Bioorganic Chemistry 43 (2012) 51–57

Contents lists available at SciVerse ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Reviews

Structures, mechanisms and inhibitors of undecaprenyl diphosphate synthase: A *cis*-prenyltransferase for bacterial peptidoglycan biosynthesis

Kuo-Hsun Teng, Po-Huang Liang *

Institute of Biological Chemistry, Academia Sinica, Taipei 11529, Taiwan

ARTICLE INFO

Article history:
Received 29 July 2011
Available online 21 September 2011

Keywords:
Isoprenoid
Prenyltransferase
X-ray structure
Pre-steady-state kinetics
Conformational change
Inhibitor

ABSTRACT

Isoprenoids are an intensive group of compounds made from isopentenyl diphosphate (IPP), catalyzed by prenyltransferases such as farnesyl diphosphate (FPP) cyclases, squalene synthase, protein farnesyltransferases and geranylgeranyltransferases, aromatic prenyltransferases as well as a group of prenyltransferases (*cis*- and *trans*-types) catalyzing consecutive condensation reactions of FPP with specific numbers of IPP to generate linear products with designate chain lengths. These prenyltransferases play significant biological functions and some of them are drug targets. In this review, structures, mechanisms, and inhibitors of a *cis*-prenyltransferase, undecaprenyl diphosphate synthase (UPPS) that mediates bacterial peptidoglycan biosynthesis, are summarized for comparison with the most related *trans*-prenyltransferases and other prenyltransferases.

Contents

1. Introduction

Isoprenoids are natural products composed of 5-carbon isopentenyl diphosphate (IPP) as the building block [1,2]. These compounds are ubiquitous in Eukarya, Bacteria and Archaea to serve a variety of different biological functions [3]. As illustrated in Fig. 1, for the biosynthesis of isoprenoid natural products, IPP is first converted to its isomer dimethylallyl diphosphate (DMAPP) by the isomerase [4]. This allylic compound can condense with one and two molecules of IPP to form geranyl diphosphate (GPP) and farnesyl diphosphate (FPP) by GPP synthase (GPPS) and FPP synthase (FPPS), respectively [5,6]. FPP serves as an outlet point leading to a variety of different isoprenoid compounds. Its cyclization by cyclases leads to cyclic sesquiterpenes such as pentalenene, trichodiene, and epi-aristolochene [7–9]. Two FPP condense to form squalene catalyzed by squalene synthase (SQS) and then to cholesterol and some hormones in animals [10]. FPP can react with one IPP to generate geranylgeranyl diphosphate (GGPP) by GGPP

Abbreviations: IPP, isopentenyl diphosphate; DMAPP, dimethylallyl diphosphate; GPP, geranyl diphosphate; FPP, farnesyl diphosphate; GPPS, geranyl diphosphate synthase; FPPS, farnesyl diphosphate synthase; SQS, squalene synthase; GGPP, geranylgeranyl diphosphate; DMATS, dimethylallyl transferase; GGPPS, geranylgeranyl diphosphate synthase; DPPS, decaprenyl diphosphate synthase; UPPS, undecaprenyl diphosphate synthase; HexPPS, hexaprenyl diphosphate synthase; HepPPS, heptaprenyl diphosphate synthase; OPPS, octaprenyl diphosphate synthase; Br-IPP, 3-bromo-3-butenyl diphosphate.

* Corresponding author. Fax: +886 2 2363 5038.
E-mail address: phliang@gate.sinica.edu.tw (P.-H. Liang).

0045-2068/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bioorg.2011.09.004

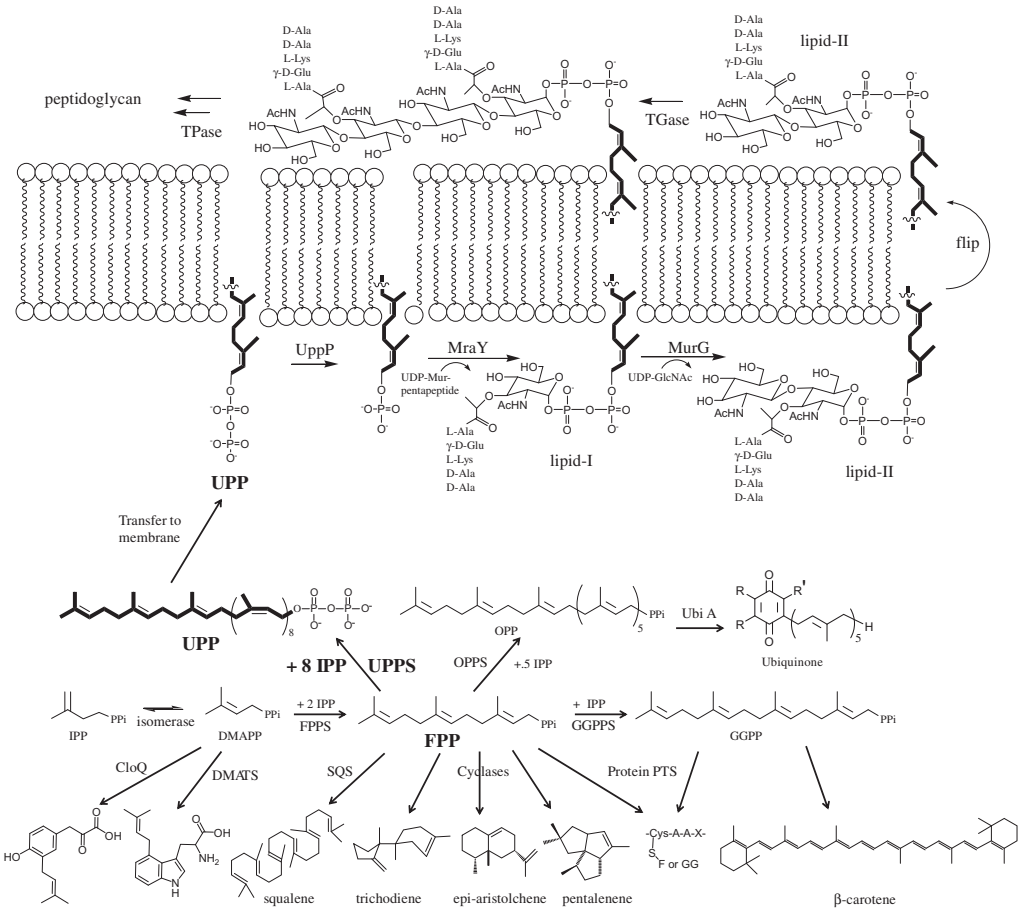

Fig. 1. Prenyltransferases discussed in this review and the biosyntheses of natural isoprenoids they are involved. The UPP highlighted serves as lipid carrier for bacterial peptidoglycan biosynthesis.

synthase (GGPPS) [11,12]. GGPP is the precursor of natural products such as ether-linked lipids in archeon, chlorophylls, α-tocopherol or longer prenyl diphosphates used in quinine biosynthesis, ent-kaurene, taxadiene, phytoene and carotenoids. Among them, carotenoids and retinoids containing highly conjugated structures for absorption of light are involved in the light-sensitive elements. Both FPP and GGPP can be added to signaling proteins on a conserved cysteine located in a C-terminal CaaX motif with "a" often an aliphatic residue and "X" Ser, Met, Ala, or Gln by protein prenyltransferases [13,14]. Prenylation (i.e. farnesylation or geranylgeranylation) of Ras, Rab, nuclear lamins, trimeric G-proteins γ subunits, protein kinases, and small Ras-related GTP-binding proteins for anchoring them into the cellular membranes is essential for signal transduction pathways [15]. Aromatic prenyltransferases such as DMAPP transferase (DMATS) and CloQ transfer prenyl moieties (e.g. DMAPP) onto aromatic acceptor molecules, forming covalent bonds between C1 or C3 of the isoprenoid moiety and an atom of the aromatic ring [16]. These products are primary and secondary aromatic metabolites in plant, fungi, and bacteria [17,18].

FPP is also a starting material for a group of prenyltransferases, each synthesizing a linear polymer with designate chain length via condensation reactions with a specific number of IPP [19,20]. Based on the stereochemistry of double bonds formed during IPP condensation, these prenyltransferases are classified as *trans*- and *cis*-types. *trans*-Prenyltransferases generate products with chain lengths ranging from C_{10} to C_{50}, whereas *cis*-prenyltransferases produce larger polymers including C_{50} by decaprenyl diphosphate synthase (DPPS), C_{55} by undecaprenyl diphosphate synthase (UPPS), C_{120} by a *cis*-prenyltransferase from *Arabidopsis thaliana* [21], to almost unlimited chain lengths by rubber prenyltransferases [22] with an exception of a short-length *cis*-type FPPS found in *Mycobacterium tuberculosis* [23]. The C_{30}, C_{35}, C_{40}, C_{45}, and C_{50} products generated by hexaprenyl diphosphate synthase (HexPPS) [24], heptaprenyl diphosphate synthase (HepPPS) [25], octaprenyl diphosphate synthase (OPPS) [26], solanesyl diphosphate synthase (SPPS), and DPPS, respectively, constitute the side chains of ubiquinone and menaquinone in different species.

For the reasons of using prenyltransferases as drug targets, oncogenic Ras farnesylated as mutant forms has been detected in approximately 30% of all human cancers [27] and oncogenic H-Ras is known for its Akt-1 activation and transforming activity [28]. Geranylgeranylated Rho GTPases play key roles in the recognition of the actin cytoskeleton and the control of gene transcription [29–31]. Bis-geranylgeranylated Rab GTPases regulate vesicular trafficking and exocytosis [32,33]. Therefore, protein farnesyltransferases have been regarded as anti-cancer targets [34–36]. Furthermore, inhibitors of prenylation of Ras and other G-proteins have been developed for therapeutics in restenosis, angiogenesis and osteoporosis [37]. FPPS for synthesizing FPP is the drug target of bisphosphonate drugs for preventing the bone loss associated with osteoporosis, Paget's disease, hypercalcemia, and metastatic bone disease [38] and GGPPS may serve as a target for some cases [39].

On the other hand, the C_{55} product of bacterial UPPS serves as a lipid carrier in cell wall peptidoglycan biosynthesis as shown in