The study of Awasthi *et al.* highlights the importance of vesicle cycling on both sides of the synapse. Clarification of the cell biology of how postsynaptic weights are weakened shifts the spotlight to questions about the spatiotemporal allocation and reallocation of such weights. We speculate that the internalized glutamate receptor vesicles are a synaptic resource too precious to waste and can be redistributed among nearby dendritic spines to strengthen nearby postsynapses (*11*), much as vesicles of neurotransmitters can be reallocated among presynaptic boutons along an axon (*12*). This study begins to show how neurons might use similar tools pre- and postsynaptically to channel resources to the most important synapses while culling synapses that no longer encode relevant information.

The work of Awasthi *et al.* has a close yet unexplored relationship to pathological processes in neuropsychiatric and neurodegenerative disorders. The exaggerated removal of glutamate receptors, including GluA2 receptors, is a feature of Alzheimer's disease (AD) (*13*) and potentially linked to the associated forgetting. This process involves protein interacting with C kinase-1 (PICK1), another mediator of GluA2 receptor endocytosis (*14*), but the role of SYT3 and the relationships between PICK1, SYT3, and other proteins involved in GluA2 receptor endocytosis remain unclear. This pathophysiological endocytosis could contribute to the memory loss experienced by AD patients, and we speculate that pharmacological interventions that restore normal GluA2 receptor endocytosis could help mitigate these defects. Furthermore, behavioral inflexibility is a hallmark of autism spectrum disorders (ASD) and might be assigned to deficits in forgetting, as supported by five fruitfly models of ASD risk genes (*2*). In another study, patients with ASD were asked to choose the location of a stimulus. Although they performed equally well as the control patients, the ASD patients showed extra reversion back to the original location even after the stimulus location changed (*15*). Elucidation of mechanisms of this inflexibility will benefit from the insights that Awasthi *et al.* have elegantly provided. ■

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METABOLISM

Improving crop yield

Synthetic photorespiration bypass increases crop yield

By **Marion Eisenhut** *and* **Andreas P. M. Weber**

The enzyme ribulose 1,5-bisphosphate carboxylase-oxygenase (RuBisCO) is one of the most abundant proteins on Earth. During photosynthesis, it assimilates atmospheric CO_2 into biomass and hence is a major driver of the global carbon cycle. However, the enzyme is catalytically imperfect. It accepts not only CO_2 as a substrate, but also O_2, which leads to the formation of a toxic byproduct, 2-phosphoglycolate (2-PGlycolate) (*1*). The metabolic pathway photorespiration detoxifies 2-PGlycolate, and it is essential for performing photosynthesis in an O_2-containing atmosphere. Importantly, photorespiration causes a 20 to 50% yield penalty, depending on the environmental conditions and the type of photosynthesis employed (*2*). Multiple attempts have been undertaken to overcome this yield penalty and thereby increase biomass production in plants, with limited success to date. On page 45 of this issue, South *et al.* (*3*) present a synthetic pathway that fully detoxifies 2-PGlycolate inside plant chloroplasts. Transgenic tobacco plants expressing this pathway show strongly enhanced biomass production in field trials, suggesting that this could be used to improve crop yields.

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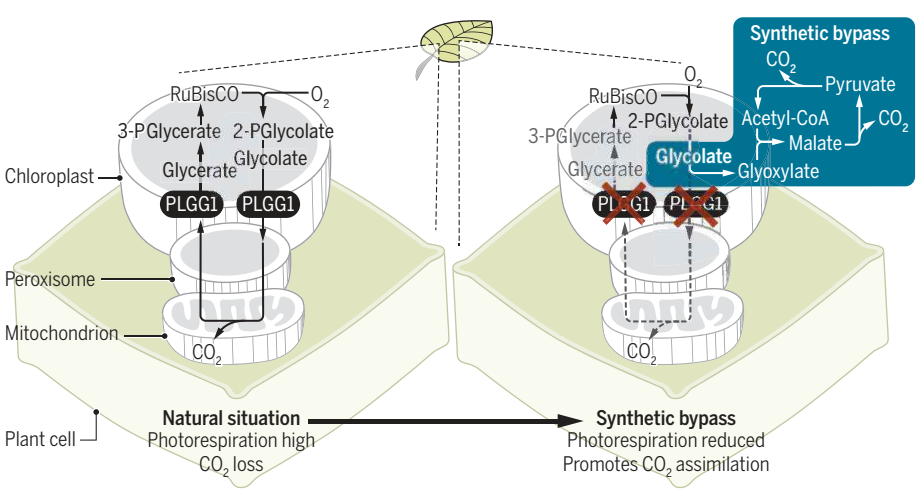
Photorespiration is an essential metabolic repair pathway in all organisms that perform oxygenic photosynthesis, from cyanobacteria, through algae, to land plants (*2*, *4*). Core photorespiratory metabolism comprises nine enzymatic steps that are distributed over chloroplast, peroxisome, and mitochondrion within a plant cell. It converts detrimental 2-PGlycolate into the Calvin-Benson cycle intermediate 3-PGlycerate and thereby returns 75% of otherwise unusable carbon to photosynthetic metabolism. However, during this salvage pathway, 25% of previously fixed CO_2 gets lost, and energy is consumed (see the figure). Hence, albeit essential, photorespiration is also considered a wasteful and inefficient process (*2*). Accordingly, photorespiration has been identified as a prime target for engineering to improve crop yields, and diverse strategies have been developed to improve photosynthetic efficiency by reducing photorespiration and/or enhancing the CO_2 fixation processes. Some of these attempts are inspired by naturally occurring CO_2-concentrating mechanisms present in, for example, cyanobacteria and algae. Others are based on implementing synthetic metabolic routes to redirect the canonical pathway of CO_2 assimilation and photorespiration (*5*).

Engineering wasteful photorespiration into a beneficial process

The fixation of O_2 by RuBisCO in chloroplasts leads to high rates of photorespiration and a concomitant loss of CO_2 from mitochondria. A synthetic bypass and the restricted activity of PLGG1 allow metabolism of glycolate with release of CO_2 inside of the chloroplasts, which promotes CO_2 fixation by RuBisCO and improves yield.



GRAPHIC: A. KITTERMAN/*SCIENCE*

South *et al.* revisited two previously established synthetic bypasses of photorespiration (*6*, *7*) and tested a newly designed pathway in genetically modified tobacco plants. These pathways aim to completely metabolize the photorespiratory metabolite glycolate, which is generated from 2-PGlycolate by phosphoglycolate phosphatase within the chloroplast. They release CO_2 close to RuBisCO (not in mitochondria, as in natural photorespiration) to increase the ratio of CO_2 to O_2 fixation. Alternative pathway (AP) 1 originates from the bacterium *Escherichia coli* and uses five enzymes that oxidize glycolate via glyoxylate and tartronic semialdehyde to glycerate (*6*). The second bypass, AP2, uses three enzymes that convert glycolate via glyoxylate and malate to acetyl–coenzyme A (CoA). AP2 also requires the expression of catalase for detoxification of hydrogen peroxide that results from conversion of glycolate to glyoxylate by glycolate oxidase (*7*). AP1 and AP2 were previously shown to increase biomass (*6*, *7*). AP3 was newly designed by South *et al.* In AP3, only two transgenes had to be introduced into the plant chloroplast: a glycolate dehydrogenase that converts glycolate into glyoxylate derived from the green alga *Chlamydomonas reinhardtii* was redirected to tobacco chloroplasts, and similar to AP2, a malate synthase was expressed to convert glyoxylate to malate and eventually to acetyl-CoA via the native chloroplast-resident nicotinamide adenine dinucleotide phosphate (NADP)–malic enzyme (see the figure). Using the green algal glycolate dehydrogenase instead of plant glycolate oxidase prevents production of hydrogen peroxide, and hence additional expression of catalase is unnecessary.

Two important differences from the original pathway designs (*6*, *7*) represent major advances. Besides introducing a synthetic bypass, South *et al.* also reduced the expression of PLASTIDIAL GLYCOLATE/GLYCERATE TRANSPORTER 1 (PLGG1) (*8*). This modification was suggested previously (*9*) to increase the potential of synthetic bypasses, because it restricts the export of glycolate from chloroplasts and hence promotes its consumption by the synthetic bypass. A larger portion of glycolate is decarboxylated within the chloroplast by the synthetically engineered bypass, leading to enhanced CO_2 fixation activity of RuBisCO. This comes with an impressive yield gain of more than 40%. Importantly, yield improvements positively correlated with the expression levels of the introduced enzymes, which highlights the importance of high and balanced expression of the transgenes. Typical annual yield gains in crop breeding are below 2%; hence, the synthetic pathway holds potential for a step change in yield improvement by genetic modification of crops. In contrast to earlier work (*6*, *7*), the pathways were introduced into the model crop tobacco, which was investigated not only in growth chambers and greenhouses, but also in field trials. Thus, the yield gains manifested in an agriculturally relevant scenario and not only in controlled environments.

Importantly, the synthetic pathways open new avenues for reevaluating long-standing hypotheses regarding the importance of photorespiration beyond detoxification of 2-PGlycolate. Photorespiration is considered indispensable for photosynthesis in an O_2-containing atmosphere, and mutants defective in photorespiration can only survive in a high-CO_2 atmosphere (*10*). Genetic suppressor screens on such mutants have been unsuccessful to date. The study of South *et al.* demonstrates that a photorespiratory phenotype (repression of *PLGG1*) can be suppressed by metabolic engineering. The true reason or reasons for the indispensability of photorespiratory metabolism are intensely debated and include the detoxification of 2-PGlycolate; carbon salvage; biosynthesis of the amino acids glycine and serine (*11*); generation of activated C1-units; and protection from photoinhibition and dissipation of excess excitation energy (*2*, *12*, *13*). The work of South *et al.* indicates that plant metabolism adapts to the synthetic pathways and compensates for reduced flux through the peroxisomal and mitochondrial parts of native photorespiration. This implies that 2-PGlycolate detoxification and carbon recycling are the critical functions of photorespiration.

Recently, the optimization of a mechanism that protects plants from excess light, nonphotochemical quenching (NPQ), which is dissipation of excess excitation energy as heat, afforded appreciable yield gains (*14*). It is important to test whether a combination of engineered photorespiration with optimization of NPQ will enable additive yield gains. Realizing the yield gains afforded by the synthetic bypass in crops will require genetic engineering because the required enzymes are not present in plant genomes and hence cannot be targeted by breeding or genome editing technologies. ■

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ATOMIC PHYSICS

Really cool neutral plasmas

Properties of laser-cooled neutral plasmas can be used to model high–energy-density plasmas

By **Scott Bergeson**

Plasmas are supposed to be hot. Hydrogen nuclei undergo fusion in the Sun because plasma temperatures and pressures are so high. On page 61 of this issue, Langin *et al.* (*1*) report on a completely different kind of plasma by photoionizing a laser-cooled gas of strontium atoms. The ion temperature is a chilly 0.05 K, so thermal speed of the ions is equivalent to a person taking a brisk walk. Surprisingly, the properties of this low-density, low-temperature plasma provide clues about the workings of high–energy-density physics relevant for fusion power research.

A very simple description of a plasma is that it is an ionized gas. In equilibrium, ionization occurs when the temperatures are high enough and when charged particles in the plasma are moving fast enough that collisions tear electrons away from their parent atoms and ions. The Boltzmann equation is the main tool for modeling the plasma environment (*2*). With a handful of approximations and extensions, this and related equations successfully describe processes used to create integrated circuits, light neon signs, and generate colorful flames. This success is somewhat surprising because the collisions occur through Coulomb interactions, which are long-range interactions and lead to many-body effects, but the Boltzmann equation is based on two-body collisions in a low-density environment. However, effective collision cross sections that include many-body effects can be calculated (with help from Chapman, Enskog, Bogoliubov, and others), so these kinetic theories can often give very accurate results (*3*, *4*).

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