Lipid modifications of proteins – slipping in and out of membranes

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Protein lipid modification, once thought to act as a stable membrane anchor for soluble proteins, is now attracting more widespread attention for its emerging role in diverse signaling pathways and regulatory mechanisms. Most multicellular organisms have recruited specific types of lipid modifications, a suite of unique enzymes to catalyze the modification of select numbers of proteins, many of which are evolutionarily conserved in plants, animals and fungi. Each of the three known types of lipid modification – palmitoylation, myristylation and prenylation – allows cells to target proteins to the plasma membrane, as well as to other subcellular compartments.

Among the lipid modifications, protein prenylation might also function as a relay between cytoplasmic isoprene biosynthesis and regulatory pathways that control cell cycle and growth. Molecular and genetic studies of an Arabidopsis mutant that lacks farnesyl transferase suggest that the enzyme has a role in abscisic acid signaling during seed germination and in the stomata. It is becoming clear that lipid modifications are not just fat for the protein, but part of a highly conserved intricate network that plays a role in coordinating complex cellular functions.

Many extrinsic membrane proteins are anchored to the membrane via mechanisms that are distinct from those employed by trans-membrane proteins. Lipid modifications facilitate the attachment of soluble proteins to biological membranes, but they also enable protein–protein interactions and, in some cases, the shuttling of proteins between the plasma membrane and the cytosol or other membrane compartments. These modifications, which are found in all eukaryotic cells, fall into three major classes and are characterized by the type of lipid and the site of modification in the protein. They include N-myristylation, palmitoylation and prenylation (Fig. 1). Unlike phosphorylation, lipid modification is limited to a small subset of cellular proteins that often participate in signaling. Certain lipid modifications are reversible, and can therefore have regulatory functions in signal transduction, such as providing a structural basis for the assembly of signaling-protein complexes on membranes, or terminating a signal cascade by hydrolysis of the lipid and dissociation of the protein from the membrane. In addition, the prenyl groups used in the modification of signaling proteins are also important branchpoint intermediates of isoprene biosynthesis, thereby providing the cell with a potential mechanism for coordinating signaling and a key biosynthetic pathway.

The biochemistry of most lipid modifications is now well established, although not all enzymes that carry out the transfer reactions have been identified. The role of N-myristylation and palmitoylation in animal cells is a well-conserved intricate network that plays a role in coordinating complex cellular functions that participate in signaling. Certain lipid modifications are reversible and can therefore have regulatory functions in signal transduction, such as providing a structural basis for the assembly of signaling-protein complexes on membranes, or terminating a signal cascade by hydrolysis of the lipid and dissociation of the protein from the membrane. In addition, the prenyl groups used in the modification of signaling proteins are also important branchpoint intermediates of isoprene biosynthesis, thereby providing the cell with a potential mechanism for coordinating signaling and a key biosynthetic pathway.

The most extensively studied examples of palmitoylated proteins are the α-subunits of trimeric GTP-binding proteins (Gα) in animal cells. Following association with an effector, Gα is depalmitoylated and subsequently relocates to the cytosol. This might be necessary to facilitate the hydrolysis of GTP to GDP to reset the protein for a new activity cycle. In this case, palmitoylation could regulate the localization and interaction of Gα with receptor and effector proteins. Although Gα-like proteins have been identified in plants, their function and palmitoylation status is unknown. To date, the chloroplast D1 protein encoded by psbA is the only plant protein for which palmitoylation has been demonstrated. D1 is an integral protein of the photosystem II (PSII) reaction center. The D1 precursor protein first inserts itself into the unstacked stroma lamellae of the thylakoid membrane, where it is processed and subsequently migrates to the stacked grana lamellae where it becomes transiently palmitoylated. The role of this transient lipid modification of D1 is not known, but it is reasonable to suggest that palmitoylation might help to increase the local concentration, as well as the specificity and efficiency of D1 interaction with other PSII components in the lipid environment of the thylakoid membrane.

Palmitoylation is often found associated with myristate or prenyl groups, but the relationship between these different lipid modifications has been investigated in detail for only one member...
of the Gsi protein family. In this case, both palmitoylation and myristylation are required for stable plasma membrane localization, and the rate of palmitate turnover is significantly increased in the non-palmitoylated protein. Interestingly, myristylated but non-palmitoylated Gsi mutant proteins are distributed between the plasma membrane and internal membranes, and a protein in which the myristylation site was mutated fails to associate with the plasma membrane and is not palmitoylated. However, myristylation per se is not required for palmitoylation because when Gsi is tethered to the plasma membrane via association with Gβγ in cells in which these proteins are expressed at high levels, Gsi is readily palmitoylated. These results re- stress the view that palmitoylation occurs only when proteins are already in close proximity to the inner surface of the plasma membrane. Thus, palmitoylation probably strengthens the reversible membrane association of plasma membrane-attached proteins independently of myristylation or prenylation, as demonstrated for Ha-Ras (Ref. 11). Because of the recent progress in the purification and cloning of a mammalian palmitoyl transferase and geranylgeranyl transferase, there is now the opportunity to search for palmitoyl transferase homologs in plants, and to gain insights into the biochemistry and function of protein palmitoylation.

Myristylation-mediated membrane attachment requires cooperation with other protein modifications

Several plasma membrane-associated proteins are modified by the 14-carbon-saturated fatty acid, myristate. Covalent linkage of myristate via an amide bond to a glycine in the N-terminal consensus sequence Met-Gly-x-x-[Ser/Thr] is catalyzed by N-myristoyl transferase and occurs co-translationally after the removal of the initiator methionine by aminopeptidase. Although the modification is stable, the hydrophobicity of a myristylated peptide alone is not sufficient to anchor the protein in the plasma membrane (Fig. 1). This suggests that additional mechanisms cooperate with myristylation to facilitate plasma membrane association of the modified protein.

The best studied examples of myristylated proteins are mammalian members of the Src family of non-receptor tyrosine protein kinases (which participate in intracellular signal transduction) and the MARCKS proteins (myristylated alanine-riche C-kinase substrate; which are substrates of protein kinase C). These proteins have N-terminal polybasic domains with clusters of positively charged amino acids, allowing them to interact with head groups of acidic lipids of the plasma membrane.
phospholipids that impart a negative charge to the cytoplasmic surface of the plasma membrane. Phosphorylation of serine residues located near to the polybasic domains of the proteins produces negative charges that reduce the net positive charge, thereby weakening the electrostatic interactions and releasing the myristylated protein from the plasma membrane. A different mechanism is employed by Recoverin, a myristylated Ca\(^2\+\) sensor in retinal rod cells, which controls the lifetime of photoexcited rhodopsin by inhibiting rhodopsin kinase. In the absence of Ca\(^2\+\), the myristyl group is masked by a hydrophobic pocket in the protein. Ca\(^2\+\)-binding causes a conformational change in Recoverin that exposes the myristyl group and thereby facilitates the binding of the protein to the membrane.

A subset of the known myristylated proteins, including certain members of the Src family and α-subunits of the heterotrimeric G proteins, contain a cysteine next to or adjacent to the myristylated glycine that is usually palmitoylated (Fig. 2). Because palmitoylation is unstable, de-palmitoylation releases the myristylated protein from the plasma membrane. Although in this case palmitoylation certainly enhances the efficiency of membrane binding, it is also possible that palmitoylation influences the subcellular localization or protein–protein interaction of the myristylated protein. N-palmitoylation, in conjunction with other functional domains or modifications, enables the reversible association of proteins with the plasma membrane in response to different cellular signals or shunting of proteins between different membrane compartments.

Three groups of plant proteins that contain putative N-myristylation sites have been characterized (Table 1), and several more might be identified through ongoing genome sequencing projects. The tomato PTO protein kinase is involved in signaling during pathogen infection, but resistant plants containing the Pto locus are also sensitive to the organophosphorous insecticide fenthion. This sensitivity is mediated by PTO, a PTO homolog, whose gene is tightly linked to Pto (Ref. 14). Both proteins have putative N-myristate-acceptor-glycines, and mutation of the FEN putative N-myristate-acceptor-glycine results in loss of fenthion sensitivity. However, a similar mutation in PTO does not affect its function when the protein is ectopically expressed in susceptible transgenic plants, suggesting that myristylation is not required for PTO-mediated bacterial resistance. It has not been established if PTO is myristylated, and consequently a mutation of the putative N-myristate-acceptor-glycine could interfere with another function of the kinase. Myristylation has been demonstrated for one of the plant Ca\(^2\+\)-dependent protein kinases (CDPKs), whose functions are unknown. Many of the conserved cysteines in positions 4 and/or 5 are present in all the members of this family of kinases, suggesting additional modification by palmitoylation as discussed for the PTO protein kinases. It remains to be seen whether the plasma membrane association of plant CDPKs is regulated in a similar way to Recoverin, in which Ca\(^2\+\)-binding exposes the myristyl group and facilitates membrane localization. It is likely that plants exploit the cooperation between myristylation and palmitoylation to anchor regulatory proteins to the cytoplasmic surface of the plasma membrane.

### Table 1. Plant proteins with conserved myristylation motifs

<table>
<thead>
<tr>
<th>Protein</th>
<th>Plant</th>
<th>Sequence</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDPKα*</td>
<td>Arabidopsis</td>
<td>M-GLX<a href="E/L">Y/F/L</a></td>
<td>Ca(^2+)-dependent protein kinase with Src kinases.</td>
</tr>
<tr>
<td>AT1*</td>
<td>Arabidopsis</td>
<td>M-GLX[Y/F/L]</td>
<td>Protein kinase with homology to G protein kinases.</td>
</tr>
<tr>
<td>PTO</td>
<td>Tomato</td>
<td>M-GSKYVS</td>
<td>Protein kinase involved in disease resistance.</td>
</tr>
<tr>
<td>FEN*</td>
<td>Tomato</td>
<td>M-GSKYYS</td>
<td>Protein kinase required for fenthion sensitivity.</td>
</tr>
</tbody>
</table>

*Genes encoding Ca\(^2\+\)-dependent protein kinases (CDPKs) have been cloned from several different plants, but myristylation has been confirmed for only one protein.  
*Mutant of AT1 has not been demonstrated.  
*The acceptor-glycine is required for FEN function, but is dispensable for PTO function.  
*The acceptor-glycine is shown in bold. Potential palmitoylation cysteine-acceptors and lysines that increase positive protein surface charge are underlined.
cysteines of a small subset of cellular proteins (Fig. 1 and Table 2). Protein prenylation was discovered in fungi,9, but has been identified since as a conserved modification in other multicellular eukaryotes (reviewed in Refs 6,7). Interestingly, most of the proteins modified by prenyltransferases have regulatory roles in cellular signaling and vesicle transport. They include almost all members of the Ras superfamily of small GTPases (Ref. 18), several y-subunits of heterotrimeric G proteins (Ref. 19), nuclear lamins,20 type I inositol 1,4,5-trisphosphate 5-phosphatase (Ref. 21), members of the Ras superfamily of small GTPases (Ref. 18), several y-subunits of heterotrimeric G proteins (Ref. 19), nuclear lamins,20 type I inositol 1,4,5-trisphosphate 5-phosphatase (Ref. 21), as well as other several proteins. Since the demonstration that prenylation inhibition could reverse the transformation of mammalian cells by activated Ras mutant proteins,21, much attention has been focused on the structure and function of protein prenyltransferases. However, our understanding of the regulation of these enzymes and their potential function in coordinating isoprenoid synthesis with cellular growth control remains incomplete.

Prenyltransferase (FTase) and type I geranylgeranyltransferase (GGTase-I) are heterodimeric enzymes that share a common a-subunit but have distinct b-subunits.6,7 The b-subunits of the Rab-GGTase catalytic component are similar (but not identical) to those of FTase and GGTase-I. The catalytic component requires a third protein component, the Rab Escort Protein (REP), for full activity. REP binds non-prenylated Rab proteins, and presents them to the catalytic component.22 Abbreviations: a, aliphatic amino acid; X, any amino acid.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Subunits</th>
<th>Recognition motifs</th>
<th>Protein substrates (examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTase</td>
<td>a, b</td>
<td>CaaX</td>
<td>Ras, Gy, a-factor, nuclear lamins, IP, 5-phosphatase, cGMP phosphodiesterase</td>
</tr>
<tr>
<td>GGTase-I</td>
<td>a, b</td>
<td>CaaX</td>
<td>REP, Rho, Rac</td>
</tr>
<tr>
<td>Rab-GGTase</td>
<td>a, b, REP</td>
<td>CC, CCC, CCX, CCXX, CXXX</td>
<td>Rab, Ypt</td>
</tr>
</tbody>
</table>

FTase and GGTase-I are heterodimeric enzymes that share a common a-subunit but have distinct b-subunits.6,7 The b-subunits of the Rab-GGTase catalytic component are similar (but not identical) to those of FTase and GGTase-I. The catalytic component requires a third protein component, the Rab Escort Protein (REP), for full activity. REP binds non-prenylated Rab proteins, and presents them to the catalytic component.22

Abbreviations: a, aliphatic amino acid; X, any amino acid.

Rab-GGTase is the third prenyltransferase; it appears to modify only Rab GTPases, which regulate secretory vesicle transport. It does not share subunits with FTase and GGTase-I and differs from the other two prenyltransferases by the presence of a third component, Rab Escort Protein (REP; Table 2), which is required for enzyme activity.22 Although Rab-GGTase has been characterized in plants and is thought to be similar to the animal and yeast enzymes,22 no molecular studies on the regulation of this prenyltransferase have been reported from plants.

Plant farnesyltransferase and protein substrates

yield surprises

In synchronized tobacco tissue culture cells, increase in FTase activity is coincident with the initiation of cell division. Conversely, manumycin, a specific inhibitor of FTase, blocks cell division.22,23 Thus, early events in the plant cell cycle probably require farnesylation of currently unknown proteins. Therefore, it was surprising when an Arabidopsis mutant (era1-enhanced response to ABA) was identified during a screen for plants with a hypersensitive response to ABA, the gene for the b-subunit of FTase is deleted in this mutant.24 Mature era1-2 has a pleiotropic phenotype, of which certain aspects can be attributed to alterations in ABA perception and/or signaling.25 Because era1-2 represents the first FTase null mutant in a multicellular organism that shows only modest effects on cell division and plant growth, it is tempting to conclude that farnesylation is not a critical protein modification for cell cycle regulation in plants. However, such a conclusion might be premature because current information on plant FTase protein substrates is limited, and promiscuous farnesylation of proteins by GGTase-I might account for the viability of era1.

The apparent role of plant FTase in the negative regulation of ABA-signaling is now less clear. FTase substrates and proteins that interact with ABA-signaling transcription factors are predicted to be conserved in other regulatory pathways. A novel biochemical screen to identify plant prenylation substrates26, and computer searches with algorithms designed to detect CaaX-box proteins in databases have
now yielded several interesting plant candidate proteins (Table 3). Prenylation of most proteins is confirmed, but tobacco ANJ1 is the first plant protein for which farnesylation was demonstrated in vivo. ANJ1 is a plant homolog of the bacterial chaperone Dnal, a protein found in a complex with the chaperone Heat shock protein70. Although the function of ANJ1 is not known, farnesylation of the protein is required for membrane binding. In yeast, farnesylation of YDJ1 (the yeast homolog of ANJ1) is essential for growth at 37°C. Wild-type ANJ1, but not the farnesyl-cysteine-acceptor mutant protein, can complement a ydj1 ts mutant to restore growth at 37°C (Ref. 34). These results imply that only farnesylated ANJ1 is active at elevated temperatures in yeast, but they do not reveal the function of ANJ1 in plants. Proteins related to ANJ1 have been identified in many divergent plants and in all cases the Cys-Ala-Gln-Gln Caax-box is conserved, suggesting that farnesylation is also a requirement for protein function in plants.

Geranylgeranyl transferase-I directs the localization of regulatory proteins

Considering the number of geranylgeranylated plant proteins identified to date (Table 4), the role of GGTase-I in various cellular processes will undoubtedly be complex. Similar to their mammalian and yeast counterparts, most known members of the Rac-related Rop family of small GTPases in plants have conserved C-terminal CaaL-box motifs and a polybasic sequence domain that is proximal to the prenyl acceptor-cysteine. Direct geranylgeranylation has been demonstrated only for one family member70, but it is likely that most Rops are substrates for GGTase-I. Rac GTPases are implicated in the reorganization of the actin cytoskeleton through the activation of phosphatidylinositol 4-phosphate 5-kinase. It is likely that Rops have a related function in the regulation of polar growth in plant cells, because overexpression of an Arabidopsis Rop protein induces isotropic growth in fission yeast, similar to the fission yeast homolog, and the protein is found at the site of growth50. In plants, certain Rop proteins localize to the tip of the growing pollen tube, which is consistent with the protein playing a role in polarized cell growth50.

The effect of geranylgeranylation on membrane localization of GGTase target proteins in plants is now best understood for CaM53, a novel type of calmodulin protein that is not found in yeast or mammalian cells. CaM53 has a typical calmodulin domain that also acts as a nuclear localization signal in mammalian cells 41. Abbreviations: SAM, S-adenosyl methionine; PCP, prenyl-cysteine protein; PCM, prenyl-cysteine carbamoyl methyltransferase; MVA, mevalonic acid; IPP, isopentenyl pyrophosphate; FPP, farnesyl pyrophosphate; GGPP, geranylgeranylated pyrophosphate; HMG-CoA, hydroxymethylglutaryl-CoA reductase; ER, endoplasmic reticulum.

### Table 4. Plant GGTase-I protein substrates

<table>
<thead>
<tr>
<th>Protein</th>
<th>CaaL-motif</th>
<th>Species</th>
<th>Proposed function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rac/Rop protein family</td>
<td>CSIL, CaFL, CVFL, CPPL</td>
<td>Several</td>
<td>Polar growth</td>
</tr>
<tr>
<td>CaM53p</td>
<td>CTL</td>
<td>Petunia</td>
<td>Calmodulin</td>
</tr>
<tr>
<td>CaM61</td>
<td>CVIL</td>
<td>Rice</td>
<td></td>
</tr>
<tr>
<td>ARG1</td>
<td>CSIL</td>
<td>Arabidopsis</td>
<td>Pathogen response</td>
</tr>
</tbody>
</table>

- Homologs have been identified in other organisms.
- Prenylation of these proteins has been confirmed in vivo and in other proteins has been shown using in vitro assays. Abbreviations: a, aliphatic amino acid.

Fig. 3. Regulation of protein prenylation – a physiological relay?

CaM53, a novel type of calmodulin protein, provides a model system to investigate the potential role of protein prenylation as a relay between metabolic and signaling pathways. In the light, or in dark-grown plants in the presence of sucrose, CaM53 is prenylated and localizes to the plasma membrane (which is appressed to the cell wall). However, in the absence of sucrose, CaM53 is not prenylated and is found in the nucleus51. Because the prenyl transferase substrates FPP and GGPP are intermediates of the mevalonate pathway, changes in the activity of the rate-limiting HMG-CoA reductase (HMGR) can influence the prenylation status of proteins. The activity of HMGR is regulated by SNF1 protein kinases, for which homologs have been identified in plants7. Members of the SNF1 family of protein kinases are activated by AMP and inhibited by ATP, thus acting as a sensor to the metabolic status of the cells. However, this model does not exclude other regulatory mechanisms, such as activation of prenyltransferases by light, or phosphorylation of the shared FTase/GGTase-I subunit that has been detected in mammalian cells. Abbreviations: SAM, S-adenosyl methionine; PCP, prenyl-cysteine protein; PCM, prenyl-cysteine carbamoyl methyltransferase; MVA, mevalonic acid; IPP, isopentenyl pyrophosphate; FPP, farnesyl pyrophosphate; GGPP, geranylgeranylated pyrophosphate; HMG-CoA, hydroxymethylglutaryl-CoA reductase; ER, endoplasmic reticulum.
plants, might prove to be an important aspect of CaM53 function, and a convenient marker of physiological changes in the cell. For example, most of the plasma membrane-localized fusion proteins between GFP and the C-terminal domain of CaM53 are targeted to the nucleus in dark-adapted leaf explants. A similar nuclear localization has been detected for the GFP-fusion protein and for the endogenous CaM53 following treatment of seedlings with mevinolin, a potent inhibitor of HMG CoA reductase (HMGR), which catalyzes the rate-limiting step in cytoplasmic isoprenoid biosynthesis. Plasma-membrane-localization of the GFP-fusion protein in dark-shifted leaf explants can be restored by adding succinate (but not mannitol) to the growth medium.  

To date, there is no known enzymatic mechanism for cleaving the thioether bond between the prenyl group and the protein, and therefore it is probable that nuclear localization of CaM53 only involves newly synthesized protein, which does not become prenylated. The potential of CaM53 for regulating protein activity in the plasma membrane or the nucleus has interesting implications because prenylation of the protein could be controlled by several physiological mechanisms (Fig. 3).

### Regulatory implications of protein prenylation

The evidence to date suggests that protein prenylation can be modulated in response to flux through the cytoplasmic isoprenoid biosynthesis pathway, a finding that is significant because FPP and GGPP are early intermediates and constitute major branch points in plants. However, the situation has become more complex in view of the recently discovered alternative isoprenoid synthesis pathway in plants. Thus, overall changes in the cellular concentrations of FPP and GGPP might not necessarily reflect local changes in the cytosol that result from changes in:  

- Metabolic status of the cells.  
- Activity of HMGR.  
- Flux between the cytoplasmic and plastidial isoprenoid pathways.  
- Activities of other enzymes in the cytoplasmic isoprenoid biosynthesis pathway.

Recent evidence in animals also supports a regulatory role for prenylation. Activation of isoprene biosynthesis in chicken cardiac muscle results in Ras farnesylation, activation of the Ras signaling pathway, and expression of muscarinic receptor and heterotrimeric G-proteins (Ref. 40). Insulin-induced phosphorylation of the FTase n-subunit also enhances Ras farnesylation. Thus, changes in cellular glucose levels or AMP:ATP ratios might regulate protein prenylation via phosphorylation and FTase activation, and probably GGTagase-I as well. To date it is not known whether the shared FTase/GGTagase-I n-subunit is also phosphorylated in plants.

The above considerations do not preclude other mechanisms that might regulate protein prenylation in plants, such as controlling the expression of FTase and GGTagase genes, which has not been extensively investigated. The cellular substrate level of a prenylation target protein might also be an important factor because concentrations below the Km would probably result in inefficient modification. In contrast with palmitoylated and N-myristoylated proteins, the affinity of prenyl transferases for different protein substrates varies considerably depending on the amino acid sequence context of the CaaX box and in some proteins it also depends on the polybasic domain proximal to the CaaX box. Prenylation of specific signaling proteins might significantly affect the activity of their pathways. Regulation of prenylation might be further complicated by promiscuity between FTase and GGTagase-I. Both enzymes inefficiently prenylate substrates that would usually be specific to FTase (CaaX) or GGTagase (CaaX), and GGTagase-I can also utilize FPP. This raises interesting questions because recent experiments with mammalian RhoB suggest a functional relevance for this alternative prenylation. The RhoB GTPase is involved in actin cytoskeleton regulation, and also plays a critical role in Ras-mediated transformation. Metabolic labeling of cells with H-mevalonate show that most of RhoB is geranylgeranylated, consistent with the CaM53 motif, but a small fraction is farnesylated also. FTase inhibitors (which do not inhibit GGTagase-I) suppress cellular transformation by oncogenic RhoB and eliminate the population of farnesylated RhoB from the cells. Together, these results also have potential implications for prenyl-transferase-modified plant proteins, and might explain why ena1-2, which lacks FTase activity, can survive. With the molecular and biochemical tools now available, it should be possible to clarify these issues and to determine the cellular role and regulation of lipid modifications in plants.

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