of the observed ΔLk. In the absence of more refined data, it remains to be seen if the omission of these factors has any significant effect upon the predicted ΔLk. A real residual discrepancy between the experimental determination of ΔLk_c and that predicted from Eqn (3) could be ascribed to either of two possibilities: (1) the neglect of possible contributions from the linker region to ΔSLk_1 and $\Delta\Phi_1$; and (2) the neglect of interaction terms between nucleosomes and the adjoining linker regions. The latter effect is almost certainly very small, in view of the independence of the measured value of ΔLk_c upon m. On the basis of the first possibility, it is predicted that any additional contribution from the linker regions via $\Delta\Phi$ would be in the direction of a reduction of h_1 relative to h_0. Alternatively, any additional contribution via ΔSLk_1 would require right-handed supercoiling of the linker DNA.

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OPEN QUESTION

How does protein phosphorylation regulate photosynthesis?

John F. Allen

Phosphorylation of light-harvesting antenna proteins redirects absorbed light energy between reaction centres of photosynthetic membranes. A generally accepted explanation for this is that electrostatic forces drive the more negatively charged, phosphorylated antenna proteins between membrane domains that differ in surface charge. However, structural studies on soluble phosphoproteins indicate that phosphorylated amino acid side chains have specific effects on molecular recognition, by ligand blocking or by intramolecular interactions which alter protein structure. These studies suggest alternative mechanisms for phosphorylation in control of pairwise protein–protein interactions in biological membranes. Thus, in photosynthesis, the surface charge model is only one possible interpretation.

IN PLANTS and photosynthetic bacteria, phosphorylation of membrane proteins is ultimately responsible for many of the physiological responses to changes in incident light and redox poise[1,2]. A major protein substrate of phosphorylation is the chloroplast light-harvesting chlorophyll *a*/*b*-binding complex known as light-harvesting complex II (LHCII), which binds perhaps half of the chlorophyll in nature, therefore absorbing half the light converted in photosynthesis. It has been known for over ten years that this light-harvesting complex changes its allegiance upon phosphorylation. In its unphosphorylated form, LHCII interacts specifically with photosystem II (PSII) of the photosynthetic electron transport chain, and the light energy it absorbs is converted into electrochemical potential at the PSII reaction centre. Upon phosphorylation of a threonine close to the amino terminus (Thr6 in the major pea polypeptide), LHCII complexes detach themselves from PSII, and reattach to PSI instead.

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Since PSI and PSII are connected in series by the electron transport chain, they must have equal rates of electron transport, with maximum efficiency achieved only when they receive light energy also at equal rates. Their intrinsic rates of energy capture will, however, vary according to light intensity and spectral composition, and their series connection may be modified by addition of more PSI turnover to produce extra ATP by cyclic photophosphorylation. The relative light-harvesting ability of the two photosystems must therefore be controlled.

Balancing the light-harvesting capacity of the two photosystems is achieved by redox activation of the LHCII protein

kinase[1–3]. This kinase is activated when plastoquinone is reduced, a consequence of PSII running faster than PSI. Phospho-LHCII then transfers energy to PSI at the expense of PSII, which balances the energy distribution. Conversely, oxidation of plastoquinone inactivates the kinase and allows the LHCII phosphatase reaction to predominate. Energy distribution between PSI and PSII will therefore tend to be self-regulating.

Many features of this model have now been critically tested. For example, the LHCII kinase has recently been isolated in a form that exhibits the required redox control when bound to the cytochrome *b/f* complex[4]. Work on the LHCII kinase has recently been reviewed[2,4,5]. Besides LHCII, protein phosphorylation affects other chloroplast membrane proteins, and has a regulatory role in photosynthetic bacteria, which have different antenna systems[2].

The mobile antenna

Chloroplast thylakoids exhibit heterogeneity in lateral distribution of PSI and PSII[6,7]; there is a greater density of PSII in membrane vesicles that originate from appressed domains of the thylakoid membrane (corresponding to chloroplast grana or thylakoid stacks) than in vesicles originating from unstacked stroma-exposed thylakoids. In contrast, PSI is present predominantly in unstacked thylakoids or grana margins[7]. If phosphorylation of LHCII polypeptides decreases the interaction of LHCII with PSII and increases its interaction with PSI, then lateral reassociation of the three complexes must occur, and movement of phospho-LHCII into PSI-rich domains now has extensive experimental support[1,2,6,8,9]. The true domain organization of the thylakoid may be more complex than this simple bipartite model suggests, with six discrete domains being possible[7]. The grana margin may therefore be an important site of protein traffic and of alteration in protein–protein interactions[6,7].

The surface charge hypothesis

Barber[8] and Arntzen and co-workers[9] have proposed a mechanism for the functional effects of phosphorylation of chloroplast LHCII. In this hypothesis, the primary effect of phosphorylation is an increase in the negative charge on the outer (cytoplasmic) surface of the appressed domain of the thylakoid membrane, and the magnitude of the change is sufficient to overcome the attractive forces otherwise holding together LHCIIs on adjacent, appressed thylakoid domains. When LHCIIs move apart, the electrostatic forces controlling protein–protein interactions act in a direction perpendicular to the membrane plane, and the initial event following phosphorylation is electrostatic repulsion between opposing phospho-LHCII complexes. The complexes then migrate laterally into unappressed thylakoid domains, where increased distance and screening cations (chiefly Mg^{2+}) in the aqueous phase (the chloroplast stroma) minimize the repulsive forces acting between them. The surface charge model is summarized in Fig. 1. However, there are several problems with this hypothesis.

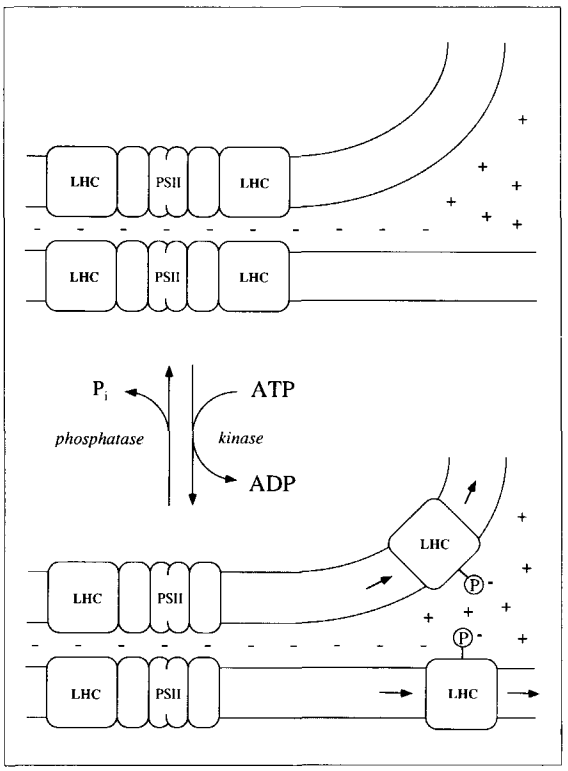

Figure 1
The surface charge hypothesis. Phosphorylated light-harvesting complexes (LHCs) are driven from appressed to unappressed thylakoid domains by intermolecular, intermembrane electrostatic forces, chiefly electrostatic repulsion between phosphate groups and fixed negative charges on appressed surfaces. Cations in the stroma serve to screen these charges from each other, thus phospho-LHCII occupies unappressed surfaces to a greater extent than does unphosphorylated LHCII. PSII represents the reaction centre of PSII.

Specificity. If protein phosphorylation works by altering electrostatic potential throughout a membrane domain, how can it avoid altering interactions between each protein and all others in its domain, whether they are phosphorylated or not? Electrostatic coupling between membrane proteins governs many of their structural and functional interactions, and general perturbation of electrostatic coupling would be likely to change all protein–protein and protein–lipid interactions. Decreased cation concentration is known to cause such alterations in membrane surface charge[8,9], and has very wide-ranging effects, including an increase in energy transfer from LHCII to PSI even in a purified pigment–protein complex[10].

Consistency. If lateral heterogeneity is maintained by charge distribution between appressed and unappressed regions of membrane, how can increased negative charge on LHCII cause it to move into unappressed domains relatively rich in protein complexes (e.g. PSI) which are already excluded from appressed domains by their more negative surface charge?

Dependence on lateral heterogeneity. Movement of pigment–protein complexes between discrete domains cannot occur in laterally homogeneous membranes, since they have no such domains. Miller and Lyon[11] go as far as to suggest that protein phosphorylation evolved in photosynthesis as a means for lateral migration of LHCII 'to overcome the difficulties introduced by the stacked membrane system'. Yet membrane protein phosphorylation seems to regulate photosynthesis in laterally homogeneous, unstacked prokaryotic membranes[2] as well as in LHCII-containing algae that show no distinct thylakoid organization into grana and stroma[12].

The local charge hypothesis

Allen and Holmes suggested that the electrostastic forces which are induced by phosphorylation and which control protein–protein interactions act in a direction parallel to the membrane plane[13]. This proposal removes the

requirement for distinct domains and replaces surface charge with more localized charge on individual protein complexes. This model can therefore accommodate prokaryotes and unstacked chloroplast thylakoids[9], circumventing the third problem of the surface charge model.

The local charge model also circumvents the problem of the non-specificity of surface charge. This is because individual complexes rather than whole domains would have their charge altered by phosphorylation. However, the requirement for this process to have specific effects on protein–protein interactions introduces the additional constraint that all participating complexes should be phosphorylated, since otherwise phosphorylation of a single protein would alter its interaction, non-specifically, with all its neighbours. This constraint is consistent with the multiple phosphorylations observed in chloroplasts, cyanobacteria and purple bacteria, and provides a basis for proposed identities and functions of purple bacterial chromatophore, cyanobacterial and chloroplast thylakoid phosphoproteins[2].

Isocitrate dehydrogenase

The quite unrelated, soluble enzyme isocitrate dehydrogenase has 416 residues and is inactivated by phosphorylation of Ser113. The molecular and structural basis of this effect is understood since structures at 2.5 Å resolution have been obtained for the *E. coli* enzyme both with and without substrate and in both phosphorylated and dephosphorylated forms[14]. These structures show that the phosphorylation site is also part of the catalytic site, since one of the six hydrogen bonds formed between isocitrate and amino acid side chains is that between O_4 of the γ-carboxyl group of isocitrate and Ser113. The effect of phosphorylation of Ser113 is therefore to block substrate binding at the active site by short-range electrostatic forces. The phosphate group has minor and local effects on the position of other side chains near the substrate-binding site, but there is no general conformational change in the protein. The effect of phosphorylation in providing an electrostatic block to substrate binding can be mimicked in site-directed mutants where Ser113 is replaced by the acidic amino acids glutamate or aspartate[14], and neither of the mutants shows significant long-range structural alterations.

The mechanism by which phosphorylation exerts its functional effect on isocitrate dehydrogenase is therefore similar to the local charge model proposed specifically for light-harvesting membrane proteins of photosynthesis[13], though in the local charge model protein–protein interactions rather than protein–substrate interactions are blocked by phosphorylation. The membrane surface charge model has no counterpart in phosphorylation of

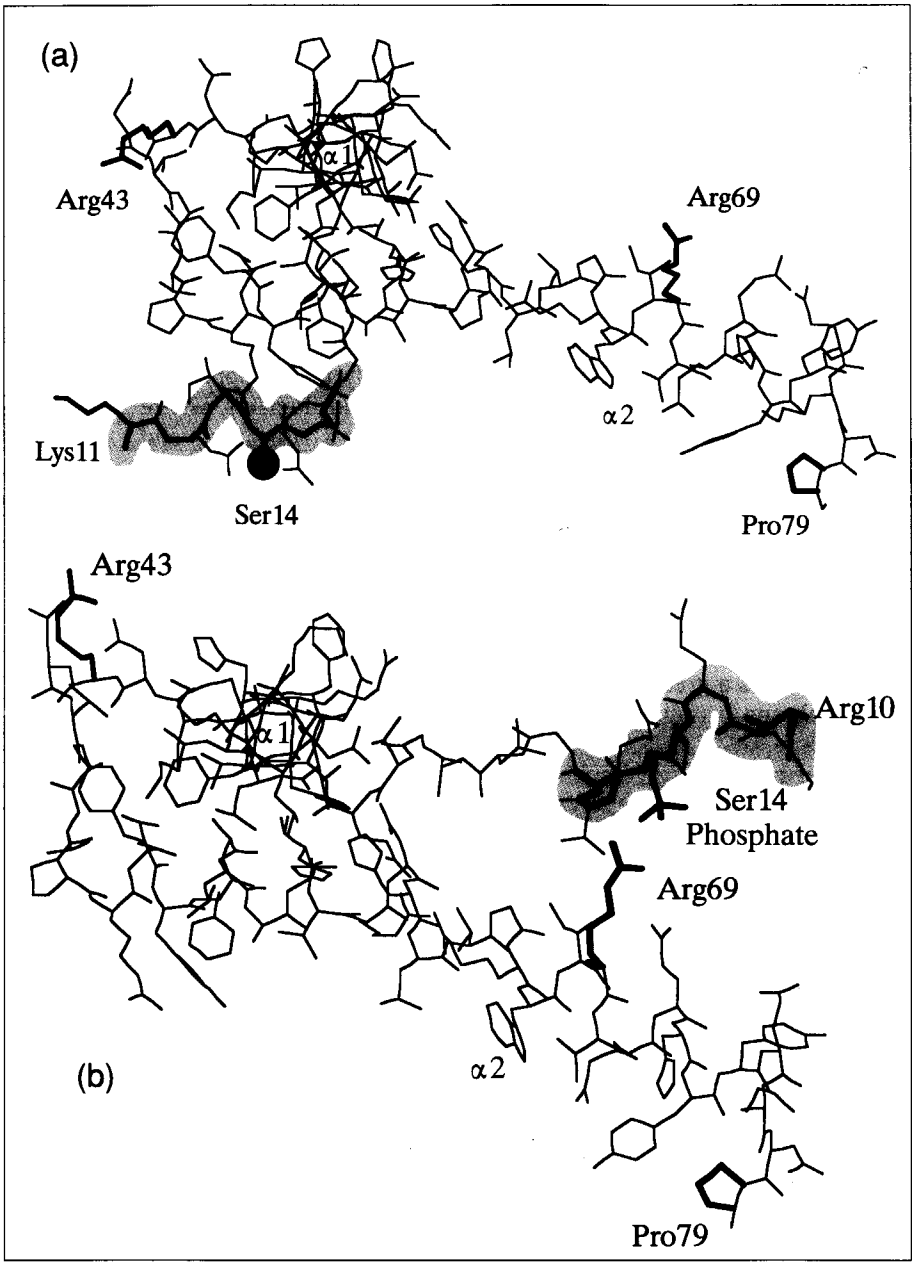

Figure 2

(a) Stick-bond model of part of the structure of the inactive, dephosphorylated, *b*-form of rabbit glycogen phosphorylase, from amino acids 11 (lysine, lower left) to 79 (proline, lower right). Pro79 ends helix α2, which runs diagonally from the upper left to the lower right. Helix α1 is viewed along its axis (upper left). The side chains of Lys11, Ser14, Arg43, Arg69 and Pro79 are highlighted in red. The α-carbon backbone of the segment 11–16 is highlighted in pink. In three dimensions this segment is separated from the helices along the Z-axis, and in this projection points towards the viewer. **(b)** Stick-bond model of part of the structure of the active, phosphorylated, *a*-form of rabbit glycogen phosphorylase, from amino acids 10 (arginine, upper right) to 79 (proline, lower right). In comparison with the dephosphorylated segment (a), the amino-terminal segment, which includes Ser14, has formed an α-helix, and has moved much closer to helix α2, where the phosphate group of Ser14 forms a salt bridge with an amino group of Arg69. The phosphate group also forms a salt bridge with Arg43 of the opposing chain (not shown). The side chains of Arg10, Ser14, Arg43, Arg69 and Pro79 are highlighted in red. The α-carbon backbone of the segment 10–16 is highlighted in pink. (a) and (b) were drawn using *Nemesis* (Oxford Molecular Ltd) from coordinates kindly provided by L. N. Johnson and D. Barford[16].

isocitrate dehydrogenase, although isocitrate binding to the glutamate site-directed mutant can be induced at high ionic strength (6.9 M) and isocitrate concentration (100 mM), where isocitrate is sterically accommodated by movements of the side chain of Glu113 and the γ-carboxylate of isocitrate[14]. This effect of forcing the formation of the enzyme–substrate complex may be comparable to the effect of altered cation concentration on chloroplast thylakoid structure and function[8,9].

Glycogen phosphorylase

Rabbit glycogen phosphorylase is activated by phosphorylation, and, like isocitrate dehydrogenase, structures have been solved from X-ray crystallography for both its phosphorylated and dephosphorylated forms[15]. Barford *et al.*[16] have recently reported structures at 2.9 Å resolution showing that phosphorylation of Ser14 at an allosteric site close to the amino terminus affects substrate binding; long-range protein structural effects cause rotation of the two identical 841-residue subunits, which exposes the catalytic site and also creates a high-affinity binding site for a cofactor, AMP.

The key event in activation of glycogen phosphorylase by phosphorylation of Ser14 is charge compensation, whereby the phosphate group shields basic amino acid side chains on either side of the phosphorylation site from each other. When these repulsive forces are neutralized, the amino-terminal segment containing the phosphoserine assumes an α-helical conformation that is absent from the dephosphorylated protein. The effect of this local change in secondary structure represented by helix formation is to move the whole amino-terminal segment from a peripheral position in the protein to a closer interaction, via salt bridges, with a number of initially remote, basic side chains, including Arg69 of the same chain and Arg43 of the opposing chain. Ser14 itself moves through about 36 Å, and Arg10 moves through 50 Å. Thus the tertiary and quaternary structural changes arising from phosphorylation of glycogen phosphorylase are generated initially by short-range electrostatic forces, and are reinforced by formation of salt bridges of about 2.6 Å between side chains that are in the region of 40 Å apart in the dephosphorylated form of the protein. Helix formation and some of the immediate tertiary structural changes are shown in Fig. 2.

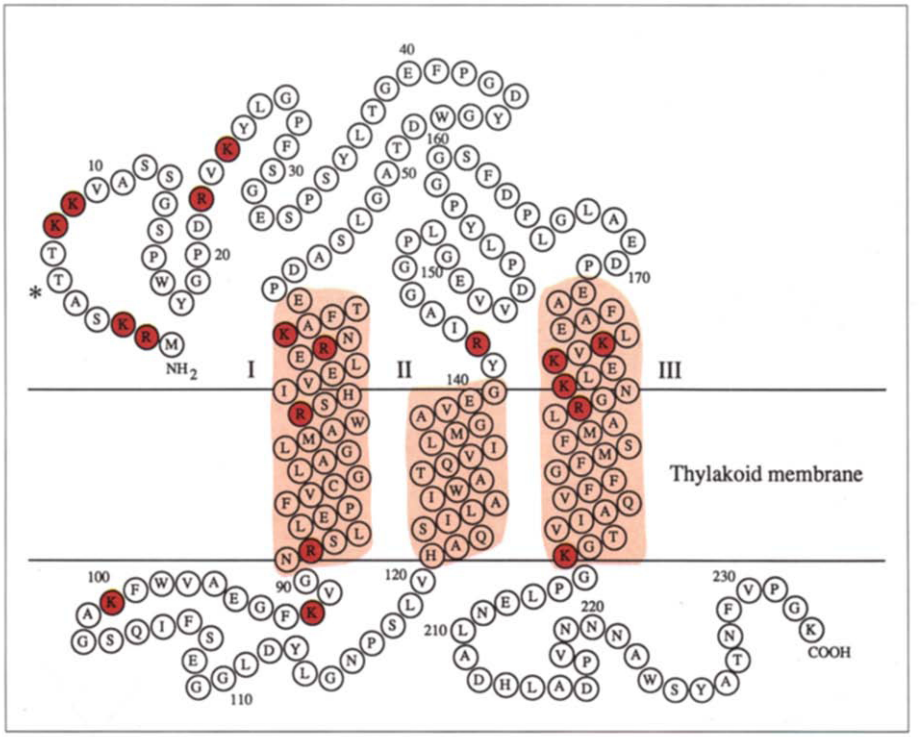

Figure 3

A model for the organization of pea LHCII, with respect to the thylakoid membrane, adapted from that of Bürgi *et al.*[19] Helices I and III (numbered from the amino terminus) are extended to Pro56 and Pro171 respectively, which gives helices corresponding in length to helices B and A, respectively, in the structure of Kühlbrandt and Wang[17]. The three helices are highlighted in pink and basic amino acids are highlighted in red. *Indicates the phosphorylation site, Thr6. See also Fig. 5.

The structure of LHCII

The best three-dimensional structure of LHCII currently available is one at 6 Å resolution and obtained by electron crystallography of dephosphorylated pea LHCII by Kühlbrandt and Wang[17]. This shows three membrane-spanning helices and 15 chlorophylls. Helices I and III (termed B and A respectively by Kühlbrandt and Wang) are 49 Å and 46 Å long – longer than any helix described previously for a membrane protein – and must protrude beyond the membrane surface. They extend for 9 Å and 7 Å beyond the top of helix 2 (helix C). The 15 chlorophylls (chlorophylls *a* and *b* cannot be distinguished at 6 Å) are arranged on two levels, the upper level of eight chlorophylls being related by the local twofold symmetry found in helices I and III, indicating conserved chlorophyll-binding sites in the internally homologous polypeptide segments.

```
                    1       5       10
                    M R K S A T*T K K V A S S      pea light-harvesting complex II

          S R P L S D Q E K R K Q I S*V R G L A G      rabbit glycogen phosphorylase
                    5       10      15      20
                    --------- helix ------

95      100     105     110     115     120     125     130     135     140
Y R V A I K G P L T T P V G G G I R S*L N V A L R Q E L D L Y I C L R P V R Y Y Q G T P S P
                                                    E. coli isocitrate dehydrogenase
```

Figure 4

Amino-terminal segments of pea LHCII*b* and rabbit glycogen phosphorylase, showing phosphorylated amino acid residues (*) and basic amino acid residues (bold) flanking the phosphorylation sites. *Helix* shows the extent of the α-helix induced by phosphorylation of glycogen phosphorylase. A segment of *E. coli* isocitrate dehydrogenase is also shown. Alignments of phosphorylation sites of the three proteins are made to permit comparison of the distribution of adjacent, basic amino acids.

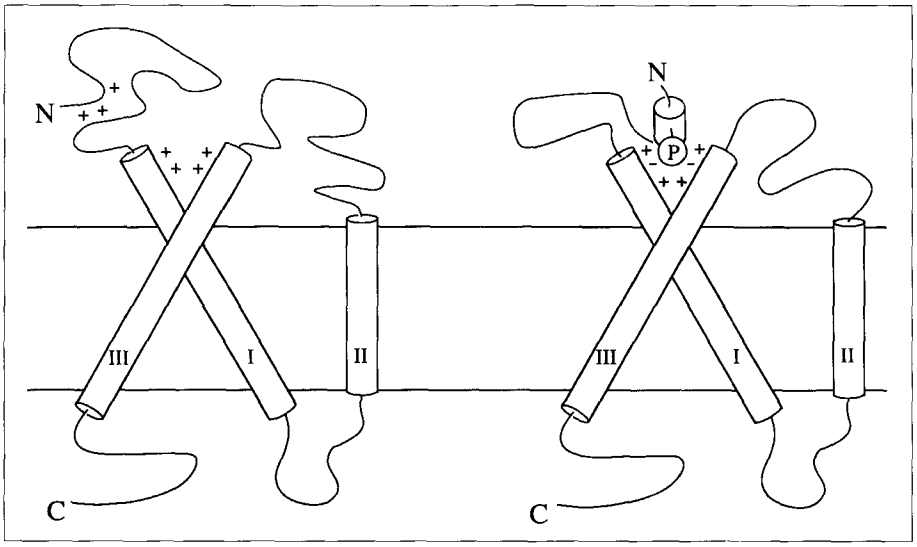

Figure 5

Outline of a possible structural change upon phosphorylation of pea LHCII*b*, proposed by analogy with glycogen phosphorylase. Left, unphosphorylated LHCII. Right, phospho-LHCII. The amino-terminal segment of phospho-LHCII is assumed to form a helix in the region of residues 1–10, and the threonine phosphate (in position 6) to form salt bridges with one or more of the following side chains: Lys61 and Arg63 close to the top of membrane helix I; and Lys178, 180 or 183 close to the top of membrane helix III. This would be expected to induce a large change in tertiary structure in the cytoplasmic (stromal) surface-exposed domain of LHCII. The membrane disposition of the LHCII polypeptide is intended to correspond to that proposed by Kühlbrandt and Wang on the basis of their three-dimensional electron density map at 6 Å resolution[17]. Helices I, II and III (numbered from the amino terminus) probably correspond to helices B, C and A respectively[17]. A and B are longer than C, are tilted with respect to the membrane plane, and protrude from the membrane. A and B also have hook-like extensions at the stromal side of the membrane, and together with the hooks show a twofold symmetry about an axis perpendicular to the membrane plane. These regions may correspond to the polypeptide segments showing internal sequence homology, and contain the basic side chains proposed here as possible ligands for the threonine phosphate. See also Fig. 3.

From the dimensions and relative orientations of the helices in the 6 Å-resolution structure of Kühlbrandt and Wang, it is necessary to modify the membrane disposition models of LHCII proposed by Thornber and co-workers[18] and Zuber and co-workers[19] along the lines shown in Fig. 3. The location of the phosphorylation site (Thr6) near the amino terminus of the extensive hydrophilic domain of LHCII, together with the proximity on each side of positively charged side chains (Fig. 4), suggests an analogy with glycogen phosphorylase; from this a third model for the basis of protein phosphorylation in photosynthesis has been proposed[20].

The molecular recognition hypothesis

The molecular recognition hypothesis[2,20] states that the electrostatic forces exerted initially by phosphorylation are entirely intramolecular, and ultimately lead to major structural changes that alter the interactions of membrane proteins through effects on the complementarity of their respective docking surfaces.

The principal proposals of the hypothesis are as follows. (1) Phosphorylation of membrane proteins reversibly increases fixed negative charge at the phosphorylation site. (2) The increased negative charge alters electrostatic interactions between the side chain of the phosphorylated amino acid and other amino acid side chains located in its immediate vicinity, within about 5 Å. (3) The negative charge of the phosphate group compensates for fixed positive charges on basic side chains, which would otherwise repel each other if brought close together (10–12 Å) in an α-helix. (4) Charge compensation usually occurs within one polypeptide segment, but may occur between polypeptides where a phosphorylation site is close to one of their amino termini. (5) Charge compensation permits a change in secondary structure of the polypeptide segment containing the phosphorylation site. In LHCII this change is formation of an α-helix. In the helix of phospho-LHCII, the phosphate group neutralizes the interaction of positive charges located on side chains 3–4 residues away on each side of the phosphorylation site, at about 5–6 Å (one helix turn) from the phosphorylation site and therefore 10–12 Å from each other. (6) The local change in secondary structure perturbs long-range interactions between side chains, and this perturbation causes a change in the tertiary structure of the hydrophilic domain. (7) The tertiary structural change may involve further electrostatic interaction between the phosphorylation site and distant basic side chains located either on the same or an adjacent polypeptide, bringing the nitrogen atoms involved to within 3.5 Å of oxygen atoms of the phosphate group. (8) Tertiary structural changes alter the shape of a surface of the phosphoprotein, which decreases its complementarity with that of a neighbouring protein complex (e.g. the inner LHCII pool or the PSII core antenna). (9) The decrease in complementarity decreases the sum of the various interactions holding the two proteins together. Their hydrophilic domains cease to bind together, and the two proteins then become free to diffuse independently of each other within the membrane. (10) If sufficient thermal energy is available, the two proteins become separated by lateral diffusion, and their functional interaction is prevented. For light-harvesting proteins, intermolecular excitation energy transfer is prevented. (11) The structural change described in (6) may create a new surface topology that is complementary to that of a third protein complex. This third protein complex (e.g. PSI) may therefore bind and interact functionally with the phosphorylated but not the dephosphorylated form of the original protein complex.

Upon phosphorylation of Thr6 of pea LHCII*b* [steps (1), (2)], charge compensation could be expected to occur between basic residues 2–3 and 8–9 [step (3)]. This could permit the amino-terminal segment of phospho-LHCII to form a helix approximately between residues 1 and 10 [steps (4), (5)], as depicted in Fig. 5. The threonine phosphate could then form salt bridges with Lys61 and Arg63 close to the top of membrane helix I, with Arg143, and with Lys178, 180 or 183 close to the top of membrane helix III [step (6)]. It may be significant that membrane helices I and III and the segments closest to them on the membrane surface which contain the basic side chains have highly conserved sequences[21]. These correspond

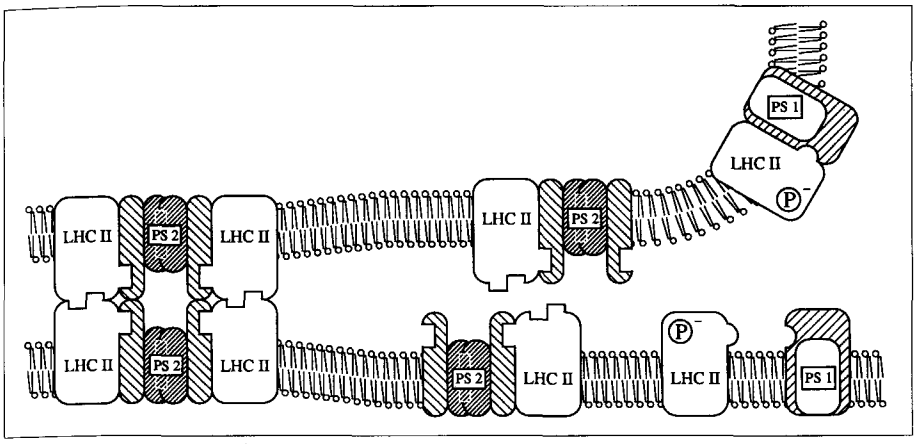

Figure 6

The molecular recognition model for phosphorylation-induced changes in the organization of the chloroplast thylakoid. PSII centres may be connected laterally and transversely for excitation energy transfer by docking of LHCII complexes with the PSII core antenna system (diagonally hatched) and with each other (left-hand side). This brings the acceptor side of PSII reaction centres into opposition. Phospho-LHCII has a decreased affinity for the PSII core (lateral protein–protein interactions) and for itself (transverse protein–protein interactions), and therefore becomes free to diffuse independently of PSII within the membrane, eventually to dock instead with the PSI antenna system (right-hand side). In contrast to the surface charge model (Fig. 1), only thermal energy is required for dissociation of phospho-LHCII from PSII. The connectivity and antenna size of PSII units are decreased, and the loss of adhesion contact surfaces may cause some transverse separation of adjacent thylakoids of the grana stack. A proportion of PSII reaction centres ceases to be in opposition. The altered shape of the block representing LHCII is intended to convey a structural change in the surface exposed domain (Fig. 5), electrostatic blocking of protein–protein interactions by the phosphate groups, or a combination of both.

to the helical regions extending beyond the membrane and to which hook-like features are attached[17]. The proposed structural change (Fig. 5) could provide the basis for alterations in the complementarity of docking surfaces of the outer, mobile and inner, immobile LHCII complexes, causing their dissociation[6]. It could also provide the basis for alteration in complementarity of opposing faces of LHCIIs located on adjacent membranes, thereby initiating the process of unstacking and perhaps blocking a transverse pathway of excitation energy transfer. The overall process of regulation by altered molecular recognition is depicted in Fig. 6.

Prospects for the molecular and structural basis of regulation

With only two exceptions – glycogen phosphorylase and isocitrate dehydrogenase – the structural basis of regulation by protein phosphorylation in general is an open question[22].

Photosynthesis is a particularly interesting example for a number of reasons. First, the process itself regulates the primary events in energy capture by life on earth, and modifies the function of the world's most abundant membrane protein complex, one visible in lunar photography, and without which life would be possible but unimaginably different from that which we know. Second, phosphorylation of LHCII guides protein–protein recognition rather than protein–small-molecule recognition, and specifically concerns membrane proteins. As such, this regulation may have features in common with control of function of receptors and components of cellular recognition and signalling pathways. Third, since the widely accepted[1,6,8,9,11] surface charge model faces problems of its own, and since recent findings[14–16] show that phosphorylation initially perturbs short-range electrostatic forces (operating typically over distances of no more than 10 Å), modification of local protein–protein recognition may be a viable alternative to the surface charge model. The relative strengths of these two different mechanisms in the actual redistribution of light energy in green plants is a subject for future research.

Progress in understanding regulation of photosynthesis by protein phosphorylation will depend upon a concerted effort of protein engineering along the lines already set out so clearly for *E. coli* isocitrate dehydrogenase[14]. For this to occur the existence of the problem must be appreciated – we cannot expect its solution to appear by accident. In addition, the problem has wide implications for control of protein–protein and protein–DNA interactions. Membrane phosphoproteins act as environmental sensors and initiate adaptive responses by controlling gene expression[23]. Photosynthesis itself may be an archetype of processes where post-translational and transcriptional levels of response can be brought into play.

Acknowledgements

I thank D. Barford and L. N. Johnson for the glycogen phosphorylase coordinates used in Fig. 2, L. N. Johnson for drawing my attention to the work[14] on isocitrate dehydrogenase, and W. Kühlbrandt for helpful discussions. Work in my laboratory is supported by NAVF and the SEFO NLVF Nordic Energy Research Programme.

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