# Structure

Volume 20
Number 1
January 11, 2012

www.cellpress.com

# The Rise of Oxygen and Aerobic Biochemistry

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DOI 10.1016/j.str.2011.12.006

**Analysis of conserved protein folding domains across extant genomes by Kim et al. in this issue of *Structure* provides insights into the timing of some of the earliest aerobic metabolisms to arise on Earth.**

If we could travel back in a time machine to more than 2.5 billion years ago, what would early biochemistry have looked like? As enticing as the question is, it is frustratingly difficult to answer for the simple reasons that so little is physically preserved from that era, and what is preserved is so old as to make any molecular biological analyses suspect. Yet, there are geochemical clues about what the oceans, where life almost certainly arose, looked like. For example, changes in the abundances of isotopic signatures for sulfur (Canfield, 1998) and iron (Rouxel et al., 2005) show the ocean to have been a chemically reduced environment, lacking in oxygen, rich in reduced iron, and with intermittent increases in sulfide. Recent analyses of the reactive iron component in ancient sedimentary rocks also show that this deepwater ferrous iron, and with it the requirement of low oxygen abundances, persisted until the late Proterozoic Era (742–542 million years ago), indicating that the reducing capacity of the ocean abyss was so great that photosynthetic oxygen could only accumulate in the surface ocean and atmosphere over a very long time (Planavsky et al., 2011; Poulton and Canfield, 2011). While the precise date of the advent of oxygenic photosynthesis has been a somewhat controversial subject in recent years, it is clear that when this event occurred, the self-replicating mechanism for production of oxygen in a reduced world was, depending on individual perspective, both a revolutionary and catastrophic event. Life up to that point was anaerobic, and the rise of a photoautotroph that would split water and release oxygen as a waste product was a threat to the biochemical status quo. The selection pressure that led to the use of water as an electron source was likely due to the depletion of sulfide (or another electron source) by sulfur-based photoautotrophy in the oceans. Yet once having arrived, abundant $O_2$ would offer a wealth of biochemical and energetic opportunities.

So what is a cell to do when its neighbor is thriving while poisoning the planet's oxygen? There are two options: hide in the refugia of anoxic ocean basins (such as the Black Sea) and vast ocean sediments, or to adapt to the new chemical environment. From extant (currently alive) life, we know that both occurred, but understanding biochemical evolution in deep time is challenging. In recent years there have been a few advances in unraveling ancient biochemistries by examining physiological and genomic datasets, with the assumption that there are characteristics that remain in extant life that are vestigial from an ancient ocean. For example, it has become apparent that the choice of metal atoms within proteins, and the resultant metal requirements (specifically Co, Zn, Cu, Fe, Mn, and Ni) of microbes descendant from early microbes, are remarkably consistent with having co-evolved with the gradual oxygenation of the surface ocean and atmosphere (Anbar and Knoll, 2002; Dupont et al., 2010; Saito et al., 2002, 2003).

In this issue of *Structure*, Kim et al. (2012) extend these efforts by applying a recently developed protein-fold-based molecular clock (Wang et al., 2011) toward the problem of unraveling the origin of the early oxygen dependent biochemical pathways. One of their key findings is that the most ancient aerobic metabolisms were related to biosynthesis rather than energy generation, with the pyridoxial 5-phosphate synthase enzyme being the oldest aerobic enzyme identified, having evolved ~2.9 billion years ago. Interestingly, this timing predates even some of the earliest estimated dates of oxygenic photoautotrophy (Summons et al., 1999). Moreover, with di-oxygen now believed to have been relegated to the surface oceans or isolated environments until ~542 million years ago (Poulton and Canfield, 2011), the authors invoke the roughly concurrent evolution of Mn catalase and its reaction with hydrogen peroxide as a potential source of di-oxygen for these early aerobic reactions, although additional mechanisms may also have existed, such as nitrite-driven anaerobic methane oxidation (Ettwig et al., 2010).

The observation that these early aerobic enzymes were involved in biosynthesis rather than energy generation makes logical sense; the scarcity of early di-oxygen abundances would have restricted the extent of oxygen-utilizing reactions, with biosynthesis reactions needing less $O_2$ than respiratory activities (although Kim et al. point out that the high $K_m$ values for $O_2$ of the pyridoxial 5-phosphate synthase enzyme, again perhaps, reflect small quantities of biosynthesis products needed). The implication here is that the onset of oxygen-utilizing biochemistry need not be tied to the advent of oxygen-evolving photoautotrophy, a notion that is consistent with the recent finding of a gradual increase in oceanic oxygen (Canfield et al., 2008; Poulton and Canfield, 2011). In addition, Kim et al. (2012) describe a sequential rise of amino acids involved in biosynthesis, which has implications for metal binding sites and corroborates previous metal binding domain estimates (Dupont et al., 2010). Finally, the authors describe a late rise of secondary metabolism, such as antibiotic resistance, UV-radiation protection, defense, and antioxidant activities.

The study of life in Earth's deep time history is exciting but fraught with difficulty. Physical rock samples are relatively rare, the biological tissue component within long degraded, and the biological

influences on isotopic, organic, and inorganic chemical signatures in rocks, while powerful, are potentially subject to the influence of diagenetic processes and assumptions about ancient biochemistries (Fischer et al., 2005). The genome-based analyses, such as the application of conserved protein folding domains used by Kim et al. (2012), offer an important new tool in constraining this Proterozoic oceanscape. Yet, with these technical advances also comes a new challenge: the building of bridges across the cultural and scientific divides between biochemists and geochemists in order to further explore the co-evolution of life and biogeochemistry throughout Earth's history.

ACKNOWLEDGMENTS

The author is grateful to Ariel Anbar and Chris Dupont for helpful comments. Funding support was from the National Science Foundation Chemical Oceanography and the Gordon and Betty Moore Foundation.

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# Couple Dynamics: PPARγ and Its Ligand Partners

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**Ligand-regulated transcriptional activity is the most important property of nuclear receptors, including PPARγ. In this issue of *Structure*, Hughes et al. determined how the dynamic conformations of ligands and the receptor contribute to the degree of ligand-dependent activation of PPARγ, which provide further insights into design of PPARγ-based anti-diabetic drugs.**

PPARγ, a key activator of adipogenesis, is also the molecular target of the thiazolidinedione (TZD) class of anti-diabetic drugs such as rosiglitazone and pioglitazone. These TZD drugs are full agonists of PPARγ that are able to promote adipocyte differentiation. Although TZDs improve insulin sensitivity and glucose metabolism, they have been associated with severe side effects including fluid retention, weight gain, and cardiovascular diseases. The major challenge of PPARγ-based drug discovery is how to retain the beneficial glucose-lowering effects of PPARγ ligands but avoid their undesired side effects. The attempts to overcome such challenges have been blocked by the lack of basic understanding of how PPARγ activation by small molecule ligands is linked with their anti-diabetic effects. A series of recent papers, including the one by Hughes et al. (2012) in this issue of *Structure*, begin to shed light into complex mechanisms that link PPARγ activity with insulin sensitivity and glucose metabolism.

PPARγ and two related receptors PPARα and PPARδ/β comprise a subfamily of nuclear receptors, whose transcription activity is tightly controlled by the conformation of an activation helix (AF-2), which resides in the C terminus of the ligand binding domain. PPARγ is known to have a ligand-independent basal activity (Xu and Li, 2008). As shown in Figure 1, in the absence of any ligand, the AF-2 helix of PPARγ is in equilibrium between closed (active) and open (inactive) conformations (Nolte et al., 1998). The binding of activating ligands, such as TZD or fatty acids, locks the AF-2 in the active conformation through a tight interaction between the AF-2 helix and the bound ligand (Gampe et al., 2000;