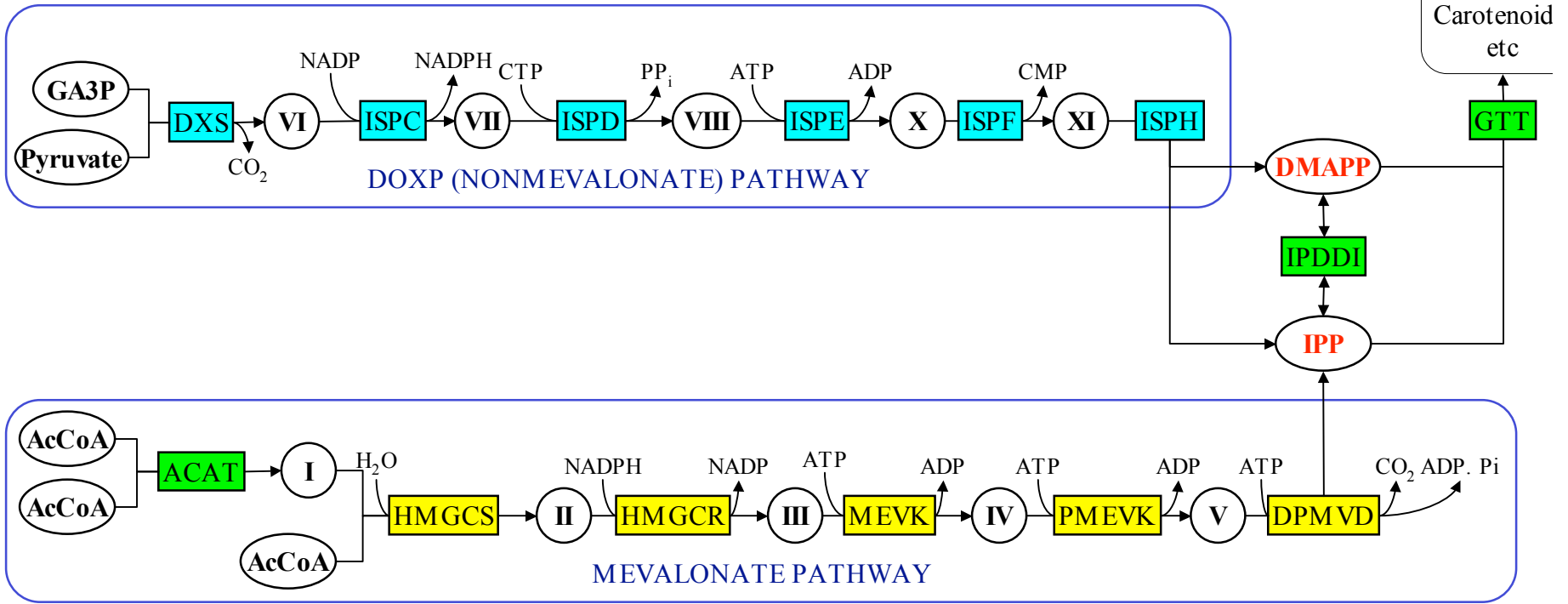
Mevalonate Pathway (columns 2-8)

Nonmevalonate (DOXP) Pathway (columns 9-16)

*IPDDI: a sub-set composed of functional roles #7 (IPDDI) and #8(IPDDIf), nonorthologous forms of isopentenyl-diphosphate delta-isomerase

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Diagram illustrating subsystem implementations in *E. coli* K12 and *H. sapiens*



Color coding

In both

In *E. coli*

In *H. sapiens*

MEVALONATE PATHWAY	
I	Acetoacetyl-CoA
II	Hydroxymethylglutaryl-CoA
III	Mevalonate
IV	Phosphomevalonate
V	Diphosphomevalonate
NONMEVALONATE PATHWAY	
VI	1-Deoxy-D-xylulose 5-phosphate
VII	2C-methyl-D-erythritol 4-phosphate
VIII	4-Diphosphocytidyl-2C-methyl-D-erythritol
IX	4-Diphosphocytidyl-2C-methyl-D-erythritol 2-phosphate
X	2C-Methyl-D-erythritol 2,4-cyclodiphosphate
XI	1-Hydroxy-2-methyl-2(E)-butenyl 4-diphosphate
COMMON COMPOUNDS	
IPP	Isopentenyl Pyrophosphate
DMAPP	Dimethylallyl Pyrophosphate
OTHER COMPOUNDS	
AcCoA	Acetyl-CoA
GA3P	D-glyceraldehyde-3-phosphate