PUBLISHED: 15 MAY 2017 | VOLUME: 3 | ARTICLE NUMBER: 17071

PHYSIOLOGICAL EVOLUTION

Genomic redox footprints

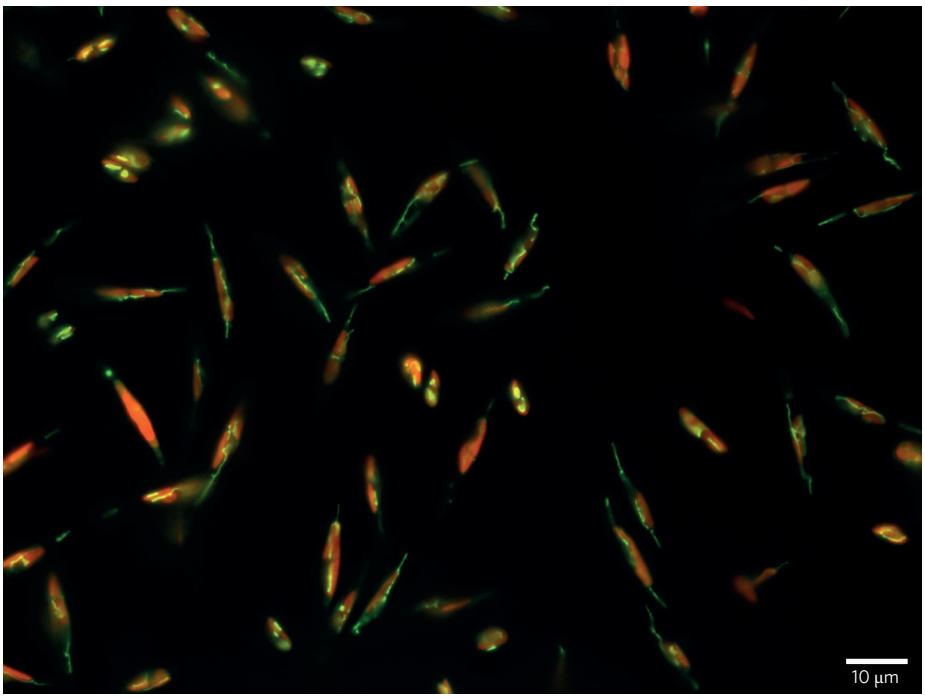
Cell metabolism relies on redox reactions to harness energy for life. Cells need to sense and regulate their internal redox state, typically with cysteine thiols. At plastid origin, cysteine residue frequency increased in the diatom genome lineage, an evolutionary redox footprint preserved in plant DNA.

William F. Martin and Helmut Sies

When plastids arose from cyanobacteria via endosymbiosis more than a billion years ago, they brought photosynthesis to the eukaryotic lineage. Photoautotrophy has many advantages, but like everything in evolution, it comes at a price. The photosynthetic electron transport chain is similar to a high-voltage power line: it delivers valuable energy, but it is dangerous. If photon-powered electron flux from water to $NADP^+$ gets only slightly out of balance, 'hot' electrons exit the thylakoid membrane to generate reactive oxygen species. Sensing such imbalances, and sending the signals to regulate it, is typically the job of nature's most underrated element: sulfur. In cells, sulfur-based signalling involves proteins that harbour cysteine residues. Did the origin of plastids induce an increase in the number of redox-sensitive cysteine residues in proteins? Yes, so say new findings.

Writing in *Nature Plants*, Woehle *et al.*[1] report the evolutionary history of the redox-sensitive cysteine residues in the diatom *Phaeodactylum tricornutum*. They find that the number of redox-sensitive cysteines in the proteome has increased during evolution and that these increases correspond to the origin of plastids. That the introduction of a new electron transfer chain (photosynthesis) into the eukaryotic lineage was accompanied by an increase of cysteine residues in proteins responding to the physiological state of the cell is an interesting finding, providing food for thought on the role of redox chemistry in evolution.

Life is a chemical reaction. At the core of all life processes is an energy-releasing chemical reaction, a redox reaction, in which electrons move from a donor to an acceptor. When harnessing chemical energy, cells do not explode, nor do they emit lightning bolts or even sparks. Rather, enzymatic reaction sequences release energy slowly and in such a way that the cell can conserve a portion of it in the form of ATP, life's currency of chemical energy. Coupling of ATP hydrolysis drives the reactions of life forward. Making the exergonic chemical reaction go forward is perhaps the essence of life itself. Electron flow fuels life, whether driven by environmentally available chemical redox couples (chemosynthesis) or light (photosynthesis).



SHIRI GRAFF VAN CREVELD

Figure 1 | Fluorescent mitochondria and chloroplasts in the diatom, *Phaeodactylum tricornutum*. The roGFP (reduction–oxidation sensitive green fluorescent protein) probe is expressed to label mitochondria (green). Chloroplasts are in red due to chlorophyll autofluorescence.

Photosynthetic electron flow needs to be carefully monitored by the cell, especially in the presence of molecular oxygen, O_2, otherwise the cell is confronted with a phenomenon known as oxidative stress — a concept that one of us introduced into the literature over 30 years ago[2]. All cells harness electron flow and therefore need to manage the threat to the cell presented by electrons that might 'step out of line' *en route* from donor to acceptor. Such rogue electrons can cause damage within the cell. To avoid that damage, all cells need to maintain redox balance, regardless of whether they are confronted with oxygen or not. In order to monitor the redox state and maintain balance, cells possess rather elaborate molecular mechanisms that are involved in redox sensing, signalling and regulation — both in prokaryotic[3] and eukaryotic[4] cells, and in aerobes as well as anaerobes[5]. These machineries utilize both one-electron and two-electron reactions and very often entail the oxidation states of sulfur[4] in the form of thiols (–RSH), disulfides (–RSSR–), trisulfides or, more recently recognized, even tetrasulfides (–RSSSSR–)[3]. Yet the most well-known and widespread mechanism to sense and transmit information about the redox state of the cell involves cysteine thiols.

A classic example in plants is the thioredoxin (Trx) system[6] in plastids that oxidizes NADPH produced by the

photosynthetic electron transport chain in order to reduce the cysteine disulfides in Trx. Reduced Trx (the thiol form) then transfers reducing equivalents to the redox-sensitive cysteine residues in several enzymes of the Calvin cycle, the reduced forms of which are active[6]. Upon light exposure, the photosynthetic electron transport chain thus switches carbon fixation on, while in the dark the redox-sensitive cysteine residues are reoxidized[6], shutting the Calvin cycle down to avoid futile cycles. Over evolutionary time, selection pressure to maintain well-regulated electron flow in a safe state within the cell is bound to leave imprints in the genome. That is exactly what the findings uncover[1], manifested as an evolutionary increase of redox reactive cysteine residues in diatom proteins.

The evolutionary influence of redox sensing and regulation on cysteine frequencies has been investigated before, but at a more coarse-grained level, and in studies that included humans[7]. In humans, redox regulation keeps the flux of electrons from sugars, fats and amino acids to O_2 in our respiratory chain in check. An average human consumes around 500 litres of O_2 (about 22 mol) per day[8]. That means that on the order of 5×10^{25} electrons flow through our mitochondrial respiratory chains each day. Ideally, those electrons need to reach O_2 properly via cytochrome *c* oxidase (complex IV). If the flow of electrons through the respiratory chain is not carefully regulated and monitored, it elicits oxidative stress. Cells sense even very slight imbalances in electron flux, however, such that even minute perturbations can have important positive regulatory and signalling effects, termed 'oxidative eustress'[4].

In plants, of course, the production of reactive oxygen species poses a double danger because is there not only the risk of generating them via the mitochondrial respiratory chain and NADPH oxidases, there is also the photosynthetic electron transport chain in plastids with the formation of electronically excited triplet states and singlet molecular oxygen for the cell to worry about (Fig. 1). Plants cannot easily turn off their photosystems, meaning that when there is light there is electron transport from water to ferredoxin within the thylakoid membrane. Plastids have mechanisms to sense the redox state of the plastoquinone pool that have been conserved since plastid origin[9]. The new findings will likely prompt a search for evidence of redox imprints in the genomes of other eukaryotic lineages. Especially in the plant lineage, the transition of life from water to land[10] looks like a prime candidate for finding further genomic redox footprints. ❐

William F. Martin is at the Institute for Molecular Evolution, Heinrich-Heine-University Düsseldorf, 40225 Düsseldorf, Germany. Helmut Sies is at the Institute for Biochemistry and Molecular Biology I and Leibniz Research Institute for Environmental Medicine, Heinrich-Heine-University Düsseldorf, 40225 Düsseldorf, Germany.
e-mail: bill@hhu.de; sies@hhu.de

References

1. Woehle, C. *et al. Nat. Plants* **3,** 17066 (2017).
2. Sies, H. in *Oxidative Stress* (ed. Sies, H.) 1–8 (Academic, 1985).
3. Shimizu, T. *et al. Proc. Natl Acad. Sci. USA* **114,** 2355–2360 (2017).
4. Sies, H., Berndt, C. & Jones, D. P. *Annu. Rev. Biochem.* http://doi.org/b6gx (2017).
5. Olson, K. R. *et al. Redox Biol.* **12,** 325–339 (2017).
6. Buchanan, B. B. & Balmer, Y. *Annu. Rev. Plant Biol.* **56,** 187–220 (2005).
7. Miseta, A. & Csutora, P. *Mol. Biol. Evol.* **17,** 1232–1239 (2000).
8. Engelberg, J. *Am J. Physiol.* **271,** S43–S44 (1996).
9. Allen, J. F. *Proc. Natl Acad. Sci. USA* **112,** 10231–10238 (2015).
10. de Vries, J., Stanton, A., Archibald, J. M. & Gould, S. B. *Trends Plant Sci.* **21,** 467–476 (2016).

Competing interests

The authors declare no competing financial interests.