The possible role of fatty acylation in proteins

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In recent years several proteins have been found to be acylated with fatty acids as well as with isoprene units. A large number of acylated proteins are associated with membranes, and it is likely that the fatty acids play an important role in modulating the association with membranes. Here we review the various aspects of fatty acylation. It has been suggested, based on available information, that fatty acids, particularly palmitiate, would reorient peptide chains near the acylation sites from the normal transmembrane orientation.

A large number of proteins undergo some kind of modification during or after their biosynthesis. These modifications include acylation, phosphorylation and hydroxylation. The importance of these modifications in subcellular localization of the proteins and in other cellular events has been well documented[1]. Several proteins have been found to be acylated with fatty acids[2], and, recently, acylation with isoprene units has also been observed[3]. Information regarding the fatty acids involved in acylation, amino acids to which fatty acids are attached and regions in the protein where acylation occurs, and the enzymology of acylation is available[4-11]. Addition of long-chain fatty acids or isoprene units to proteins would undoubtedly increase hydrophobicity at the site of attachment. Since a large number of these proteins are associated with membranes, it is likely that the fatty acids play an important role in modulating the association with membranes. However, it is not yet clear how this modification dictates the orientation of peptide chains in membranes. We review various aspects of acylation, and, on the basis of the available information, suggest how this modification may affect the orientation of polypeptide chains in membranes.

Sites of attachment of fatty acids

Fatty acids covalently bound to proteins were first detected in proteolipids from myelin and sarcoplasmic recticulum of muscle[12-14]. Subsequently it was observed that several viral membrane glycoproteins had covalently bound fatty acids[15,16]. Research in this area indicated that, in addition to viral proteins, several cellular proteins were also acylated with fatty acids[17]. In all these proteins, the fatty acid was almost exclusively palmitic acid. Examination of source and function of palmitoylated proteins of eukaryotic and viral origin[8] indicates that acylated proteins have very diverse bilogical functions. Usually acylated membrane proteins are oriented with their carboxy terminus towards the cytoplasmic side of the membrane. However, there are several proteins with opposite orientation that are also palmitoylated, like the transferrin receptor[18]. Some acylated membrane proteins are monomers[19] whereas others are either homooligomers or heterooligomers[15,20]. In the insulin receptor, only the β-subunit is palmitoylated[21,22]. All DNA and RNA viruses with a lipid envelope contain at least one structural protein with covalently bound palmitic acid. The only exceptions are two serotypes of vesicular stomatitis virus (VSV) and sendai virus[23,24]. All the acylated proteins are located in the viral envelope and glycosylated. Viral spike proteins, which have the ability to cause fusion at low pH, are also palmitoylated[25,26]. In the case of non-viral structural proteins palmitoylation is not as common as myristoylation. Some viral proteins expressed 'early' are palmitoylated. In addition to the plasma membrane, internal membranes like the Golgi body also contain proteins covalently linked with fatty acids[27,28]. However, as far as intracellular localization is concerned, a small group of palmitoylated proteins are secreted by cells, and cellular cytoskeletal elements are also palmitoylated[29-33].

The observation that palmitic acid could be removed from proteins by treatment with mild alkali and hydroxylamine indicated that fatty acids were bound by ester-type linkage[15,16,20,34]. However, there was considerable ambiguity regarding the actual site of acylation and also the amino acid that was acylated, as fatty acid attached to serine, threonine cysteine can be removed by mild treatment. Limited-proteolysis experiments suggested that the acylation sites were near the membrane-spanning regions of the proteins[18,20,35,36]. Direct structural analysis as well as site-directed-mutagenesis experiments have indicated that the site of palmitoylation is cysteine (refs. 37-39).

Covalently bound myristic acid was first observed in the catalytic subunit of cyclic AMP-dependent protein kinase prepared from bovine cardiac muscle[40]. Linkage of myristic acid to the amino-terminal glycine residue of the protein was determined by gas chromatography and fast-atom-bombardment mass-spectrometric analysis of

peptides from the amino-terminal region. Subsequently, several proteins, especially retroviral proteins, were found to have this co-translational modification[41,42]. Interestingly, many of these proteins participate in regulation of cell growth and signal transduction[43,44].

Recent studies have indicated that some proteins are covalently modified with isoprene groups. This modification was first observed in yeast mating factor[45]. Subsequently prenylation has also been detected in ras protein[46] and the nuclear protein lamin B (ref. 47). Sequence analysis of prenylated proteins has indicated the presence of the motif CAAX, where prenylation occurs at the C (cysteine) residue, A represents an aliphatic amino acid and X is any amino acid. The ras protein also has a palmitic acid attached to a cysteine a few residues upstream to the cysteine that is linked to a prenyl group[48].

Enzymology of acylation

The fatty-acid donor of palmitic acid has been identified as palmitoyl CoA, but purification of palmitoyl fatty acyl transferase (PAT)[49] has not been very successful. However, a large number of studies using inhibitors of glycosylation, genetic analysis, and cell fractionation have indicated the probable intracellular site(s) of acylation. Studies wherein various stages of oligosaccharide processing and timing of proteolytic processing were monitored indicated that palmitoylation of viral proteins occurred shortly after translation just prior to acquisition of endoglycosidase H resistance[50]. Experiments in which various inhibitors of glycosylation were used indicated that glycosylation *per se* was not required for fatty acylation[51]. When transport from endoplasmic reticulum (ER) to Golgi was rendered defective, acylation was not observed, whereas block of transport between Golgi and plasma membrane had no influence on fatty-acid acylation[52]. Thus palmitoylation occurs at an earlystep in protein biosynthesis, probably in the Er region. In a few cases palmitoylation has been observed late, in the Golgi, like in the case of SV40 large T antigen and transferrin receptor[53-55]. Nonenzymatic autoacylation has also been observed in the case of myelin lipophilin and bovine rhodopsin[56,57]. In plants it appears that chloroplasts have palmitoylating activity[58].

The enzyme *N*-myristoyl transferase (NMT), which transfers myristic acid to proteins, has been purified to homogeneity from yeast and partially purified from rat tissue[59-61]. The enzyme shows high specificity for myristic acid, and only myristoyl CoA thioester acts as lipid donor. NMT is conserved through evolution. The sequence requirement for myristoylation has been identified using synthetic substrates and extensive sequence analysis of the amino-terminal region of *N*-myristoylated proteins. N-terminal glycine has been found to be an absolute requirement for myristoylation[59,60]. It has also been shown that cleavage of N-terminal methionine of nascent peptide chains occurs while the growing peptide chain is still attached to the ribosome and is brought about by another enzyme. Cell fractionation studies indicate that this enzyme is only loosely attached to membranes and is probably associated with ribosomes[62,63]. This is supported by the observation that peptide chains are myristoylated as they are being synthesized and inhibitors of protein synthesis prevent myristoylation[64]. Thus, unlike palmitoylation, myristoylation is a co-translational modification. There have been some reports that acetylcholine receptor, insulin receptor, and heavy and light chains of immunoglobulin M have myristic acid attached to regions other than the N-terminus[65-67]. However, details of where the fatty acid is attached and how myristoylation helps in cellular location are not clear.

The protein transferase responsible for incorporation of isoprene group in proteins like $p21^{ras}$ has been recently purified to homogeneity from rat brain[68]. Interestingly the enzyme recognized and prenylated tetrapeptides corresponding to the CAAX motif or corresponding to the prenylation site in ras protein[69].

Topography of the fatty-acid and peptide chains in membranes

While there have been many biochemical studies on fatty-acid acylation, studies directed towards understanding the topography of the fatty-acyl chain and the peptide chain near the fatty-acylation site in the membrane have been few. In one study, a viral protein was acylated with a fluorescent fatty acid[70]. Fluorescence studies indicated that the fatty acid was oriented perpendicular to the lipid bilayer surface, as one would expect. However, this study did not reveal how the polypeptide chain might be oriented in the lipid bilayer. In an effort to understand how fatty-acid acylation might modulate orientation of the peptide chain in the lipid bilayer, we began studies on the interaction of fatty-acylated peptides with membranes. Hydrophobic peptides with covalently attached fatty acid with an anthroyl fluorophore and containing the fluorescent amino acid tryptophan were synthesized. Fluorescence studies indicated that the fatty acid was oriented normal to the bilayer surface, whereas the peptide chain was oriented at an angle to the bilayer surface[71]. This observation was made in more than one hydrophobic peptide to rule out any sequence-related orientation. It thus seems that, when a hydrophobic peptide stretch has a fatty acid in its vicinity, the orientation of the fatty-acid chain normal to the bilayer surface forces the peptide chain, which could otherwise span the lipid

bilayer, to be oriented at an angle to the bilayer surface. Recently studies on the orientation of influenza haemagglutinin, which has covalently linked palmitic acid in a membrane surface, were reported[72]. The authors have argued for a structure in which the peptide chains near the acylation sites are associated with the membrane surface.

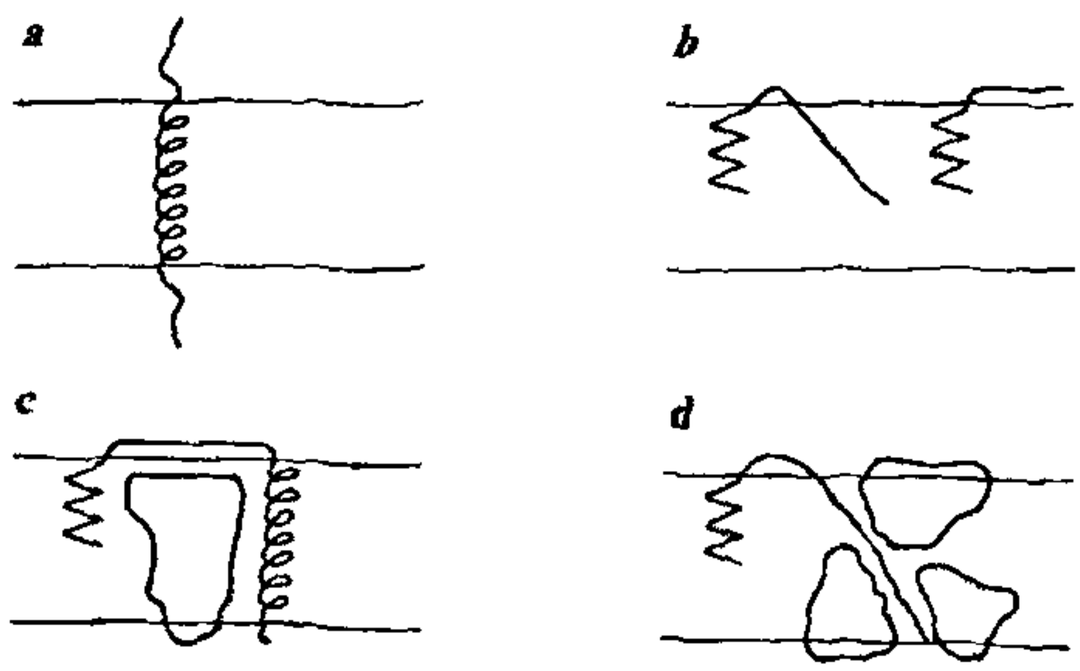

Figure 1. Modes of association of fatty-acyl and peptide chains in fatty-acylated peptides and proteins with membranes. *a*, Transmembrane orientation of the peptide chain; *b*, orientation of fatty-acyl chain (∧∧) normal to the membrane surface and orientation of the peptide chain (——) at the angle or parallel to the bilayer surface; *c* and *d*, association of peptide chains near the fatty-acylated region with other transmembrane proteins.

Role of fatty-acid acylation

Presence of the hydrophobic moieties palmitate, myristate and the isoprene group in proteins would undoubtedly create hydrophobic sites in proteins. However, studies aimed at elucidating the role of fatty-acid acylation have not provided an unambiguous role for this modification. There are some variants of the VSV G protein in which the palmitoylation site is absent and yet there is no impairment in assembly and budding of the virus. In the case of influenza virus haemagglutinin, when the acylation sites were removed by site-directed mutagenesis, its membrane-fusion activity was severely inhibited, indicating a crucial rule for fatty acylation[72]. Similarly, in ras protein, mutation of the palmitate-binding site resulted in loss of membrane localization. This resulted in the inability of the protein to transform NIH 3T3 cells[37]. Likewise, in yeast proteins homologous to ras proteins palmitoylation was essential for membrane location and optimal growth[73]. The ras proteins, unlike most other palmitoylated proteins, are hydrophilic and do not have any membrane-spanning segment. Hence, in the case of ras proteins, it is clear that palmitolylation helps in membrane association of a protein that would otherwise not be membrane-bound[38]. Almost all other palmitoylated proteins have at least one transmembrane-spanning region, which should be sufficient for membrane anchorage. Yet, fatty acylation takes place near the membrane-spanning region. It is unlikely that the role of the fatty acid is to merely reinforce membrane association of the acylated protein. on the basis of our results for model acylated peptides[71,74], as well as those of Naeve and Williams[72], it is conceivable that palmitoylation results in reorientation of the membrane-spanning region of proteins from the normal transmembrane topography as well as in association of non-transmembrane regions near the acylation site with the membrane surface. Figure 1 shows a schematic sketch of the ways in which fatty acids can reorient peptide chains in the membrane surface as well as in the lipid bilayer. We speculate that such reorientations would favour association of the peptide chains of the acylated proteins with other transmembrane proteins, as shown in the figure. Such interaction may be important as many of the palmitoylated proteins are growth-factor receptors and play an important role in transmembrane signalling and other cellular functions[10]. Studies on β-adrenergic receptor[75] and neuronal protein GAP-43 (ref. 76) support this view. In β-adrenergic receptor, when the palmitate-binding cysteine was changed to glycine, the protein was incorporated into plasma membrane but no longer showed agonist-induced cAMP stimulation. Thus, here, the role of palmitate is clearly not merely to provide membrane anchorage but to mediate coupling between the receptor and G-protein. In experiments on GAP-43, a protein found only in nerve growth cones, addition of the N-terminal sequence containing the palmitoylation site to the protein chloramphenicol acetyl transferase resulted in its translocation specifically to growth cones[76]. This again indicates some specificity in the interaction of palmitate-containing region of protein with membranes.

Palmitate has been found to have a faster turnover than transferrin receptor and $p21^{ras}$ (ref. 77). Acylation and deacylation have also been observed in response to stimulus to cells. Thus the acylation-deacylation cycle could provide a novel means of regulation of proteins.

N-myristoylated proteins are not necessarily membrane- associated. The X-ray structure of polio virus shows a pocket in which N-myristoylated VP4 protein residues in an environment devoid of lipids. The N-terminus of VP4 polypeptide interacts with the N-terminus of VP3 polypeptide and the myristoyl moiety interacts with hydrophobic residues of VP3 protein[78]. Site-directed-mutagenesis studies indicate that myristic acid plays an important role in the assembly of nonenveloped viruses, clearly pointing to the importance of myristate–protein interactions. There are several reports that indicate that association of myristate with membranes is important also for function. Mutants of $p60^{src}$ in which the N-terminus was removed (region

containing the myristoylation site) retained normal kinase activity but failed to induce morphological transformation and anchorage-independent growth of cultured cells[79,80]. Unlike in the case of palmitoylated proteins, specific, saturable and high-affinity binding sites for p60^{src} and N-terminal myristoylated p60^{src} peptide were observed in cells[81,82].

Conclusions

It thus seems highly unlikely that palmitic and myristic acids merely provide sites for nonspecific hydrophobic interaction. For such interaction, stearic or a higher-carbon fatty acid would have provided more favourable conditions. Clearly, there is specificity involved in the interaction of fatty-acyl sites with membranes. To unravel this, a more detailed description of the topography of the fatty-acid chain and the polypeptide chain near the acylation site in membranes would be necesssary. While such studies may be difficult with acylated proteins, structural investigations with acylated peptides might provide useful information about the topography of fatty acids and peptide chains in membranes.

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RESEARCH ARTICLE

Frequency distribution of seed number per fruit in plants: A consequence of the self-organizing process?

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Plants exhibit wide variation in the frequency distribution of seed number per fruit. These distributions have been explained on the basis of proximate factors such as limitation of pollen and resource, lethal alleles, and developmental abnormalities. However, such explanations are inadequate and are not parsimonious in explaining the wide range of distributions of seed number per fruit. In this paper we propose an alternative model, based on the process of self-organization, involving simple rules of resource flow into ovules. We show that the wide range of observed frequency distributions of seed number per fruit can be generated as a function of resource-drawing ability of ovules, which interact stochastically during their development.

PLANTS exhibit species-specific patterns of frequency distribution of seed number per fruit ranging from highly positively skewed (where the majority of fruits have few seeds) to normal to negatively skewed (where the majority of fruits have many seeds)[1-7]. These patterns have been shown to be a consequence of specific rates of seed abortion, and are argued to be adaptive[1]. For instance, species with fruits as the units of dispersal through wind, water or animals show a high rate of seed abortion (hence positively skewed distribution) in order to increase dispersal efficiency of fruit. On the other hand, those in which seeds themselves are the units of dispersal show a low rate of seed abortion (hence negatively skewed distribution)[1,2,7].

The species-specific rates of seed abortion have been explained on the basis of several factors such as resource[8] and pollen limitation[9-12], predators[13,14], developmental abnormalities and lethal alleles[15,16]. These explanations, however, are either true for only specific instances or have been proved inadequate[1,17]. For instance, seed abortion is often species-specific, and nonrandom with respect to the position of the aborted ovule in the ovary[1,6,17,18]. Manipulation of pollen or resource level were shown to be ineffective in altering the species-specific rates of abortion and the position of the ovule aborted[1]. Further, the above factors also cannot explain the association between dispersal mode and seed abortion[1].

In other words, these proximate factors cannot parsimoniously explain the wide range of seed abortion and hence the distribution patterns of seeds per fruit. In this paper we propose the process of self-organization as an alternative model that involves simple intrinsic rules regulating the flow of resource into ovules. We simulate the process of fruit development as a self-