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HISTORICAL CORNER

Discoveries in Rubisco (Ribulose 1,5-bisphosphate carboxylase/oxygenase): a historical perspective

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Abstract Historic discoveries and key observations related to Rubisco (Ribulose 1,5-bisphosphate carboxylase/oxygenase), from 1947 to 2006, are presented. Currently, around 200 papers describing Rubisco research are published each year and the literature contains more than 5000 manuscripts on the subject. While trying to ensure that all the major events over this period are recorded, this analysis will inevitably be incomplete and will reflect the areas of particular interest to the authors.

Keywords Carbamylation · Carbon fixation · History · Inhibitors · Light regulation · Photorespiration · Rubisco · Rubisco activase

Introduction

In photosynthetic carbon fixation, Rubisco (Ribulose 1,5-bisphosphate carboxylase/oxygenase, EC 4.1.1.39) catalyzes the combination of 10^{11} metric tons of CO_2 each year with ribulose 1,5-bisphosphate (RuBP) (Siegenthaler and Sarmiento 1993). For an overview of the role and functioning of Rubisco in the context of photosynthetic carbon metabolism, see Buchanan et al. (2000), Lodish et al. (2000) and Heldt (2005). Each CO_2 fixed in this way forms two molecules of D-3-phosphoglyceric acid (PGA). Rubisco also initiates photorespiration by catalyzing the oxygenation of RuBP to form one molecule each of 2-phosphoglycolate and PGA. In order to catalyze photosynthetic CO_2 fixation at high rates, large amounts of Rubisco are needed to compensate for the enzyme's slow catalytic rate (3–10 s^{-1}). Rubisco accounts for a quarter of leaf nitrogen and up to half of the soluble protein in the leaves of C_3 plants. Nevertheless, in bright light, Rubisco usually limits CO_2 fixation. Rubisco activity is regulated to match RuBP regeneration with RuBP utilization. Gross regulation of Rubisco activity can be accomplished through alteration of the abundance of the enzyme. The catalytic activity of Rubisco can also be regulated by: (a) the reversible carbamylation of an essential lysine residue on the large subunit, which is subsequently stabilized by a Mg^{2+} ion forming a catalytically active ternary complex; and (b) by the interaction of both carbamylated and non-carbamylated Rubisco with certain phosphorylated metabolites, which block the active site of the enzyme. Such inhibition is rendered reversible by the action of the ancillary enzyme, Rubisco activase, whose activity promotes the release of such compounds.

There are two distinct forms (Forms I and II) of Rubisco among photosynthetic *Bacteria* and *Eucarya* (Fig. 1). Form II Rubiscos are the simplest, comprised of two identical large subunits, and confined to certain photosynthetic bacteria. Form I Rubiscos contain a central core, composed of four large subunit dimers, as well as eight additional small subunits. Form I Rubiscos are found in plants, algae, cyanobacteria, and autotrophic proteobacteria. In higher plants the small subunits are nuclear encoded, but those for the large subunit are chloroplast encoded. The synthesis and assembly of the subunits is complex and involves molecular chaperones and post-translational modification (Fig. 2). In addition to Forms I and II, there are two groups

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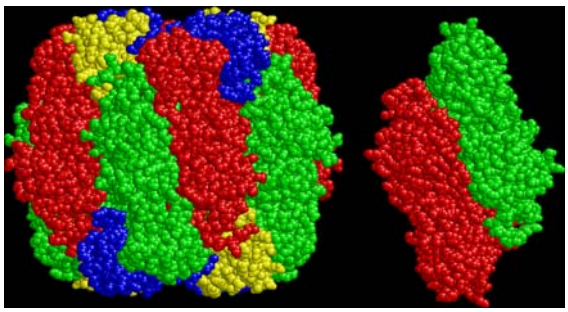

Fig. 1 Molecular structures of photosynthetic Rubiscos—Forms I (L8S8, 8RUC) and II (L2, 9RUB). The other Rubisco forms (III and IV) also have L2 structures, which in one case are arranged in a pentagonal ring (Kitano et al. 2001). Large subunits (L) are colored *green* or *red* and the small subunits (S) are colored *blue* or *yellow*. Image created with RasWin

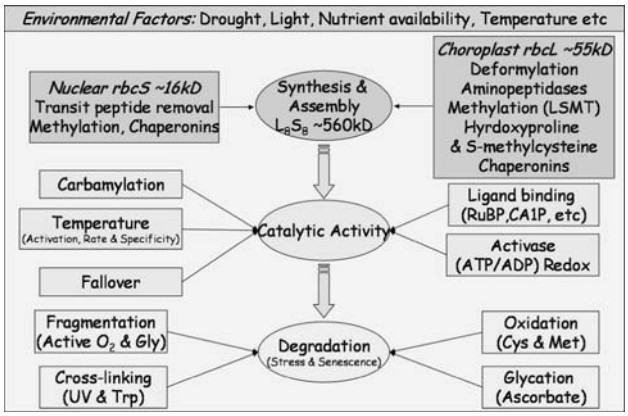

Fig. 2 Rubisco processing and regulation. Redrawn after Houtz and Portis (2003)

of structurally related proteins that have been designated as Form III and Form IV Rubiscos which consist only of large subunits (Hanson and Tabita 2001). Form III Rubiscos are found only in *Archea* and catalyze the carboxylation of RuBP after its formation via alternative pathways to the Calvin–Benson–Bassham cycle. Form IV Rubiscos are found in *Bacteria* and *Archea* and are also called Rubisco-like proteins because they lack several key active-site residues necessary for the carboxylation of RuBP.

This review provides a historical timeline of important discoveries and observations in Rubisco. We have elected to start in 1947 with the first purification of Rubisco, although by doing so, we realize that we will omit some significant earlier work, later shown to be directly relevant to Rubisco (e.g., Warburg 1920). In addition to the literature provided by this timeline, readers are encouraged to consult some of the earlier personal historical perspectives (e.g., Bassham 2003; Benson 2002; Bogorad 2003; Ellis 2004; Ogren 2003; Tabita 2004; Wildman 2002), comprehensive reviews on Rubisco (Jenson and Bahr 1977; Ellis 1979; Lorimer 1981; Miziorko and Lorimer 1983; Andrews and Lorimer 1987; Morell et al. 1992; Hartman and Harpel 1994; Gutteridge and Gatenby 1995; Spreitzer 1993; Spreitzer 1999; Cleland 1998; Tabita 1999; Spreizer and Salvucci 2002), Rubisco regulation (Portis 1992; Salvucci and Ogren 1996; Parry et al. 1999; Portis 2003) and most recently, reviews evaluating the prospects for increasing photosynthesis by overcoming the limitations of Rubisco by a transgenic approach (Zhu et al. 2004; Raines 2006; Long et al. 2006; Parry et al. 2007).

For timelines of oxygenic and anoxygenic photosynthesis, see Govindjee and Krogmann (2005) and Gest and Blankenship (2005), respectively.

1947

Wildman and Bonner (1947) isolate, by ammonium sulfate fractionation, a very abundant protein from leaves, which they call "Fraction I" protein. However, it would be almost a decade before its biological role is recognized. For a personal account, see Wildman (2002).

1948–1950

Melvin Calvin (Director of Bio-Organic Chemistry Group) and Andrew Benson (Director of the Photosynthesis Laboratory) at the University of California, Berkeley resume the earlier attempts by Sam Ruben and Martin Kamen using carbon-11 to identify the early products of photosynthesis. They use $^{14}CO_2$ coupled with anion exchange fractionation initially and subsequently paper chromatography to separate the early products of photosynthesis and identify PGA as the earliest product (Calvin and Benson 1948, 1949; Benson et al. 1950). This and subsequent work resulted in Calvin being awarded the Nobel Prize in Chemistry in 1961. For personal accounts of these experiments, see Calvin (1989), Benson (2002) and Bassham (2003).

Tamiya and Huzisige (1949) conduct studies that lead them to conclude that CO_2 and O_2 compete at a common site during photosynthesis. Benson and Calvin (1950) observe that oxygen enhances the formation of glycolate from $^{14}CO_2$ in the light. Intrigued by this report, Hiroshi Tamiya visits Benson in 1952 and they conduct additional experiments using $^{14}CO_2$ but the results are not published (see Benson 2002).

1951

Benson (1951) identifies ribulose bisphosphate as an early product of photosynthesis and notes that its oxidation in air produces PGA and phosphoglycolate.

1954

Rapid labeling with $^{14}CO_2$ and analysis of the incorporation patterns in the sugar phosphates results in completion of a cyclic path for the incorporation of carbon in photosynthesis by Calvin's group (Bassham et al. 1954). Addition of CO_2 to the enediol form of RuBP is proposed as the carboxylation step. Rabinowitch (1956) provides a contemporary review of the difficulties and uncertainties along the way in the elucidation of the pathway and the competition between Calvin and other groups particularly that at the University of Chicago (E.W. Fager, J.L. Rosenberg, and Hans Gaffron; see Gaffron 1960), not discussed here. For personal accounts of this research, see Bassham (2003) and Benson (2002).

Using extracts from *Chlorella* (Quayle et al. 1954) and spinach (Weissbach et al. 1954), simultaneous reports of CO_2 fixation appear in the Journal of the American Chemical Society.

1955

Ephraim Racker and Bernard Horecker purify and characterize key enzymes in the "pentose phosphate pathway," which were also proposed components in Calvin–Benson's cyclic pathway (see Horecker 2002). Racker (1955) reconstitutes the proposed cyclic pathway using purified preparations of the key enzymes.

Studies of CO_2-dependent transients of the photosynthetic intermediates by Wilson and Calvin (1955) reveal a reciprocal relationship between RuBP and PGA and thus provide key support for the proposal that RuBP is the CO_2 acceptor in the pathway. Wilson and Calvin (1955) propose that the glycolic acid produced during photosynthesis at low CO_2 concentrations is derived from a transketolase reaction.

1956

In a tour de force, Horecker's lab publishes three consecutive papers reporting: (a) the purification of phosphoribulokinase, a key enzymatic activity required for the cycle (Hurwitz et al. 1956); (b) the enzymatic synthesis of substrate quantities of RuBP using this enzyme (Horecker et al. 1956); and (c) the purification to near homogeneity of an enzyme from spinach that catalyzes the formation of PGA from RuBP and CO_2 (Weissbach et al. 1956). Horecker (2002) provides a personal account of the work and states that "with this work and our earlier demonstration of the reversible reactions for the interconversion of pentose and hexose phosphates, with sedoheptulose phosphate as a prominent intermediate, all of the enzymes for the reactions of the Calvin [–Benson] Cycle were identified."

Horecker's group uses the term "carboxylation enzyme" in contrast to Calvin's choice of carboxydismutase (Benson 2002). Further contributing to controversy in naming of the enzyme (including a change from RuDP to RuBP) the International Union of Biochemistry introduces, in 1961, the name 3-phospho-D-glycerate carboxy-lyase (dimerizing) (see Report of the Commission on Enzymes of the International Union of Biochemistry, Oxford. Pergamon, p. 121, 1961). Curiously Horecker's group does not consider that their purified enzyme might be identical to the Fraction I protein of Sam Wildman.

Immediately following these papers in Journal of Biological Chemistry, a paper from Severo Ochoa's lab (Jakoby et al. 1956) also reports the formation of RuBP and PGA with partially purified spinach leaf enzymes.

1957

In a report (Dorner et al. 1957) on studies of leaf senescence and the decay of Fraction I protein, Wildman's group speculates that based on similar physical properties, Fraction I protein and the carboxylation enzyme isolated by Weissbach et al. (1956) are the same. Benson, working with others in Calvin's group, had concluded that Fraction I protein had carboxylation activity in 1954, but had left the lab and the work was not published until 1957 (Mayaudon 1957; Mayaudon et al. 1957; see Benson 2002).

1958

Moses and Calvin (1958) attempt to trap and identify the proposed six-carbon carboxylation intermediate, 2-carboxy-3-ketopentitol 1,5-bisphosphate. After dephosphorylation, evidence for 2-carboxy-3-ketopentitol was obtained, but 2-carboxy-4-ketopentitol was much more abundant. Almost a quarter of a century passed before the intermediate was successfully trapped (Schloss and Lorimer 1982).

1961

Electron micrographs of spinach chloroplasts show Fraction I protein located in the chloroplast stroma. Fraction I protein in dried samples appeared as oblate spheres 100 Å in height and 200 Å in diameter (Park and Pon 1961). Park and Epstein (1961) demonstrate that Rubisco plays a key role in carbon isotope fractionation by plants.

1962

Bassham and Kirk (1962) report that the inhibition of photosynthesis and formation of glycolate and phosphoglycolate are well correlated with the presence of O_2 during photosynthesis by *Chlorella*. They note that the stimulation of gycolate formation is consistent with the oxidation of the glycolaldehyde-thiamine pyrophosphate addition compound in the transketolase reaction in a metabolic path competing with the formation of RuBP. They also suggest that the increased phosphoglycolate could be explained by oxidation of an early intermediate during the carboxylase reaction.

1963

Calvin's group discovers "activation" of Rubisco by preincubation with magnesium ion and bicarbonate as well as inhibition with RuBP. An enzyme—Mg—bicarbonate/CO_2 complex is proposed as the active form of the enzyme and formation of enzyme-bound CO_2 as an intermediate in the reaction is also proposed (Pon et al. 1963; Akoyunoglou and Calvin 1963).

1964

Müllhofer and Rose (1964) demonstrate that cleavage of RuBP in catalysis occurs between carbons two and three by using $^{14}CO_2$ and $^{2}H_2O$.

1965

Haselkorn et al. (1965) report the first high-resolution electron micrographs of Fraction I protein (Fig. 3) and they reveal a "central depression" which we now recognize is the "solvent channel hole." The results were interpreted to suggest a structural model consisting of 24 subunits; later this proposed structure was shown to be incorrect (Sugiyama and Akazawa 1970; Knight et al. 1989, 1990).

Trown (1965) convincingly demonstrates with spinach that Fraction I is crude Rubisco. Thornber et al. (1965) use gel electrophoretic and amino acid analysis to assess homogeneity and reach similar conclusions.

Levine and Togaski (1965) identify the first mutant lacking Rubisco in the green alga *Chlamydomonas*.

1966

Paulsen and Lane (1966) purify Rubisco to homogeneity from spinach (free of phosphoriboisomerase and phosphoribulokinase). A molecular weight of 557,000 and basic kinetic parameters are reported.

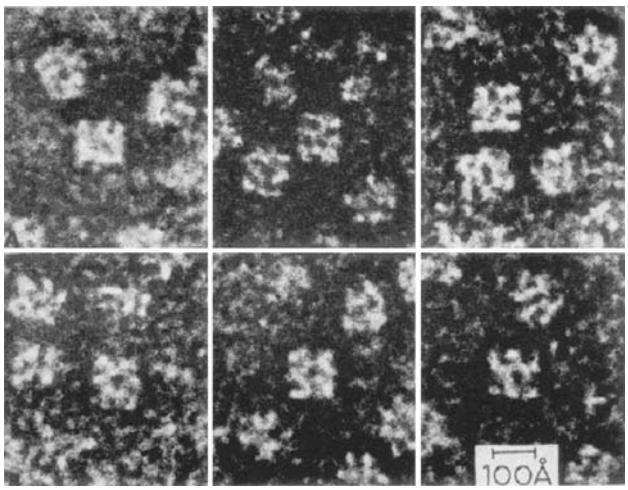

Fig. 3 Electron micrograph images of Rubisco. (From Haselkorn et al. 1965. Reprinted with permission from American association of Advancement of Science)

Based on studies of light–dark transients in metabolite levels with *Chlorella*, Al Bassham's group (Pedersen et al. 1966) concludes that there is "light activation" of Rubisco and the two bisphosphatase enzymes. Light activation of Rubisco is also indicated by subsequent studies with isolated spinach chloroplasts (Jensen and Bassham 1968). Richard Jensen and Al Bassham suggest that stromal changes in pH and Mg^{2+} are responsible for the light–dark regulation.

1967

Gel electrophoresis and gel permeation chromatography in the presence of sodium dodecyl sulfate show that Rubisco from spinach is composed of two non-identical subunits (Rutner and Lane 1967; Sugiyama and Akazawa 1967).

Irwin Rose's group (Fiedler et al. 1967) uses RuBP labeled with tritium at carbon three to demonstrate that proton abstraction is the slow step in the overall reaction and thus provide support for the Calvin group's proposed reaction mechanism of enolization followed by addition of CO_2.

1968

The first reports that Rubisco and not the physical resistance to CO_2 diffusion can be a limiting component in leaf photosynthesis appear (Waring et al. 1968; Björkman 1968a, b)

Neales and Incoll (1968) hypothesize that photosynthetic rate is controlled by the amount of assimilate in a leaf.

Rubisco in some microorganisms is found to have a molecular size that is significantly different from Fraction I protein (Anderson et al. 1968).

Evidence is obtained that phytochrome regulates the synthesis of Rubisco and other enzymes (Graham et al. 1968).

Bender (1968, 1971) shows that C_3 and C_4 plants can be distinguished by carbon isotope content, providing a simple method to classify plants with unknown pathways. These studies apparently were the result of a chance conversation between Margaret Bender and R.H. Burris about technical difficulties in ^{14}C dating of artifacts from plants (Osmond et al. 1994). Carbon isotope fractionation soon became an important tool for understanding photosynthesis and water use efficiency in ecological and physiological studies (see Farquhar et al. 1989 for details).

1969

CO_2 and not bicarbonate is shown to be the substrate for Rubisco (Cooper et al. 1969).

1970

Wishnick et al. (1970) report potent tight-binding inhibition by 2-carboxy-D-ribitol 1,5-bisphosphate, an analogue of the proposed six-carbon intermediate in the carboxylation reaction (Calvin 1954). From binding studies of the inhibitor and RuBP, Wishnick et al. (1970) propose a basic structure of eight large and eight small subunits (L8S8) for Rubisco from higher plants. This structure is consistent with contemporary studies determining molecular weight and amino acid composition (see e.g., Sugiyama and Akazawa 1970).

Using the classic inhibitors of protein synthesis, chloramphenicol and cycloheximide, Criddle et al. (1970) conclude that large subunit synthesis occurs in the chloroplast, whereas the small subunit is synthesized in the cytoplasm.

Andersen et al. (1970) identify the first Rubisco mutant in higher plants.

Huffaker et al. (1970) undertake the first studies of the effects of water stress on Rubisco but find little effect on Rubisco activity.

1971

Studies of the oxygen inhibition of isolated soybean Rubisco and comparison with earlier studies (Forrester et al. 1966) of the O_2 inhibition of soybean leaf photosynthesis lead Ogren and Bowes (1971) to conclude that Rubisco is responsible for photorespiration. Along with R.H. Hageman, they then discover that Rubisco catalyzes a reaction of the RuBP substrate with oxygen, producing phosphoglycolate (Bowes et al. 1971). Acceptance by some scientists that the oxygenase activity accounted for almost all of the glycolate entering the photorespiratory pathway was slow and controversial, partly because other proposed routes for glycolate formation had earlier received experimental support. Ogren (2003) provides a personal account of this and later contributions by his group.

Holdsworth (1971) reports that pyrenoids present in many algae contain Rubisco.

1972

Using crosses between various tobacco species and tryptic peptide mapping, Sam Wildman's group demonstrates that the small subunit is encoded in nuclear DNA (Mendelian inheritance), whereas the large subunit is encoded in chloroplast DNA (maternal inheritance) (Kawashima and Wildman 1972; Chan and Wildman 1972).

Zeigler (1972) proposes that SO_2 decreases photosynthetic rate by competitive inhibition of Rubisco.

1973

Ed Tolbert's group confirms that the Rubisco oxygenase reaction produces glycolate in studies using enzymatic synthesis of ^{14}C-RuBP and $^{18}O_2$/mass spectrometry to characterize the products (Andrews et al. 1973; Lorimer et al. 1973).

Key support for Calvin–Benson's proposed mechanism of the carboxylation reaction is provided by the chemical synthesis and studies with a key intermediate, 2-carboxy-3-ketoribitol-1,5-bisphosphate, by Siegel and Lane (1973).

Using ^{35}S-methionine, Blair and Ellis (1973) demonstrate the synthesis of the large subunit with isolated pea chloroplasts. This work removed lingering doubts about the previous use of protein synthesis inhibitors to determine sites of Rubisco synthesis.

Shively et al. (1973) discover that the polyhedral inclusions commonly found in blue-green algae (cyanobacteria) and chemoautotrophic bacteria contain Rubisco and propose the name "carboxysomes."

1974

Tabita and McFadden (1974a, b) report the first homogeneous preparation of single subunit (L2) Rubisco from

Rhodospirillum rubrum, which allows a detailed analysis of its properties (see Tabita 2004).

Laing et al. (1974) develop and validate competitive inhibition equations for Rubisco kinetics with CO_2 and O_2 as substrates by comparing the kinetic properties of soybean net photosynthesis with those of isolated soybean Rubisco. They also examine the effect of temperature on the relative affinities of Rubisco for CO_2 and O_2 and the relative carboxylase and oxygenase activities, allowing them to account for previous reports of the increase in O_2 inhibition and photorespiration with temperature.

Long-standing discrepancies in apparent affinity for CO_2 and maximal velocities of carboxylation between the isolated enzyme and chloroplasts/leaves are largely resolved by Bahr and Jensen (1974) and Lilley and Walker (1975).

Sam Wildman and co-workers (Kung et al. 1974) obtain evidence that the Rubisco small subunits might be encoded by more than one gene. This was later confirmed with Southern blotting of restriction digests of soybean nuclear DNA to reveal a multigene family of more than ten members (Berry-Lowe et al. 1982).

1975

John Ellis and co-workers (Hartley et al. 1975) report the first in vitro translation of mRNA for a plant enzyme and it results in Rubisco large subunit synthesis.

David Eisenberg's group (Baker et al. 1975) obtains a low-resolution structure of tobacco Rubisco that reveals a two-layered structure with 4-2-2 symmetry and a central channel. However, it would be over 10 years before a high-resolution tobacco Rubisco structure is obtained.

Peterson and Huffaker (1975) show that the total soluble protein lost during senescence is accounted for by a decrease in Rubisco amount but that Rubisco is still being synthesized during senescence.

1976

After years of confusion, Lorimer et al. (1976) clearly elucidate the mechanism by which pre-incubation with CO_2 and Mg^{2+} increases the activity of Rubisco.

In a review of Fraction I protein, Kung (1976) states that it is "the most abundant protein in nature." A subsequent review by Ellis (1979) popularizes this view.

O'Toole et al. (1976) show that Rubisco activity is sensitive to changes in leaf water potential and declines rapidly under severe stress.

Huber et al. (1976) discover that Rubisco is confined to the bundle sheath chloroplasts in C_4 plants.

1977

Dobberstein et al. (1977) use a cell-free wheat germ system to translate polyadenylated mRNA from *Chlamydomonas* and identify a small subunit precursor among the products, which can be processed to the correct size. They propose that the small peptide portion of the precursor plays a role in the transfer of the small unit into the chloroplast. Highfield and Ellis (1978) report similar studies of small subunit synthesis and transport into pea chloroplasts. They postulate a general model for Rubisco synthesis that proves to be applicable to other chloroplast proteins.

1978

Tobin (1978) shows that light increases the small subunit transcript.

In what might be considered an early biotechnology application, Wildman and Kwanyuen (1978) attempt to develop the ease of crystallization of the tobacco enzyme and exploit the abundance of Rubisco for commercial applications.

Several groups study the relationship between loss of Rubisco and the decline in photosynthesis during leaf senescence (Hall et al. 1978; Wittenbach 1979; Wittenbach et al. 1980; Friedrich and Huffaker 1980; Peoples et al. 1980). These studies built upon the earlier studies of the decline of Fraction I protein during senescence (see e.g., Dorner et al. 1957).

Nakamura and Saka (1978) report that ozone exposure reduces the Rubisco activity in rice leaves.

The first symposium devoted exclusively to Rubisco is held at the Brookhaven National Laboratory, Upton, NY with over 150 participants and the proceedings are published (Siegelman and Hind 1978).

1979

David Eisenberg coins the term "Rubisco" at a seminar honoring Sam Wildman (Wildman 2002).

Wong (1979) provides the first report that growth at high-CO_2 concentrations causes reduced Rubisco activity.

Pell (1979) suggests that the crystalline structures found in the chloroplast stroma of bean and cotton following ozone fumigation are Rubisco crystals.

Ku et al. (1979) find that C_3 species have 3- to 6-fold higher concentrations of Rubisco than C_4 species.

1980

Full length nucleotide sequences for the maize large subunit (McIntosh et al. 1980) and pea small subunit

(Bedbrook et al. 1980) are obtained. One year earlier, Martin (1979) obtained the amino acid sequence of the small subunit by the classic means of Edman degradation.

Barraclough and Ellis (1980) report the assembly of newly synthesized large subunits into Rubisco in isolated pea chloroplasts.

Using *Chlamydomonas*, the first structural mutation (in the large subunit) of Rubisco is obtained by Spreitzer and Mets (1980). The mutant has normal levels of Rubisco, but low rates of photosynthesis. Earlier, Nelson and Surzycki (1976) had reported the isolation of a Rubisco mutant, but it was subsequently lost and never fully characterized.

Farquhar et al. (1980) develop their now-classic biochemical model of leaf photosynthesis that merges Rubisco kinetics (developed by Laing et al. 1974), the energy requirements of carbon reduction and photorespiratory carbon oxidation and electron transport, and the dependence of electron transport on light.

Lorimer and Miziorko (1980) follow up their independent reports the previous year that the activator CO_2 is discrete from the substrate CO_2 and show that carbamate formation on a lysine residue is the basis for activation of the enzyme by CO_2 and Mg^{2+}.

Pierce et al. (1980) extend the earlier work by Wishnick et al. (1970) with epimeric transition-state analog mixtures by chemically synthesizing various transition-state analogs of the carboxylation reaction and characterize their interactions in detail. 2-carboxy-D-arabinitol 1,5-bisphosphate (CABP) is found to bind with the highest affinity and almost irreversibly.

1981

Perchorowicz et al. (1981) find that in limiting light, the extractable activity (i.e., activation state) of Rubisco and not the RuBP level changes proportionally with the steady-state photosynthetic rate of leaves. Jensen (2004) later provides a personal account of his contributions. Mächler and Nösberger (1980) performed similar studies examining the effects of light, CO_2, and temperature on extractable activity.

Using a sensitive dual-label assay, Jordan and Ogren (1981) show that the relative rates of carboxylation and oxygenation vary in different species, reflecting evolutionary change.

Weis (1981a, b) observes that the light activation of Rubisco is more temperature sensitive (and largely reversible) than electron transport and thus proposes that it plays a role in the temperature regulation of the overall photosynthetic process.

Smith and Ellis (1981) observe that light regulates the accumulation of mRNAs encoding both genes of Rubisco in peas.

Tobin (1981) finds that phytochrome regulates the expression of the small subunit of Rubisco.

Sasaki et al. (1981) show that light increases small subunit mRNA level and the rates of small subunit and Rubisco synthesis proportionately, suggesting nuclear control of Rubisco synthesis by small subunit mRNA level.

Work by several groups (Hatch and Jensen 1980; McCurry et al. 1981; Badger and Lorimer 1981; Jordan et al. 1983) clarifies the role of binding of various sugar phosphates to Rubisco in promoting either increased or decreased activation/carbamylation.

Simpson et al. (1981) follow Rubisco degradation in maize leaves and determine half lives for Rubisco ranging from 5 to 8 days that apparently vary little with the photoperiod.

The first extensive survey (Yeoh et al. 1981) of Rubisco kinetic parameters in diverse plants indicates that Rubiscos in C_4 species, aquatic plants, and algae have lower affinity for CO_2 than do C_3 and CAM species. In contrast, the variation in RuBP affinity does not correlate with the photosynthetic pathway.

1982

Schloss and Lorimer (1982) demonstrate that the transition-state intermediate of the carboxylase reaction is 2-carboxy-3-keto-D-arabinitol 1,5-bisphosphate.

Recognition that enzyme in the absence of CO_2 is inactive allows Saver and Knowles (1982) to verify that enolization of RuBP is an intermediate step in the reaction. These results are soon confirmed by ^1H NMR (Gutteridge et al. 1984a).

Somerville et al. (1982) isolate an *Arabidopsis thaliana* mutant that is defective in Rubisco activation in vivo. This mutant soon leads to the discovery of Rubisco activase (Salvucci et al. 1985).

Winter et al. (1982) conduct the first detailed analysis of the amounts of Rubisco and PEP (phosphoenol pyruvate) carboxylase in CAM (Crassulacean Acid Metabolism) plants.

1983

In contrast to previous observations with many species, the first reports (Vu et al. 1983; McDermitt et al. 1983) appear indicating that the "total" extractable Rubisco activity of soybean leaves varies diurnally due to light intensity. These

findings would later be extended to several other species and led, in 1986, to the discovery of the "nocturnal inhibitor," 2-carboxy-D-arbinitol 1-phosphate.

Jordan and Chollet (1983) characterize the tight binding of RuBP to the uncarbamylated and inactive form of Rubisco, clearly showing that it severely inhibits activation by CO_2 and Mg^{2+} and binding constants are determined.

Schmidt and Mishkind (1983) show that there is a proteolytic mechanism in chloroplasts that selectively degrades the imported but unassembled small subunits so that a precise stoichiometric accumulation of both subunits occurs.

Ozone fumigation is shown to lead to a loss of Rubisco protein (Pell and Pearson 1983).

Sasaki et al. (1983) show that phytochrome regulates the expression of both large subunit and small subunit mRNAs.

1984

Coruzzi et al. (1984) show the tissue specific and light regulated expression of one of the small unit genes present in peas.

A pea small unit gene is inserted into the Ti plasmid of *Agrobacterium tumefaciens* and transferred into petunia cells by in vitro transformation by Broglie et al. (1984). The transcripts were processed correctly and translated to yield a peptide that was located in the chloroplasts. Although the amounts of the foreign small subunit were very low relative to the native small subunit, this work raised the possibility for genetic engineering of the small subunit as well as the expression of foreign genes targeted to the chloroplasts.

Following the cloning and sequencing of the L2 Rubisco found in *Rhodospirillum rubrum* and its successful expression in *E. coli* by Chris Somerville's group (Somerville and Somerville 1984; Nargang et al. 1984), the first site-directed mutagenesis study of Rubisco is reported by Gutteridge et al. (1984b).

Using a sensitive assay procedure, Jordan and Ogren (1984) report that the CO_2/O_2 specificity of Rubisco decreases with temperature, thus largely explaining the increased inhibition of net photosynthesis by oxygen with increasing temperature. Jordan and Ogren (1984) also obtain a complete data-set on the effects of temperature on the kinetic constants. These results are soon confirmed in vivo by Brooks and Farquhar (1985) using gas-exchange measurements on spinach.

Parry and Gutteridge (1984) report reversible 'fallover' inhibition during catalysis by fully activated Rubisco.

Seemann et al. (1984) find that the specific activities of Rubiscos from C_4 species and the alga *Chlamydonomas* are about 2-fold higher than those from C_3 species.

1985

Rubisco activase is discovered by Salvucci et al. (1985). Portis and Salvucci (2002) have provided a personal account of the research.

Servaites (1985) discovers that the diurnal variation in Rubisco activity in tobacco is caused by the binding of a phosphorylated inhibitor at night. A similar inhibitor is discovered in garden bean (*Phaseolus vulgaris*) and characterized (Seemann et al. 1985).

Expression of an active L8S8 enzyme in *E. coli* is reported by three groups (Gatenby et al. 1985; Tabita and Small 1985; Gutteridge et al. 1986b), allowing future site-directed mutagenesis studies of this form of the enzyme.

Van den Broeck et al. (1985) fuse the transit peptide of the Rubisco small subunit to a foreign protein allowing its expression in the chloroplasts of tobacco. In vitro uptake and processing by isolated pea chloroplasts is also demonstrated by expression of the fusion protein in *E. coli*.

In a comprehensive study, John Bedbrook's group (Dean et al. 1985) finds wide variation in small subunit mRNA levels corresponding to the eight genes in petunia in both leaves and other organs.

J.O. Berry et al. (1985) measure polypeptide and mRNA levels of both subunits and conclude that both transcriptional and post-transcriptional controls modulate Rubisco expression in developing amaranth cotyledons.

The second major meeting devoted to Rubisco is held at a Royal Society Discussion Meeting in London, England and the proceedings are published (Ellis and Gray 1986).

1986

The "nocturnal" inhibitor is isolated from potato (Gutteridge et al. 1986a) and garden bean (J.A. Berry et al. 1987) and identified as being 2-carboxy-D-arabinitol 1-phosphate (CA1P).

Servaites et al. (1986) determine the species variation in the predawn inhibition of Rubisco which suggests that CA1P is not produced in the common crop grasses.

The first chloroplast genome is fully sequenced by Shinozaki et al. (1986).

Fluhr and Chua (1986) show that the effects of light on small subunit gene expression depend on the developmental stage of the leaves and to involve both phytochrome and a putative blue-light receptor.

Schneider et al. (1986) obtain a high-resolution structure for *Rhodospirillum rubrum* Rubisco which consists only of a dimer of large subunits.

Portis et al. (1986) obtain maximal and light-dependent activation of Rubisco at physiological concentrations of CO_2 and RuBP with a reconstituted system containing

Rubisco, activase and thylakoid membranes and thus resolve the apparent discrepancy between the CO_2 dependence of Rubisco activation in vivo and in vitro.

1987

Ritland and Clegg (1987) demonstrate the usefulness of the large subunit gene to reconstruct phylogenetic topologies. A large co-operative effort then emerges to produce a detailed phylogeny of seed plants as reviewed later by Clegg (1993).

Higher resolution (3.0 and 2.6 Å) structures of tobacco Rubisco (L8S8) are obtained by David Eisenberg's group (Chapman et al. 1987, 1988), but the fold of the small subunit proves to be incorrect.

Richard Jensen, Hans Bohnert, and George Lorimer organize a Rubisco workshop at the University of Arizona, USA with over 40 invited speakers (Fig. 4). Plans for publication of the contributions do not materialize.

1988

Boynton et al. (1988) report plastid gene transformation which raises the prospect of the genetic engineering of the large Rubisco subunit.

John Ellis' group (Hemmingsen et al. 1988) discovers that an abundant chloroplast protein, involved in the assembly of Rubisco, is related to *Escherichia coli gro*EL and the term "chaperonins" is introduced to describe these proteins (see Ellis 2004).

Werneke et al. (1988) clone the gene encoding Rubisco activase and obtain evidence of aberrant processing in the *Arabidopsis rca* (activase null) mutant.

Robinson and Portis (1988) show that Rubisco activase can release CA1P from activated Rubisco, restoring its activity.

Fig. 4 Logo from the Program Book of the 1987 Rubisco meeting at the University of Arizona

Brooks and Portis (1988) show that the changes in Rubisco activation state with light intensity in *Arabidopsis* are correlated with changes in the amount of inactive Rubisco with tightly bound RuBP.

Kobza and Seemann (1988) document variations in the mechanism (nature and amount of the inhibitor) for the light-dependent regulation of Rubisco using three different plant species.

Studies by Sage et al. (1988) of the short-term in vivo response to elevated CO_2 of Rubisco and levels of RuBP and other metabolites indicate that changes in Rubisco activation state occur to regulate the pool sizes of key photosynthetic intermediates.

Lawrence Bogorad's group (Rodermel et al. 1988; also see Bogorad 2003) creates transgenic tobacco plants containing antisense small subunit DNA in the nuclear genome and shows that Rubisco levels and plant growth, but not large subunit mRNA, is reduced. This is one of the earliest applications of antisense technology to reduce native protein expression in plants. These plants are later used in numerous investigations of photosynthesis, plant growth, and development.

1989

A high-resolution structure (2.4 Å) of spinach Rubisco is obtained by Carl-Ivar Brändén's group (Knight et al. 1989, 1990), which shows the correct fold of the small subunit and gives better assignments of the structural features for L8S8 Rubiscos in plants.

George Lorimer's group (Goloubinoff et al. 1989) achieves in vitro assembly of a prokaryotic L2 Rubisco (*Rhodospirillum rubrum*) using *E. coli* chaperonins (cpn60 and cpn10) and Mg-ATP.

Ed Tolbert's group (Houtz et al. 1989) establishes the different nature of several post-translational modifications of the Rubisco large subunit using several species.

During a sabbatical in Archie Portis' lab, Simon Robinson characterizes several key activities of Rubisco activase including ATP hydrolysis (Robinson and Portis 1989a), release of the nocturnal inhibitor, CA1P (Robinson and Portis 1988) and restoration of the slow decline of Rubisco activity with reaction time in vitro (Robinson and Portis 1989b) due to what will eventually be shown to be inhibitor formation during catalysis.

A variety of approaches (Price and Badger 1989; Pierce et al. 1989; Friedberg et al. 1989) demonstrate that Rubisco and carbonic anhydrase localization in the carboxysomes is essential for the CO_2 concentrating mechanism in cyanobacteria as proposed by a theoretical model from Aaron Kaplan's group (Reinhold et al. 1987).

Woodrow and Mott (1989) show that the rate limitation to the increase in photosynthesis, following a step increase in light intensity, is the activation of Rubisco. Subsequently, measurements on plants expressing reduced amounts of activase demonstrate that the rate of increase is proportional to activase content (Mott et al. 1997; Hammond et al. 1998a).

A convincing early report of alternative splicing in plants explains the occurrence of two polypeptides for Rubisco activase of different sizes (Werneke et al. 1989).

Gutteridge and Julien (1989) and Holbrook et al. (1989) demonstrate that the Rubisco inhibitor, CA1P, is degraded in vivo by a specific chloroplast phosphatase to yield 2-carboxyarabinitol (CA). The enzyme is purified to homogeneity by Salvucci and Holbrook (1989).

In an extensive, comparative study of acclimation of photosynthesis to elevated CO_2 in five C_3 species (Sage et al. 1989), variations in the loss of Rubisco and decline in its activation state are observed.

1990

John Andrew's group characterizes the biochemical basis of "fallover", the slow decline in the activity of some Rubiscos with reaction time as being due to side reactions that form the inhibitors, xylulose 1,5-bisphosphate and 3-ketoarabinitol 1-5-bisphosphate, during catalysis (Edmondson et al. 1990a, b, c, d). Zhu and Jenson (1991a, b) make similar observations. Later it becomes clear that 3-ketoarabinitol 1,5-bisphosphate was likely mis-identified in these studies and that the second inhibitor is D-glycero-2,3-pentodiulose 1,5-bisphosphate (Kane et al. 1998).

Pal Maliga's group creates tobacco lines with stably transformed plastids (Svab et al. 1990) and opens the way to modify the Rubisco large subunit in transgenic plants.

J.O. Berry et al. (1990) find that the mRNAs for both Rubisco subunits do not associate with polysomes in the dark and that neither subunit is synthesized in the dark. These results indicate a lack of translational initiation of both subunits in the dark.

1991

Transgenic plants expressing varying levels of Rubisco are used for a Control Theory analysis of the flux-control coefficients of Rubisco under various environmental conditions (Stitt et al. 1991).

Andrews and Kane (1991) discover that pyruvate is a minor byproduct of Rubisco carboxylation and results from the β-elimination of a phosphate ion.

For the five tomato small subunit (*rbc*S) genes, Wanner and Gruissem (1991) establish a general correlation between *rbc*S transcription and abundance but also significant post-translational control of gene expression during development.

Bartholomew et al. (1991) show that abscisic acid, increased by water stress, inhibits *rbc*S transcription in tomato plants.

Bowes (1991) provides an early, comprehensive review of the role of Rubisco in the responses of plants to elevated CO_2.

1992

Read and Tabita (1992) discover a Rubisco from a marine alga with an unexpectedly high CO_2/O_2 specificity, significantly greater than that observed in terrestrial plants. (See Tabita (2003) for his personal perspective.)

In a comprehensive study (Holiday et al. 1992) of changes in enzyme activity and metabolites in leaves during short and long-term exposure of spinach and bean (chilling-sensitive) to low temperature, Rubisco amount increased in both, but activation state increased in spinach and declined in bean.

1993

Mark Stitt's group reports (Krapp et al. 1993) detailed experiments to support the hypothesis that photosynthetic gene expression (including the transcription of the Rubisco small subunit) is inhibited by metabolic factors related to a high-carbohydrate content, thus representing a basic mechanism for the 'sink regulation' of photosynthesis.

Guy et al. (1993) characterize oxygen isotope discrimination by Rubisco and show it to be an important factor contributing to the 'Dole effect'—the steady-state difference in the oxygen isotope composition of the atmosphere and seawater.

John Andrew's group (Mate et al. 1993; Hammond et al. 1998b) demonstrates the role of activase in facilitating the rapid release of CA1P (the nocturnal inhibitor) from Rubisco in vivo by studies of tobacco plants expressing reduced levels of activase via antisense RNA transformation.

In an extensive survey, Moore et al. (1993) find that carboxyarabinitol is present in all of the vascular plants examined but it is not detected in non-vascular plants. Although the highest amounts are in the leaves, carboxyarabinitol is also present in other tissues.

In support of earlier work showing a decrease in Rubisco activity (Nakamura and Saka 1978) and content (Pell 1979) following ozone exposure, Reddy et al. (1993) measure decreased amounts of *rbc*L and *rbc*S transcripts.

Parry et al. (1993) measure the diurnal activity of Rubisco in water stressed tobacco plants and suggest a role for inhibitors other than CA1P in Rubisco regulation.

Pilgrim and McClung (1993) demonstrate differential involvement of the circadian clock in the expression of the genes involved in Rubisco synthesis (small subunit), assembly (alpha and beta chaperonin) and activation (Rubisco activase) in *Arabidopsis*.

Hartman and Harpel (1993) provide a comprehensive review of the numerous chemical modification and site-directed mutagenesis studies of the active site of Rubisco.

1994

Transgenic plants expressing reduced levels of Rubisco allow its kinetics to be inferred from gas-exchange analysis (von Caemmerer et al. 1994), further validating the mechanistic model of Farquhar et al. (1980).

Nuclear transformation of a tobacco line lacking the chloroplast *rbc*L gene with the *rbc*L preceded by a plastid targeting sequence functionally complements the defective plastids which partially restores Rubisco activity (Kanevski and Maliga 1994).

1995

Fred Hartman's group (Harpel et al. 1995) provides evidence for presumed intermediates in the oxygenase reaction by showing that hydrogen peroxide can be eliminated from an improperly stabilized peroxy adduct of the enediol to form D-glycero-2,3-pentodiulose 1,5-bisphosphate in a Rubisco mutant. Kim and Portis (2004) later use hydrogen peroxide formation to characterize oxygen-dependent Rubisco fallover with wildtype enzymes.

In a review, Bainbridge et al. (1995) report the inverse correlation between specificity factor and catalytic rates and the uncertainty surrounding the extent to which these two components can be uncoupled.

At a meeting at Institute of Arable Crops Research-Rothamsted to mark his contributions and retirement, Keys suggests that inhibitors other than CA1P and RuBP regulate Rubisco in vivo (Keys et al. 1995). Speakers at the meeting are shown in Fig. 5.

1996

Andralojc et al. (1996) propose that CA1P is synthesized from newly assimilated CO_2 via hamamelose and 2-carboxyarabinitol.

Studies (Furbank et al. 1996) of transgenic C_4 plants expressing reduced levels of Rubisco demonstrate that Rubisco activity is also a major determinant of photosynthesis in C_4 plants under high light and air levels of CO_2.

Further analysis of *rbc*S antisense lines allows Rodermel et al. (1996) to clearly show that the abundance of small subunits specifically contributes to the regulation of large subunit accumulation at the level of *rbc*L translation initiation.

Active oxygen species are shown to stimulate the association of Rubisco with the insoluble fraction of chloroplasts and the specific degradation of Rubisco large subunits into an N-terminal 37-kDa (Desimone et al. 1996) and a C-terminal 16-kDa fragment products (Ishida et al. 1997).

An extensive phylogenetic analysis of Rubisco sequences indicates rampant horizontal transfer and duplication in eubacteria and plastids (Delwiche and Palmer 1996).

1997

Parry et al. (1997) devise measurements of 'maximal' Rubisco activity and provide further evidence for the regulation of Rubisco activity by inhibitors other than CA1P but which, like CA1P, can be displaced by SO_4^{2-} ions.

The research groups of Archie Portis and Robert Spreitzer use site-directed mutagenesis of the large subunit in *Chlamydomonas* to identify a residue conferring activase preference in its interaction with Rubisco (Larson et al. 1997). Later the same approach identifies another residue (Ott et al. 2000).

1998

Cleland et al. (1998) provide a comprehensive review of all the important work contributing to our current detailed understanding of the carboxylase and oxygenase reaction mechanisms.

Kane et al. (1998) discover that non-enzymatic oxidation of RuBP produces a tight-binding inhibitor of Rubisco, D-glycero-2,3-pentodiulose 1,5-bisphosphate (PDBP). The properties of PDBP match that of the daytime inhibitor reported by Keys et al. (1995). Degradation of RuBP to form inhibitors was first systematically studied by Paech et al. (1978).

Feller et al. (1998) provide evidence that the decline in Rubisco activation state at moderately high temperatures is associated with direct effects of temperature on Rubisco activase.

Fig. 5 Speakers at the IACR-Rothamsted meeting in 1994. Front row (left to right): Roger Leigh, Bill Ogren, Peter Lea, Ulf-Ingo Flűgge, Christine Foyer, Alfred Keys, David Walker, Stephen Rawsthorne, Dimah Habash and Tristan Dyer. Middle row: Jerry Servaites, Paul Quick, Hipolito Medrano, Archie Portis, Steve Gutteridge, Barry Osmond, Ulrich Lűttge and John Andrews. Back row: Martin Parry, Richard Leegood, Howard Griffiths, J.J. van Oosten, John Gray, Nick Kruger, Matthew Paul, David Lawlor and Chris Pollock. Not pictured: D.H. Bringlow, H. Jones, M. Chaumont and G.D. Price

1999

Zhang and Portis (1999) report redox regulation of the ATP/ADP response of the larger activase isoform by thioredoxin-f and use site-directed mutagenesis to identify the critical cysteines. The results indicate that both ATP/ADP ratio and the redox state of the stroma are used to control Rubisco activity and this provides a mechanism for the light intensity dependence of Rubisco activation (see Perchorowicz et al. 1981).

Chloroplast transformation is used for targeted replacement of the large subunit of Rubisco in a higher plant (tobacco), advancing the prospect of improving photosynthesis by the genetic engineering of Rubisco (Kanevski et al. 1999).

Khan et al. (1999) show that CA1P binding protects activated Rubisco against proteolytic breakdown.

Two groups (Watson et al. 1999; Ezaki et al. 1999) characterize novel forms of Rubisco (later called Form III) from the *Archaea*.

2000

Crafts-Brandner and Salvucci (2000) demonstrate that at elevated temperatures the rate of Rubisco deactivation exceeds the capacity of Rubisco activase to promote activation. Gas-exchange studies show that when adjustments are made for the decline in activation state, the kinetic properties of Rubisco predict the response of photosynthesis to high temperature and CO_2.

A comparison by John Andrews group (Duff et al. 2000) of high-resolution structures for Rubisco complexed with various substrate analogs leads them to conclude that phosphate binding per se does not trigger closure, but that if the distance between the terminal phosphates (P1 and P2) falls below 9.1 Å the active site closes.

The "International Symposium on Photosynthetic CO_2-Assimilating Enzymes: RuBisCO and PEPC" is held at Hakone, Japan.

2001

Gas-exchange analysis of transgenic tobacco plants, with a low level of Rubisco, allows improved temperature response functions to be derived for models of Rubisco-limited photosynthesis (Bernacchi et al. 2001).

Hanson and Tabita (2001) identify a fourth form of Rubisco that lacks several conserved active-site residues. The Rubisco-like protein (RLP) in *Chlorobium tepidum* is shown to have no carboxylase activity and mutants have a pleiotropic phenotype suggesting that the RLP is involved in sulfur metabolism and the response to oxidative stress.

The structure of a Form III Rubisco with pentagonal symmetry (L2 × 5) from the hyperthermophilic archaeon *Thermococcus kodakaraensis* is reported (Kitano et al. 2001).

To test whether a foreign Rubisco can support photosynthesis in a transgenic plant, Whitney and Andrews (2001a) employ plastid transformation to replace tobacco L8S8 Rubisco with the simple L2, *R. rubrum* Rubisco and

confirm that it can function effectively within the tobacco chloroplast.

Whitney and Andrews (2001b) show that *rbc*S gene can be relocated to the chloroplast, expressed, and correctly assembled into functional Rubisco. However the plastid transgenes never exceeded 1% of the total small subunits.

2002

Transformation of an *Arabidopsis* mutant (*rca*) lacking Rubisco activase with cDNAs encoding different forms of Rubisco activase definitively shows that redox regulation of the larger activase isoform is responsible for the regulation of Rubisco activity by limiting light in species containing both isoforms (Zhang et al. 2002).

Using classic radio-tracer studies and the analysis of transgenic plants with decreased chloroplastic fructose 1,6-bisphosphate phosphatase expression, Andralojc et al. (2002) confirm the biosynthetic pathway for CA1P from newly assimilated carbon.

Sage (2002) provides an insightful review of the current understanding of Rubisco control over C_3 and C_4 photosynthesis at different temperature and CO_2 conditions and documents how Rubisco kinetic properties evolved to improve performance in the environment that the plants normally experience.

2003

A Rubisco-like protein (Form IV) in a non-photosynthetic bacteria (*Bacillus subtilis*), which lacks several critical residues for carboxylation, is shown to catalyze an enolase reaction in a methionine salvage pathway. Furthermore a growth-defective mutant is rescued by the presence of the Form II Rubisco from *Rhodospirillum rubrum*. It is suggested that Rubisco-like proteins may be the ancestral enzymes of those found in photosynthetic bacteria (Ashida et al. 2003).

2004

Rubiscos (Form III) in some anaerobic archaea are catalytically active but lack the enzyme phosphoribulokinase, necessary to form RuBP. Finn and Tabita (2004) provide evidence for an alternative route for RuBP formation using 5-phospho-D-ribose-1-pyrophosphate. Most recently, another Form III Rubisco was found to participate in adenosine 5′-monophosphate metabolism (Sato et al. 2007).

Rubisco without a complete Calvin–Benson–Bassham cycle is shown to improve the carbon efficiency of *Brassica nappus* L. embryos in the conversion of carbohydrate to oil (Schwender et al. 2004).

Onizuka et al. (2004) discover that the *rbc*X gene product can function as a Rubisco chaperonin by promoting the production and assembly of *Synechococcus* Rubisco expressed in *E. coli*.

Kim and Portis (2004) report oxygen-dependent H_2O_2 production by Rubisco.

2005

Robert Spreitzer's group identifies a small set of residues that can impart land-plant kinetic properties to *Chlamydomonas* Rubisco (Spreizter et al. 2005).

Li et al. (2005) identify two residues of Rubisco activase that are involved in substrate recognition of Rubisco.

Consistent with the hypothesis that C_3 plants growing in hot, arid conditions may have evolved forms of Rubisco with higher specificity factors, Galmes et al. (2005) identify two Mediterranean species of the genus *Limonium* whose constituent Rubiscos have high specificity factors.

Figure 6 shows a photograph of Spencer Whitney, Martin Parry, Archie Portis, Akiho Yokota, Inger Andersson, and Mike Salvucci, at an informal workshop, discussing highlights of research on Rubisco.

2006

Mutation and directed evolution of recombinant *Synechococcus* with selection in an *E. coli* strain engineered to require Rubisco catalytic activity, identifies variants with increased catalytic activity (Parikh et al. 2006).

Carré-Mlouka et al. (2006) discover that the planktonic cyanobacterium *Microcystis* contains both Form I and

Fig. 6 Spencer Whitney, Martin Parry, Archie Portis, Akiho Yokota, Inger Andersson, and Mike Salvucci *(left to right)* hold an informal Rubisco workshop at the 2005 Aussois Gordon Research Conference

Form IV enzymes. The Form IV enzyme does not display CO_2 fixation activity but catalyzes the enolization of 2,3-diketo-5-methylthiopentyl-1-phosphate, a key step in the methionine salvage pathway in bacteria.

Tcherkez et al. (2006) re-examine the inverse correlation between specificity factor and catalytic rates reported by Bainbridge et al. (1995) and conclude that Rubiscos are well adapted to their differing subcellular environments.

Interest in catalytic fallover is renewed. Consistent with earlier experiments (Salvucci and Crafts-Brandner 2004) showing that the synthesis of the catalytic misfire product, xylulose-1,5-bisphosphate, increases with temperature, Kim and Portis (2006) demonstrate that Rubisco fallover is facilitated by high temperature, a low concentration of CO_2 or Mg^{++}, and high O_2. Schrader et al. (2006) also report increased production of misfire products at elevated temperatures but suggest that structural flexibility at higher temperatures releases the inhibitors more easily and decreases fallover.

Diversions and dead-ends

In many areas of research, provocative papers appear that later become discredited or remain unresolved. Some of the more interesting ones in Rubisco research are presented below.

- As an alternative to the ene-diol intermediate, the formation of covalent bond between the RuBP substrate and enzyme via formation of a thiohemiacetal intermediate is proposed (Rabin and Trown 1964).
- Stimulation of Rubisco activity by a small pigment-containing protein (absorbance maximum at 325 nm) is reported by Wildner and Criddle (1969).
- Kung and Marsho (1976) suggest that the small subunit modifies the relative rates of carboxylation and oxygenation and that the oxygenase activity is probably not the principal source of phosphoglycolate in vivo.
- Garrett (1978) suggests that increases in ploidy increases the specificity of Rubisco thereby decreasing photorespiratory losses.
- Several groups claim that chemicals and other treatments can modify the relative rates of carboxylation and oxygenation (Wildner and Henkel 1976; Bhagwat and Sane 1978; Bhagwat et al. 1978; Okabe et al. 1979; Wildner and Henkel 1980; Van Assche et al. 1987; Schmid et al. 1987).
- Brändén (1978) claims that the carboxylase and oxgenase activities are not catalyzed by the same

Fig. 7 Several pioneers in Rubisco research. Photographs were provided by the scientists, their families or friends

enzyme and that L-3-phosphoglyceric acid formed by the enzyme is the primary substrate for photorespiration (Brändén 1978; Brändén et al. 1980a, b).

- Kaul et al. (1986) claim that dephosphorylation of the Rubisco small subunits results in dissociation of the small subunits from the large subunits and a large loss in catalytic activity.
- A non-cyclic pathway for carbon fixation is proposed by Fong and Butcher (1988).
- Anwaruzzaman et al. (1996) propose a non-chloroplast location for CA1P.
- Supercomplexes containing variable amounts of Rubisco and other stromal proteins that might allow metabolic channeling and/or regulation have been a recurring topic in Rubisco research. A review of research in this area is provided by Winkel (2004). However a general consensus on the significance, composition, and function of the Rubisco-containing complexes awaits future research.

We end this historical perspective by honoring several key players in Rubisco research (Sam G. Wildman, N. E. (Ed) Tolbert, Richard G. Jensen, William L. Ogren, T. John Andrews, George H. Lorimer, and Fred C. Hartman) by showing their photographs (Fig. 7).

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