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Current development in isoprenoid precursor biosynthesis and regulation

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Isoprenoids are one of the largest classes of natural products and all of them are constructed from two precursors, isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP). For decades, the mevalonic acid (MVA) pathway was proposed to be the only IPP and DMAPP biosynthetic pathway. This review summarizes the newly discovered IPP and DMAPP production pathways since late 1990s, their distribution among different kingdoms, and their roles in secondary metabolite production. These new IPP and DMAPP production pathways include the methylerythritol phosphate (MEP) pathway, a modified MVA pathway, and the 5-methylthioadenosine shunt pathway. Relative to the studies on the MVA pathway, information on the MEP pathway regulation is limited and the mechanistic details of several of its novel transformations remain to be addressed. Current status on both MEP pathway regulation and mechanistic issues is also presented.

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Introduction

Isoprenoids (also known as terpenoids or terpenes) are found in all domains of life (bacteria, archaea, and eukaryotes) and many have important biological functions [1]. For example, quinones act as part of the electron transport chain, sterols as eubacterial and eukaryotic cell membrane components, carotenoids as essential biopigments, dolichol in glycoprotein and bacterial cell wall biosynthesis, and linear prenyl diphosphates as protein prenylation units for intra-cellular protein targeting. In addition, isoprenoids are widely utilized in biomedical and commercial applications including pharmaceuticals, flavoring agents, fragrances, and nutrition products. In this paper, we review recent progress made in understanding the biosynthesis of the isoprenoid precursors, dimethylallyl diphosphate (DMAPP, **1**) and isopentenyl diphosphate (IPP, **2**).

Biosynthesis of IPP and DMAPP

The mevalonic acid (MVA) pathway

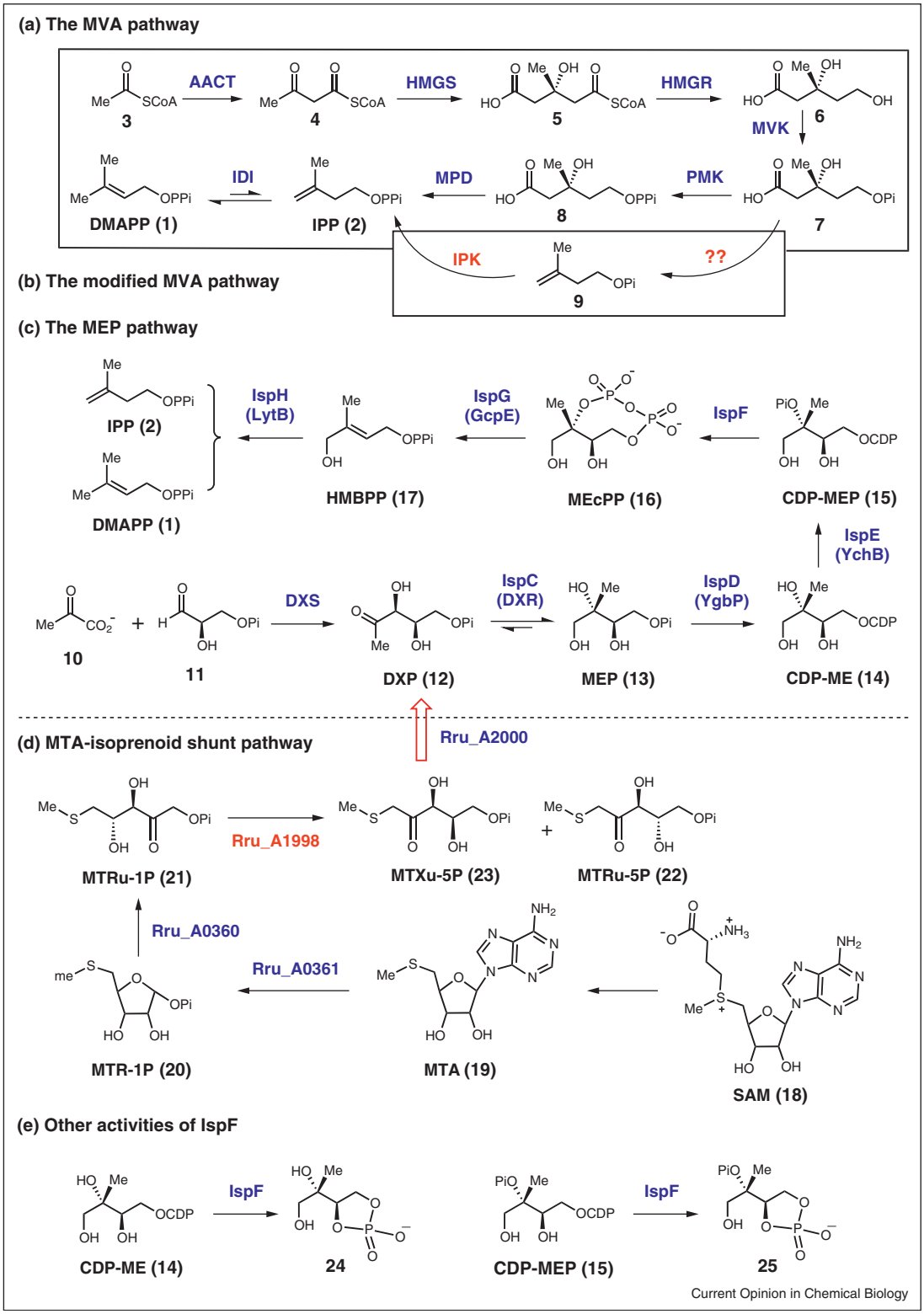
The mevalonic acid (MVA, **6**) pathway of DMAPP (**1**) and IPP (**2**) biosynthesis (see Figure 1a) has been known for over half a century, and its discovery led to the awarding of the Nobel prize in physiology to Lynen and Bloch in 1964, and in chemistry to Cornforth in 1975 [2]. The pathway starts with the acetyl-CoA acetyltransferase (AACT) catalyzed condensation of two acetyl-CoA (**3**) molecules to form **4**. This is followed by the hydroxylmethylglutaryl-CoA synthase (HMGS) catalyzed reaction to produce 3-hydroxy-3-methyl-glutaryl-CoA (**5**, HMG-CoA). The rate-limiting step of the carbon flow through the MVA pathway is the reduction of **5** by HMG-CoA reductase (HMGR) with two equivalents of NADPH. The resulting MVA (**6**) is activated by two phosphorylation steps catalyzed by mevalonate kinase (MVK) and phosphomevalonate kinase (PMK). This is followed by an ATP-coupled decarboxylation of **8** catalyzed by mevalonate pyrophosphate decarboxylase (MPD) to yield IPP (**2**) as the product. Two structurally unrelated IPP:DMAPP isomerases (IDI-1 and IDI-2) are then responsible for the interconversion of IPP (**2**) and DMAPP (**1**) [3,4•].

Recently, the existence of a modified mevalonate pathway (Figure 1b) was suggested based on the observation that genes encoding enzymes catalyzing the late steps of the MVA pathway are absent in some archaeal genomes. Grochowski *et al.* [5•] identified an enzyme (isopentenyl phosphate kinase, IPK) from *Methanocaldococcus jannaschii*, which is capable of phosphorylating **9** to form IPP. It was thus proposed that **7** is decarboxylated to form **9** and then phosphorylated to produce IPP (**2**). However, the hypothesized decarboxylase (for **7** → **9**) has not yet been identified. Hence, we cannot rule out the option of the existence of a classical MVA pathway in *M. jannaschii*, while its PMK and MPD have no or very low sequence similarities to the well-studied PMK and MPD enzymes.

The methylerythritol phosphate (MEP) pathway

In the 1990s and early 2000s, efforts by Rohmer, Arigoni, Lichtenthaler, and Seto, *etc.* led to the discovery of a new isoprene biosynthetic pathway in both bacteria and the chloroplasts of green algae and higher plants [6–11]. This pathway begins with the condensation of pyruvate (**10**) and glyceraldehyde phosphate (**11**) to afford 1-deoxy-D-xylulose 5-phosphate (**12**, DXP) in a reaction catalyzed by

Figure 1



Pathways for the production of isoprenoid precursors: **(a)** The mevalonic acid (MVA) pathway. **(b)** A modified MVA pathway in *Methanocaldococcus jannaschii*. **(c)** The methylerythritol phosphate (MEP) pathway. **(d)** A newly discovered isoprenoid shunt pathway related to *S*-adenosylmethioneine metabolism. Two new activities found for IspF are shown in **(e)**.