Minireview

H^+-proton-pumping inorganic pyrophosphatase: a tightly membrane-bound family

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Abstract The earliest known H^+-proton-pumping inorganic pyrophosphatase, the integrally membrane-bound H^+-proton-pumping inorganic pyrophosphate synthase from *Rhodospirillum rubrum*, is still the only alternative to H^+-ATP synthase in biological electron transport phosphorylation. Cloning of several higher plant vacuolar H^+-proton-pumping inorganic pyrophosphatase genes has led to the recognition that the corresponding proteins form a family of extremely similar proton-pumping enzymes. The bacterial H^+-proton-pumping inorganic pyrophosphate synthase and two algal vacuolar H^+-proton-pumping inorganic pyrophosphatases are homologous with this family, as deduced from their cloned genes. The prokaryotic and algal homologues differ more than the H^+-proton-pumping inorganic pyrophosphatases from higher plants, facilitating recognition of functionally significant entities. Primary structures of H^+-proton-pumping inorganic pyrophosphatases are reviewed and compared with H^+-ATPases and soluble proton-pumping inorganic pyrophosphatases.

Key words: H^+-proton-pumping inorganic pyrophosphatase; H^+-proton-pumping inorganic pyrophosphate synthase; H^+-ATPase; H^+-ATP synthase; Amino acid sequence; Evolution; Enzyme family

1. Introduction

Photophosphorylation of inorganic orthophosphate (Pi) to pyrophosphate (PPi), in chromatophores isolated from the photosynthetic, purple, non-sulfur bacterium *Rhodospirillum rubrum*, was discovered in 1966 [1] and found to be sensitive to uncouplers but uninhibited by oligomycin [2]. This light-induced formation of PPi, which provided a raison d' être for the tightly membrane-bound, uncoupler stimulated, inorganic pyrophosphatase (PPase) activity in chromatophores [3,4], is still the only known alternative to ATP formation in biological electron transport phosphorylation. In isolated chromatophores, PPi was used to drive several energy requiring reactions [5–8]. Proton movement, which was induced by light in chromatophores [9], was shown by addition of PPi in the dark to be linked also to the PPase [10], thus showing it to be a H^+-PPase (H^+-PPi synthase, compare H^+-F_oF_1ATPase, H^+-F_oF_1ATP synthase).

A membrane-bound PPase activity was found in 1975 in homogenates from higher plants [11] and was later localized to plant vacuoles [12]. In plants, the vacuoles contain two enzymes for acidifying the interior of the vacuole, the well known V-ATPase and the V-PPase (V for vacuolar).

Nine amino acid sequences of plant V-PPases have been solved and shown to form a distinct protein family [13–21]. Two are from green algae and have been published very recently [20,21]. The higher plant sequences show identities of more than 85% [18]. From bacteria, the *R. rubrum* H^+-PPase (PPi synthase) sequence [22] belongs to the same family, as do two homologues which have emerged from genomics work with hyperthermophiles, namely the archaeon *Pyrobaculum aerophilum* and the bacterium *Thermotoga maritima*.

H^+-PPase activity has also been documented in several other membranes from higher plants [23–25], as well as in acidocalcisomes from the protozoan *Trypanosoma cruzi* [26] and the cell membrane of the chemotrophic anaerobic bacterium *Syntrophus gentianae* [27].

An excellent review [28] on pyrophosphate as an energy donor in plant cells discusses in great detail the possible interplay between ATP-linked and PPi-linked reactions. As several recent review articles [29–31] cover the eukaryotic H^+-PPases, this minireview is somewhat focussed on the prokaryotic homologues. Emphasis is also on H^+-PPases with a known primary structure and on comparison with both H^+-ATPases and soluble PPases. X-ray structures at high resolution of crystals from soluble PPases from both pro- and eukaryotes have provided the background for most of the detailed knowledge about the structure and reaction mechanism, also in other PPases. Whereas the membrane-bound PPases are directly involved in bioenergetic reactions, soluble PPases have long been recognized to function in the hydrolysis of the PPi emerging as a byproduct from various ATP requiring biosyn-

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CGCTCCCCGCGGGTAGTTCTGGCAGGCTGCCCCTACCCTTGCGGCGAAGACCCGGCGGTCG

ATGTGGCTATTCGATCGCGGCGGGGTTTTTCCGCATTGCCCGCCGTTAGGCCCATTCAGGGGAG

GGATCGAACGAATCATGGCTGGCATCTATCTTTTCGTCGTAGCCGCCGCACTCGCGGCC
                  M  A  G  I  Y  L  F  V  V  A  A  A  L  A  A
CTTGGTTATGGCGCTCTCACCATCAAAACAATCATGGCGGCTGATGCCGGCACCGCGCGGATGC
 L  G  Y  G  A  L  T  I  K  T  I  M  A  A  D  A  G  T  A  R  M
AGGAGATTTCCGGCGCCGTGCAGGAAGGCGCCAGCGCGTTTCTCAATCGTCAGTACAAGACCAT
Q  E  I  S  G  A  V  Q  E  G  A  S  A  F  L  N  R  Q  Y  K  T
                  M
          Alternative start
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Fig. 1. The first 319 nucleotides from the N-terminal end of the clone RrPP4. The two identical Shine Dalgarno regions (GGAG) and the two possible start codons (ATG and GTG, in bold script) are underlined. Corresponding amino acids for the two alternatives are given.

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Abbreviations: PPi, inorganic pyrophosphate; PPase, inorganic pyrophosphatase; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase

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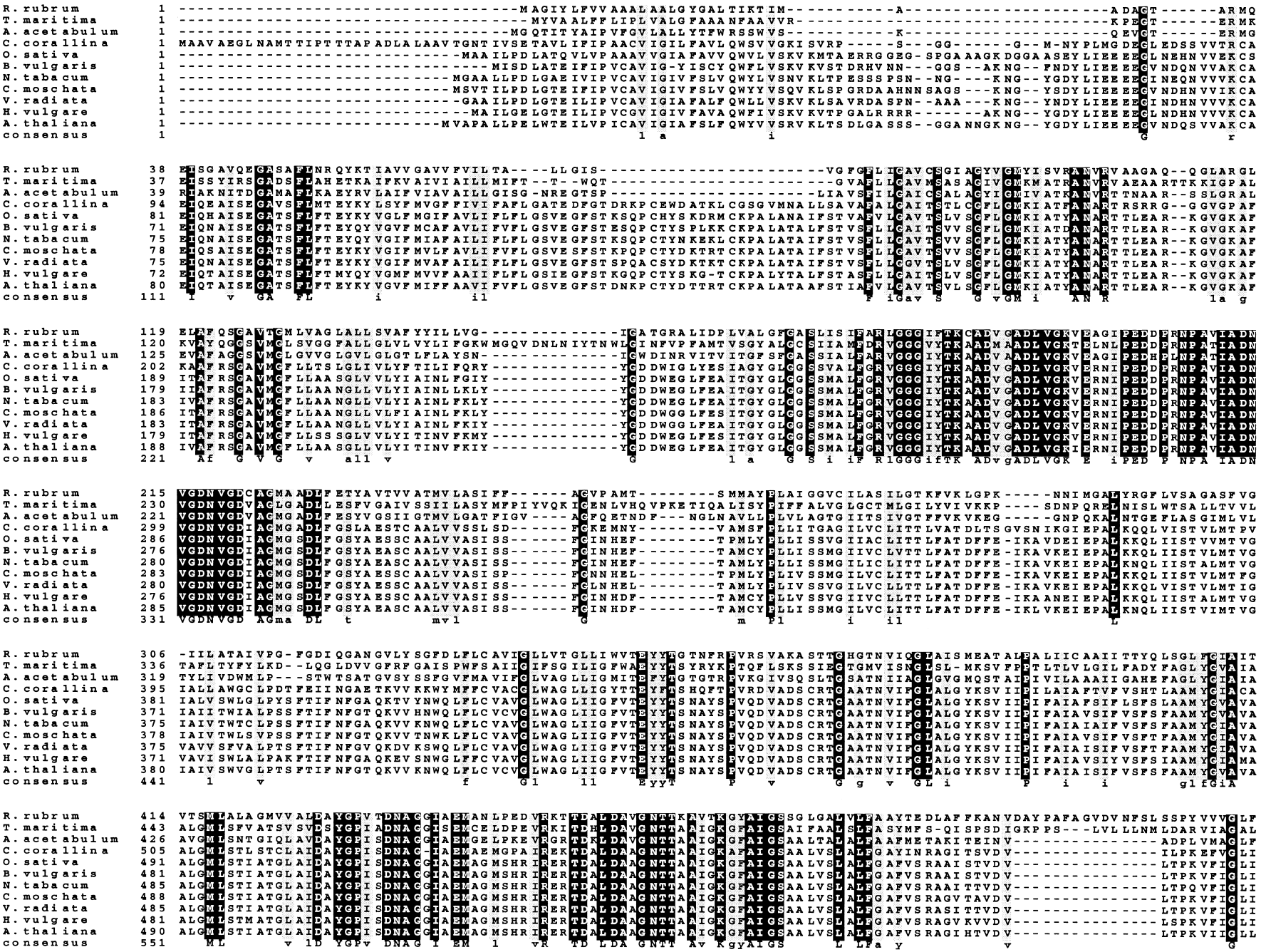
R.rubrum
T.maritima
A.acetabulum
C.corallina
O.sativa
B.vulgaris
N.tabacum
C.moschata
V.radiata
H.vulgare
A.thaliana
consensus

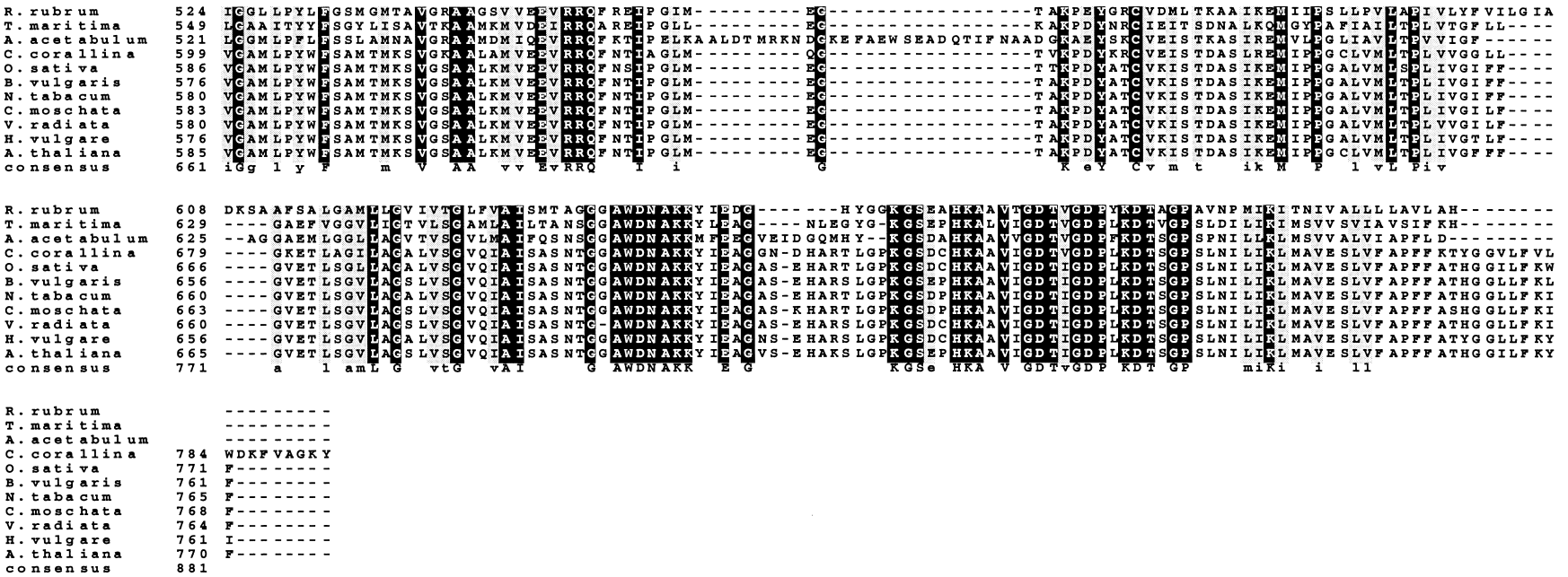

Fig. 2. Multiple sequence alignment with H^+-PPase sequences from *R. rubrum*, the thermophilic bacterium *T. maritima*[1], the unicellular algae *A. acetabulum*, the green algae *C. corallina* and the plants *Oryza sativa*, *Beta vulgaris*, *Nicotiana tabacum*, *Cucurbita moschata*, *Vigna radiata*, *Hordeum vulgare* and *A. thaliana*.

thetic reactions, thus facilitating the actual biosyntheses. The known PPase families are briefly described in Table 1.

2. The *R. rubrum* H^+-PPi synthase and homologues from prokaryotes

A very tightly membrane-bound enzyme was found to be responsible for the PPase and the PPi synthase activity [4] in *R. rubrum*. The energetic capacity of PPi was further elucidated when it was possible to drive a reversed electron flow with the energy released by the hydrolysis of PPi [5,6], as well as to create a membrane potential [32–34] over both the chromatophore membrane and artificial membranes. It was also possible in chromatophores to drive the phosphorylation of ADP to ATP in the dark with PPi [8]. The 'cost' of PPi in this experiment was about eight per ATP synthesized, which leads to the question of the proton stoichiometry in PPi hydrolysis. Values obtained vary between 0.5 [10] and two H^+ [35,36] per PPi hydrolyzed. Very interesting in this connection is that in plasma membrane vesicles from *S. gentianae* [27], the hydrolysis of one ATP yields three PPi and vice versa, three PPi yield one ATP, indicating a H^+ stoichiometry of one for PPi hydrolysis. The isolated and purified enzyme could be reconstituted in artificial liposomes with a retained activity [37] and when co-incorporated with the complete F_oF_1 complex from *R. rubrum*, ATP synthesis driven by PPi hydrolysis was obtained also in the liposomes [38]. In the bacteria, the PPi synthase is situated in the plasma membrane with the same polarity as the ATP synthase, with the catalytic site towards the cytosol. PPi synthesis and ATP synthesis compete for the available proton gradient, at least in isolated chromatophores [39]. The rate of PPi synthesis, at a saturating light intensity, is 12–15% of the rate of ATP synthesis.

The enzyme is extremely hydrophobic, a property which has caused considerable difficulty in both the original isolation and the determination of the amino acid sequence. Several attempts have been made to make a direct analysis on the isolated and purified protein, all of which have failed, probably due to the high percentage of detergent necessary to keep it active in solution. The cloning and sequencing of the gene encoding the PPase left one problem unsolved. Two possibilities for the start codon of the gene appeared, separated by 126 bp, one yielding a deduced protein of 660 amino acids with a molecular mass of 67 453 [22], the other giving a structure with 702 amino acids with the molecular mass 71 609 (Fig. 1). The two bacterial H^+-PPase homologues which both contain more than 700 amino acids are more similar to the longer version of the *R. rubrum* sequence. So is the suggested dimer structure of the *R. rubrum* PPi synthase with a molecular mass of 167.7 ± 30.7 kDa [40], as determined by radiation inactivation. A dimer has also been suggested based on ultrafiltration results [41]. Another argument favoring the 702 amino acid length is that there are only 15 predicted transmembrane segments in the 660 amino acid structure [22], whereas the 702 amino acid one has 16, as have all the other homologues in the H^+-PPase family. No striking homology with the N-terminals of known H^+-PPases is found, but a new homologue from the *Arabidopsis thaliana* genome (Vysotskaia, V.S. et al., GenBank, accession AC005679) shows a particular similarity to the *R. rubrum* sequence, both with respect to the complete protein and to the N-terminal part, unique to its longer version, which is used in this paper. A final conclusion about the actual start may have to await successful sequencing of the N-terminal part of the *R. rubrum* enzyme.

Table 1
Known PPase families

Family	Members
1. Tightly membrane-bound H^+-pumping PPases	a. Bacterial PPase
	b. Archaeal and bacterial homologues
	c. Vacuolar PPases
2. Earlier known family of soluble PPases	a. Cytoplasmic PPases (archaeal, bacterial and eukaryotic)
	b. Mitochondrial (and chloroplast?) PPases (probably soluble parts of H^+ pumps)
3. Recently found family of soluble PPases	a. Some archaeal and bacterial PPases

The *Rhodospirillum*, *Pyrobaculum* and *Thermotoga* sequences show only about 38–39% identities between themselves, which indicates that they are much more diverged from each other than the higher plant enzymes are. An intriguing question is whether the two prokaryotic H^+-PPase homologues will be physiologically active and also capable as PPi synthases as those from *R. rubrum* and *R. viridis* [42].

3. H^+-PPases in plant vacuoles

The main role of V-PPases seems to be to participate in the acidification of vacuoles. In tonoplasts from *Zea mays* L., PPi synthesis has been obtained in response to a H^+-gradient created by ATP hydrolysis, as well as ATP synthesis in response to a PPi-generated H^+-gradient [43]. The dependence of V-PPase activity on K^+ ions [44] has led to a debated suggestion of V-PPase-mediated physiological transport of K^+ ions into vacuoles [28]. Also, V-PPases probably occur as dimers in vivo [45].

The V-PPase from *Arabidopsis* has been heterologously expressed in yeast [46]. At least four V-PPases have been reconstituted in liposomes [47] with a retained activity. Site-directed mutation studies of *Arabidopsis* V-PPase expressed in yeast have revealed some amino acids of apparent functional importance [48]. E427, located on the cytosolic side immediately after the predicted transmembrane segment 9, is of particular interest since an E427Q mutant preferentially impairs H^+ translocation over PPi hydrolysis and the E427D mutant enhances H^+ translocation [48]. E427 is included in a motif, EYYT, present in all sequenced H^+-PPases, except in *Pyrobaculum*, where it is the similar DYYT. D504 is also conserved in the H^+-PPases and mutant D504N essentially lacks both PPase activity and H^+ translocation.

The first indicated family relationship between vacuolar and bacterial H^+-PPases was found when antibodies directed against the V-PPase of *Vigna radiata* cross-reacted with the *R. rubrum* PPi synthase [49]. Both bacterial and vacuolar H^+-PPases show few sequence similarities with soluble PPases. An

[1] Sequence data were obtained through early release from The Institute for Genomic Research at www.tigr.org and/or through NCBI at www.ncbi.nlm.nih.gov.

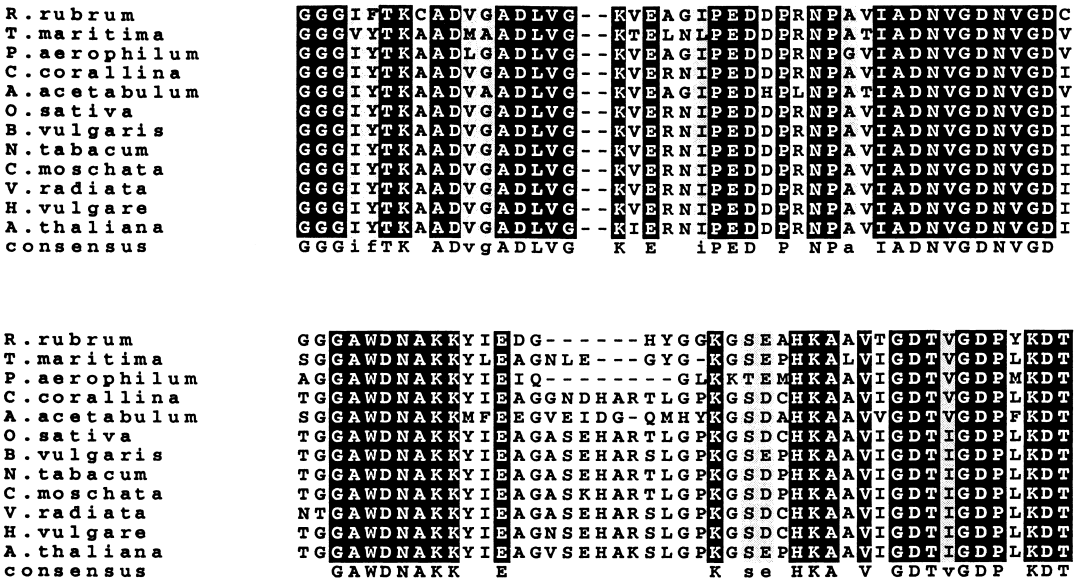

Fig. 3. Alignment with the parts of two loops between transmembrane segment 5-6 (above) and 15-16 (below) in H^+-PPases, where the part of loop 5-6 contains the three motifs GGG, DVGADLVGK and DNVGDNVGD. Residues in black/gray boxes are identical/similar in all sequences. The consensus of similarities follows that of the first organism.

exception is the motif DX_7KXE [44] in the loop after transmembrane segment 5 which is similar to the active site motif $EX_{7-8}KXE$ in soluble PPases [50]. Antibodies directed to this motif in *V. radiata* V-PPase were recently shown to strongly inhibit the hydrolytic and proton-pumping activity of membrane vesicles and the hydrolytic activity of the purified enzyme [51]. A specific chemical inhibitor for H^+-PPases from both plants and photobacteria is aminomethylenediphosphonate [52].

Amino acid sequences of algal V-PPases from *Acetabularia acetabulum* [20] and *Chara corallina* [21] have very recently emerged. The *A. acetabulum* sequence shows approximately as many identities with the *R. rubrum* sequence as with the one from *A. thaliana* (see Fig. 2), whereas the *C. corallina* sequence is much more like that of *A. thaliana*. A possible link between vacuolar and bacterial H^+-PPases is the new homologue from *A. thaliana*. It shows more sequence identities with the the *R. rubrum* H^+-PPase (40.1%) than with any of the vacuolar H^+-PPases (33.4–37.2%). Furthermore, the homologue contains one of two cysteines of the putative active site loop of the *R. rubrum* H^+-PPase. The substitution of E in the motif EYYT to K indicates that the homologue may no longer possess coupling activity.

4. Some further structural and evolutionary aspects

The amino acid sequences of the bacterial PPi synthase from *Rhodospirillum*, the homologue from *Thermotoga* and nine published vacuolar H^+-PPases are shown in Fig. 2. Comparisons with hydrophobic plots show that identical (blackened) and similar (shadowed) residues are particularly abundant between transmembrane segments, in the loops 5, 11 and 15.

The homology between all membrane-bound H^+-PPases has led to various questions, about common structural properties of functional significance and about evolution, both within these archaeal, bacterial, algal and higher plant enzymes and between this protein family and possibly related families, such as membrane-bound ATPases and soluble PPases.

4.1. Within the H^+-PPase family

Attention is here first restricted to corresponding parts of two loops in the PPi synthase from *R. rubrum*. A 45 amino acid piece from the 57 amino acids in the putative active site loop 5 is compared with a similar part of loop 15, which may contain a duplicated and subsequently evolved segment of an ancestral version of loop 5. Three motifs of loop 5 are GGG, DVGADLVGK and DNVGDNVGD

The first motif, the triglycyl sequence, occurs in all H^+-PPase family members and may be expected to have the potential to provide, to the extent that other structural properties of the enzyme allow, an unusually high local conformational change capability. In the PPi synthase, uniquely, the loop 15, with the 'duplicated segment', contains a similarly positioned sequence of three glycyl residues, in contrast to just two or one in all other known H^+-PPases (Fig. 3). In view of the conformational change mechanism of the ATP synthase function [53,54], one may ask the question if the fact that only the PPi synthase of the H^+-PPase family may function physiologically in the PPi synthesis direction is related to this uniqueness. Notably, a GGG sequence has recently been used as a spacer to allow mimicking the swing of the lever arm of a myosin motor [55].

It should be pointed out that in the H^+-PPi synthase, a mechanism of rotation in energy coupling, similar to that of ATP synthase [54], seems impossible since the H^+ translocation and the catalytic site are on the same subunit, as in P-type ATPases. The alternative phosphorylation system, generating PPi, thus would appear to utilize a fundamentally different coupling mechanism from that involved in the ATP synthesis.

Results from high resolution studies of crystals from soluble PPases [50] indicate that the second motif, DVGADLVGK,

where the first VG may vary, at least in bacteria and algae, may be involved in the binding of metal (with first D) and substrate (with K). From comparison with ATP synthases and P-type ATPases, a similar role may be suggested for aspartyl residues of the third motif, DNVGDNVGD, which, in contrast to the second, are found also in the 'duplicated segment' of loop 15. A similarity between the second and the third motifs is seen in the tetrapeptide sequences DVGA and DLVG of the second and DNVG of the third, which is seen to be a repeat of 2.25 U of it. Uniquely, in the new *Arabidopsis* homologue with its sequence similarities to the *Rhodospirillum* PPi synthase, the first of the two expected DNVG sequences of the third motif is DLVG! Possible evolutionary relationships between these three tetrapeptide sequences, which consist of only very early and early amino acids and which may be traces of active site motifs in early phosphate metabolism, will be discussed elsewhere.

4.2. Between families

Certain similarities, but no clear indications of evolutionary relations, have been found between the H^+-PPase family and those of ATP synthases and P-type ATPases. The H^+-PPi synthase shares with the P-loop [56] of the ATP synthase the amino acid sequence GX_3VGK (the homologue from *Pyrobaculum* shares with the P-loop the sequence VGKT), these sequences apparently being involved in the binding of phosphate residues of the respective substrates. Similarities in the DNVGDNVGD sequence with active site regions of both ATP synthases and P-type ATPases will be discussed elsewhere.

Functionally important similarities between H^+-PPases and the well known family of soluble PPases seem to occur [46,57], for example the metal- and substrate-binding region (E/D)X_{7-8}K which was established by high resolution studies of soluble PPases from both prokaryotic and eukaryotic organisms [50] and found in the putative active site region of all H^+-PPases. A new family of soluble PPases [58,59] has not shown any significant sequence similarity to the other PPase families. Future kinetic results with this family may be of value in connection with current concepts about very similar reaction mechanisms in different PPase families.

The structure of the soluble PPases from both prokaryotes and eukaryotes has long been extensively studied and it is in this family that we have good basic knowledge about various molecular details, i.a. of the active site and the reaction mechanism [60–63].

5. Outlook

Some attractive directions for future work are, in addition to more general knowledge about the distribution and properties of H^+-PPases: structural requirements for the physiological reversibility of the H^+-PPase function; isolation and characterization of H^+-PPase homologues with deduced amino acid sequences from known genomes; sequencing the gene(s) for and/or protein(s) of additional H^+-PPases, also from mitochondria [64], chloroplasts and other possible H^+-PPase containing membranes and overexpression of H^+-PPases for studies of the coupled phosphorylation capability, site-specific mutation and crystallization.

Further significant progress with the tightly membrane-bound H^+-PPase family should lead to an increased insight into basic requirements for the biological transport of protons through membranes and its coupling to phosphorylation, as well as into the question whether PPi was a direct predecessor to ATP in the origin and early evolution of life.

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