What We Do and Do Not Know About the Cellular Functions of Polyisoprenoids

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Abstract

Natural compounds classified as products of secondary metabolism are widely studied as to their potential biological role. Identification of possible cellular functions of polyisoprenoids, generally considered as secondary products, has been our focus for some 30 years already. The results of these studies for instance in the context of membrane permeability and protein modification are briefly described and discussed in this chapter.

Keywords

Polyisoprenoid alcohols • *cis*-/*trans*-polyprenols, dolichols • *cis*-prenyltransferases • Solanesol (all-*trans* prenol-9) • Bactoprenol (prenol-11) • Membrane fluidity • Protein glycosylation • Polyisoprenylated proteins • [^{3}H]farnesol • [^{3}H]geranylgeraniol

21.1 Structural Aspects of Polyisoprenoids

The term polyisoprenoids is used here to designate linear polymers of several up to more than 100 isoprene units (Fig. 21.1). Neither short-chain oligoterpenes ($n<5$) nor higher isoprene polymers ($n>300$) such as natural rubber or gutta-percha will be discussed (but see elsewhere in this volume). Although the simple and modest polymeric structure of polyisoprenoids does not leave too much room for diversification, still some structural variants are known, and their structures together with newly described compounds have been summarized recently (Skorupinska-Tudek et al. 2008b; Surmacz and Swiezewska 2011).

Two main types of polyisoprenoid alcohols have been described so far differing in the hydrogenation status of their OH-terminal (α-) isoprene unit; these are polyprenols (α-unsaturated) and dolichols (α-saturated) compounds. Further diversity of natural polyisoprenoid alcohols concerns the *cis*/*trans* (*Z*/*E*) configuration of double bonds and the chain-length of molecules (Hemming 1985). Typical polyprenols and dolichols are of "mainly *cis*-" configuration; thus,

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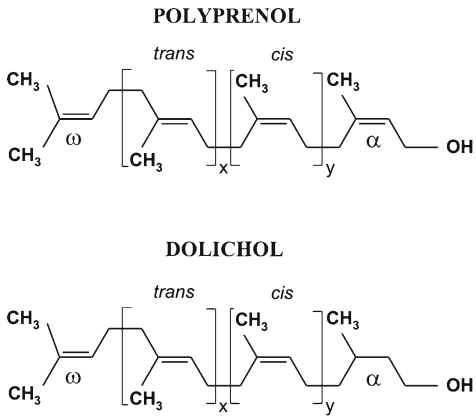

Fig. 21.1 Structure of polyprenol and dolichol. The isoprenoid units in *trans* and *cis* configuration are indicated, *x* and *y* stand for the number of internal *trans* and *cis* units, respectively, while ω and α represent the terminal ones

their molecules consist of a few (two or three for some polyprenols) *trans* isoprene units adjacent to the α-unit. Solanesol (all-*trans*-Prenol-9) is almost the unique representative of the all-*trans* polyisoprenoids. Polyprenols are found in plant photosynthetic tissues and bacterial cells, while dolichols are typical animal and yeast lipids. Recently, dolichols have also been identified in plant roots (Skorupinska-Tudek et al. 2003).

A unique feature of polyisoprenoids is their occurrence in the tissues as mixtures of homologues. Prenol-11, bactoprenol typical for bacteria, and all-*trans*-Prenol-9 are the best known exceptions accumulated as single homologues. Dolichol families are quite "small" (6–8 dolichols accumulated in the tissue). Dolichol chain-lengths are rather homogenous in nature – the dominant Dol consists of 16 isoprene units (i.e., in the yeast *Saccharomyces cerevisiae* and in plant roots), 18 i.u. (mice and rat tissues), 19 i.u. (human), and 21 i.u. (second less abundant yeast family). In contrast, plant polyprenol families found in green tissues are really diverse (from 5 to more than 130 polyprenols, with dominant polyprenols from Pren-7 to Pren-28), and their composition can be considered as a species-specific chemotaxonomic marker (Swiezewska and Danikiewicz 2005).

21.2 Biosynthesis of Polyprenols and Dolichols in Plants

Recently, the origin of isopentenyl diphosphate used for construction of polyisoprenoid alcohols in plants has been studied in detail. Incorporation experiments performed with plant roots (where dolichols are the dominant form) revealed that both the MVA and the MEP pathways served as the source of IPP molecules, integrated into the polyisoprenoid hydrocarbon skeleton. According to the model derived from this study, the biosynthesis of dolichols starts in plastids with IPP of mixed origin (MEP and MVA), and oligoprenyl diphosphates thus formed are exported to the cytoplasm where a few α-terminal isoprene units of solely MVA origin are used for the last steps of elongation and termination of the dolichol molecule (Skorupinska-Tudek et al. 2008a). Consequently, this model predicts a constitutive exchange of intermediates between cellular compartments – a more or less unidirectional flow of IPP from cytoplasm to plastids and of oligoprenyl diphosphates from plastids to the cytoplasm. Whether the biosynthesis of α-unsaturated polyisoprenoid alcohols in photosynthetic tissue is also spatially organized in a similar manner requires further experiments.

Several steps of this model remain elusive, e.g., the mechanism of the intracellular transport of intermediates and the identity of the prenyltransferases involved. Enzymes responsible for the head-to-tail condensations of successive IPPs leading to the formation of polyisoprenoid chains in plants, i.e., the putative plastidial farnesyl diphosphate synthase and *cis*-prenyltransferases (CPT), await their characterization. A few genes encoding CTP have been cloned in plants. The Arabidopsis genome contains a family of nine putative genes with homology to yeast CPTs (*RER2* and *SRT1*) (GenBank); however, only one of them, *ACTP1*, was characterized at the molecular level (Cunillera et al. 2000; Oh et al. 2000). Two cDNAs encoding CPT from *Hevea brasiliensis* (HRT1 and HRT2) have also been reported (Asawatreratanakul et al. 2003). Very recently,

the Nogo-B receptor has been described as an essential component of the CPT machinery necessary for dolichol biosynthesis and protein *N*-glycosylation in mammalian and yeast (NUS1) cells (Harrison et al. 2011). A plant orthologue of Nogo-BR has not been identified so far.

21.3 Function of Polyprenols and Dolichols

All eukaryotic cells studied so far contain polyisoprenoid alcohols. Polyisoprenoids are accumulated as free alcohols and/or esters with carboxylic acids, while a fraction (usually a small portion) is also found in the form of phosphates; for dolichols, conjugates with sugars were also reported (Hemming 1985). The content of polyisoprenoid alcohols is highly increased in the tissues during the life span: in senescing plant leaves, a 20-fold increase has been noted, and in the richest plant sources (photosynthetic tissue), the concentration of polyprenols is up to 5% of dry mass (Swiezewska et al. 1994). In mammalian tissues, a 100-fold increase in human brain has been observed, and the highest content reaching mg quantities per g of wet weight was found in endocrine tissues (in pituitary glands, the amount of dolichols is equal to that of phospholipids) (Chojnacki and Dallner 1988).

Besides the increased content of polyisoprenoids related to aging, several external factors have been shown to further increase free polyisoprenoid concentration in plant tissue. Significant light-stimulated accumulation of polyisoprenoid alcohols in the leaves has been reported (Bajda et al. 2005). Recently, viral infection (tobacco mosaic virus) has been shown to considerably induce the accumulation of solanesol (all-*trans*-Pren-9) and polyprenols in tobacco leaves; virus-inoculated leaves contained a 2.5- and 7-fold higher concentration of polyprenols and solanesol, respectively, and a similarly increased concentration of both types of polyisoprenoids was measured in leaves located above the site of infection (systemic leaves) (Bajda et al. 2009). This observation indicates the possible role of polyisoprenoids in plant defense against pathogens, both locally and at a systemic level; however, the underlying mechanism remains elusive. Two possibilities are currently taken into consideration. Firstly, polyisoprenoid alcohols modulate the biophysical properties of biological membranes. This statement is based on the results of *in vitro* experiments where polyisoprenoids were shown to increase the fluidity and permeability of model membranes and to modulate the surface curvature of membranes by formation of fluid microdomains (Valtersson et al. 1985; Janas et al. 2000; Ciepichal et al. 2011). Increased stress tolerance in plants has been correlated with increased membrane fluidity, and this property is most often attributed to increased unsaturation of fatty acids (Wallis and Browse 2002). It seems plausible to assume that polyisoprenoids work in concert with polyunsaturated fatty acids and also exert their bilayer-fluidizing effect *in vivo*. The influence of α-*cis*- and α-*trans*-polyprenols on the structure and properties of model membranes was investigated, from which it was inferred that the *cis*/*trans* isomerization of the α-residue of polyisoprenoid molecules might constitute some mechanism responsible for modulation of cellular membrane permeability (Ciepichal et al. 2011). The concomitant occurrence of alloprenols and ficaprenols in plant tissues is a strong argument into this direction (Ciepichal et al. 2011). Secondly, the putative role of polyisoprenoids as scavengers of reactive oxygen spices in the membranes should also be discussed. Several reports suggest that in plants, volatile isoprenoids confer additional protection in cooperation with carotenes and tocopherols or serve as an alternative defensive mechanism when other well-conserved mechanisms are not efficient enough against oxidative stress (Peñuelas and Munné-Bosch 2005). Moreover, direct antioxidant properties of isoprene and other monoterpenes have been suggested (Loreto et al. 2004). Similarly, a role of dolichol in the antioxidant defense in mammalian cells has been proposed (Bergamini et al. 2004).

Worth noting are the results that were obtained by phenotypical analysis of yeast mutants devoid

of one of the two CPT encoding genes. The involvement of polyisoprenoids in intracellular traffic of proteins was suggested (Sato et al. 1999). Later, dolichols were considered as being essential for anterograde vesicle trafficking (Belgareh-Touze et al. 2003). Very recently, an impairment of dolichol phosphorylation has been recognized as a cause of a new inherited human disorder, and severely diminished protein glycosylation was considered as a major reason of metabolic dysfunctions, whereas protein prenylation had not been analyzed (Kranz et al. 2007). Most recently, the new type of the congenital disorder of glycosylation (CDG) has been attributed to the mutation in a human gene *SRD5A3* identified as necessary for the reduction of the α-isoprene unit of polyprenols to form dolichols (Cantagrel et al. 2010). This CDG type 1 severely disrupts infant eye and brain development; supplementation of the diet with dolichol has been suggested as a potential treatment for this syndrome (editorial comment in American Journal of Medical Genetics A 2010 Oct;152A).

In human brain, dolichol is increased in lysosomal storage disorders, including mucopolysaccharidosis and neuronal ceroid lipofuscinosis (Sakakihara et al. 1994), in liver cancer and preneoplastic noduli (Olsson et al. 1991, 1995), and in regenerating liver (Trentalance 1994). Several xenobiotics are known to induce dolichol accumulation in mammalian liver (Chojnacki and Dallner 1988), but somehow contradictory in this context was the observation of a decrease of dolichol content in rat hepatocytes upon carbon tetrachloride treatment (Parentini et al. 2003).

21.4 Functions of Polyprenyl and Dolichyl Phosphates

The well-documented function of polyisoprenoid diphosphates is their role as cofactors of protein glycosylation in eukaryotic and prokaryotic cells. In mammalian and yeast systems, dolichyl phosphates function as cofactors in the biosynthesis of *N*- and *O*-glycoproteins and GPI-anchor (Burda and Aebi 1999; Samuelson et al. 2005). Also in the plant system, dolichyl rather than polyprenyl phosphates are thought to serve as lipid carriers in this process (Lehle and Tanner 1983; Kaushal and Elbein 1989; Wilson 2002). In prokaryote, prenyl (bactoprenyl) phosphate has been proved to also act as a cofactor of peptidoglycan biosynthesis (Shibaev 1986).

Since the discovery of polyisoprenylated proteins, the putative role of polyisoprenoid phosphates as donors of the polyprenyl group has been discussed. This phenomenon was observed for the first time in rat kidney (Bruenger and Rilling 1986), and later was characterized in rat liver (Thelin et al. 1991). Further evidence for protein dolichylation in rat was the mass spectrometry identification of dolichol (Hjertman et al. 1997) or short-chain (5 and 6 isoprenoid units) polyprenols (Parmryd and Dallner 1999) cleaved from covalently linked protein–lipid adducts. Studies on prenylation of proteins in plants were initiated by identification of farnesylated and geranylgeranylated proteins in tobacco suspension cells and *Atriplex nummularia* (Randall et al. 1993; Zhu et al. 1993) and in parallel in spinach (Swiezewska et al. 1993; Shipton et al. 1995). In the latter case, analysis of isoprenoid groups cleaved from lipid-modified proteins showed that phytol and a family of polyprenols were covalently linked to the proteins besides farnesol and geranylgeraniol. Initially, identification of these isoprenoids was based on chromatographic co-elution of standards with tritiated hydrophobic products released by hydrolytic cleavage from proteins obtained after metabolic labeling with [^{3}H]mevalonate. Since different mixtures of isoprenoid products were cleaved from [^{3}H]-labeled proteins by methyl iodide (mainly farnesol and geranylgeraniol) and alkali (mainly phytol and long-chain polyisoprenoids); a different nature of the chemical linkages between isoprenoids and peptides was postulated in these cases (thioether and ester for the former and latter compounds, respectively). In line with the ester type of the chemical bond linking proteins and polyprenols was the recovery of a fraction of polyprenols in a polar lipid fraction. Later, the structure of the bound phytol was confirmed by GC–MS (Parmryd et al. 1999). Structural analysis of polyisoprenoids covalently linked to proteins in Arabidopsis using

HPLC/MS was performed later (Gutkowska et al. 2004). A family of polyprenols (Pren-9 and Pren-11 with Pren-10 dominating) together with dolichols (Dol-15–17 with Dol-16 dominating) were identified by mass spectrometry analysis of polyprenols released from native polyprenylated proteins, while the same spectrum of [^{3}H]isoprenoids released from metabolically ([^{3}H]mevalonate) labeled proteins was recorded by HPLC/radiometric detection. Use of other metabolic precursors ([^{3}H]farnesol and [^{3}H]geranylgeraniol) confirmed the occurrence of several proteins metabolically labeled with these precursors. A brief fractionation procedure revealed that a significant portion of these proteins was recovered from the light vesicles/cytoplasmic fraction.

The role of plant proteins modified by farnesyl or geranylgeranyl groups has been summarized in several reviews (Nambara and McCourt 1999; Rodríguez-Concepción et al. 1999; Yalovsky et al. 1999; Crowell 2000; Galichet and Gruissem 2003). Some recent studies describing the functions of farnesylated and geranylgeranylated proteins are mentioned below. Farnesylated and geranylgeranylated proteins were shown to be involved in regulation of meristem growth since mutants identified in PLURIPETALA (encodes the α-subunit shared between protein farnesyltransferase and protein geranylgeranyltransferase I) were found to have a spectacularly increased meristem and increased floral organ number (Running et al. 2004). Downregulation of protein farnesylation in Arabidopsis, through downregulation of either the α- or β-subunit of farnesyltransferase, enhances the plant's response to ABA and drought tolerance (Wang et al. 2005). Farnesylation status of a nucleosome assembly protein 1 (AtNAP1;1) regulates leaf cell proliferation vs. cell expansion during Arabidopsis leaf development (Galichet and Gruissem 2006). Geranylgeranylated AtRab7 protein was shown to control the plant response to salt and osmotic stress through regulation of intracellular vesicle trafficking (Mazel et al. 2004). The γ subunits of heterotrimeric G proteins, AGG1 and AGG2, required prenylation for their activity, and both proteins can be prenylated by either geranylgeranyltransferase I or farnesyl protein transferase (Zeng et al. 2007).

So far, the peptide moiety of any endogenous polyprenyl- or dolichyl-modified proteins has not been identified. It could be only speculated that the long hydrophobic tail of polyisoprenylated proteins is required for tight association of proteins with membranes.

Interestingly, the MEP-derived IPPs were shown to be built into the isoprenoid groups utilized for covalent modification of proteins by application of [^{14}C]deoxyxylulose. According to the mobility of [^{14}C]proteins labeled from this precursor on SDS-PAGE, prenyl groups of small G proteins were derived from the MEP pathway. This observation was independent of the inhibition of the MVA pathway by mevinolin; however, the precise structure of isoprenoid moiety has not been confirmed yet (Hemmerlin et al. 2003). This problem was somewhat overcome when tobacco BY-2 cells were stably transformed with a dexamethasone-inducible gene coding for a GFP fused with a carboxy-terminal polybasic domain from rice calmodulin CaM61, bearing a geranylgeranylation motif. Re-isolation of the plasma membrane-bound, covalently modified protein, followed by digestion by a specific protease and HPLC-MS/MS analysis of peptides, led to the identification of a geranylgeranylated peptide of the predicted mass and sequence (Gerber et al. 2009). In the same study, it was demonstrated that nearly exclusively the plastidial MEP pathway provided the substrate for cytoplasmic protein geranylgeranylation under the conditions applied, i.e., in the presence of pathway-specific inhibitors like mevinolin or fosmidomycin (Gerber et al. 2009).

In conclusion, it should be underlined that the biological role of polyisoprenoids is still far from being clear. The general conclusion based on recent data suggests that polyprenols and dolichols, so far known as markers of aging, might be perhaps also considered as markers of stress. The elucidation of the putative role of polyisoprenylated proteins, be it those that form chemically stable thioether bonds with isoprenyl residues or those that form easily hydrolyzable thioester bonds, still requires more experimental effort and awaits explanation. The same holds true as to the identification and intracellular localization of putative protein isoprenyl

transferases that catalyze the thioesterification of target proteins and the peptide motives being involved in recognition.

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