to demonstrate with certainty that disease risk is mediated through one specific type of regulation. Further complicating matters, many genetic effects on gene expression or splicing are restricted to highly specific cell types or cell states[5]. Consequently, variants that seem to be specifically associated with RNA editing in the GTEx data set might turn out to control gene expression or splicing in cell types not included in GTEx, such as immune cells.

Because Li and colleagues focused on *cis* variants, a key next question is whether *trans* variants, which have broad effects on RNA editing across the genome, might also have a part to play in the risk of autoimmune disease. If so, does this effect involve innate immune activation triggered by the formation of double-stranded RNA, as the authors propose for *cis* edQTLs? Perhaps large-scale meta-analyses of genomes and RNA sequences such as those conducted by the eQTLGen consortium[6] could help to provide an answer.

Li and colleagues' study reaffirms the value of open data sharing — this work would not have been possible without publicly available data sets. At the same time, it highlights the limitations of current data-sharing systems. Although smaller data sets covering immune cell types exist (for example, those documented in refs 7 and 8), obtaining access to many smaller studies is a bureaucratic maze that few are willing to navigate. To increase the pace of science, researchers need to come up with mechanisms to reduce these administrative hurdles while protecting the privacy of study participants.

Li and colleagues' study highlights the importance of considering all possible mechanisms by which a genetic variant might influence disease risk, and raises the intriguing prospect that at some loci, the genetic effect might be entirely mediated by RNA. Although these individual loci probably have small effects on disease risk, more loci are likely to be discovered as autoimmune genetic studies increase in scale. Thus, researchers and clinicians should be mindful of this possibility when prioritizing new therapeutic targets for autoimmune disease.

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Palaeoceanography

Plate tectonics lets the ocean breathe

Katrin J. Meissner & Andreas Oschlies

Variations in ocean oxygen levels during Earth's history have been linked to evolution and mass extinctions. Simulations now suggest that the configuration of the continents has a substantial impact on ocean oxygenation. **See p.523**

On page 523, Pohl *et al.*[1] present simulations of ocean states spanning the past 540 million years — the first study to systematically investigate ocean circulation and oxygenation changes over such a long time frame. They find that changes in the configuration of the continents alone can generate large variations in deep-ocean (benthic) oxygenation through changes in ocean circulation. The simulations were conducted using present-day levels of atmospheric oxygen, and demonstrate that benthic oxygen records of the past are not a reliable proxy for ancient atmospheric oxygen concentrations. Moreover, under certain continental arrangements, the authors' simulations produce self-sustained oscillations of ocean oxygen levels on timescales of several thousand years.

> **"The study highlights the complexity of the processes that can affect ocean oxygenation."**

Oxygen is a prerequisite for the evolution of complex organisms, and essential for those that have aerobic metabolisms. Although today's atmospheric oxygen levels are more than sufficient to sustain multicellular life on land, many regions in the present-day ocean are starved of oxygen. Global warming will lead to further ocean oxygen loss, a situation that has precedence in Earth's history — there is evidence for previous large-scale deoxygenation events[2,3], some of which are thought to have caused mass extinctions[4].

Seawater oxygen levels depend on a series of complex biological, chemical and physical processes. The oxygen is supplied through photosynthesis and air–sea gas exchange in the surface layer, and consumed by the breakdown (respiration) of organic matter by microorganisms, both at the surface and in the dark ocean interior. Sea-surface oxygen concentrations are largely controlled by the temperature-dependent solubility of oxygen in seawater. Wherever sea-surface waters are carried to the deep ocean, they initially retain the oxygen levels associated with the surface temperature. In the ocean interior, oxygen concentrations then decline along the flow of the water, because the oxygen is increasingly consumed as a result of bacterial respiration of organic matter sinking from biomass produced at the surface.

Ocean circulation controls the period of time that waters spend in the deep ocean without contact with the atmosphere; during this time, they continuously lose oxygen through respiration. Circulation also controls the supply of nutrients to the surface ocean — and thus the productivity of marine phytoplankton and the amount of organic matter available for respiration. Changes in ocean circulation, and the resulting effects on oxygen supply and consumption, are thought to be a dominant mechanism for the ocean deoxygenation that has been observed during the past few decades[5,6].

Pohl *et al.* simulated the global ocean at 28 points in time, producing a snapshot every 20 million years. Two series of simulations were generated, one with constant global mean surface air temperatures and another with constant greenhouse-gas concentrations. In both series, the authors used the continental configuration appropriate for each time point, but kept solar luminosity, atmospheric oxygen levels and the ocean's nutrient inventory the same. Their approach was therefore not designed to reconstruct climate and ocean oxygen concentrations to match current best knowledge of the prevailing conditions, but to estimate the impact of ocean circulation on oxygen levels through time.

The simulations show that surface oxygen concentrations are mostly temperature-driven, with cold waters being more oxygenated than warm waters. Changes in oxygen concentrations in the subsurface (around 90–190 metres depth in their study) are influenced by biological activity, with high production rates at the

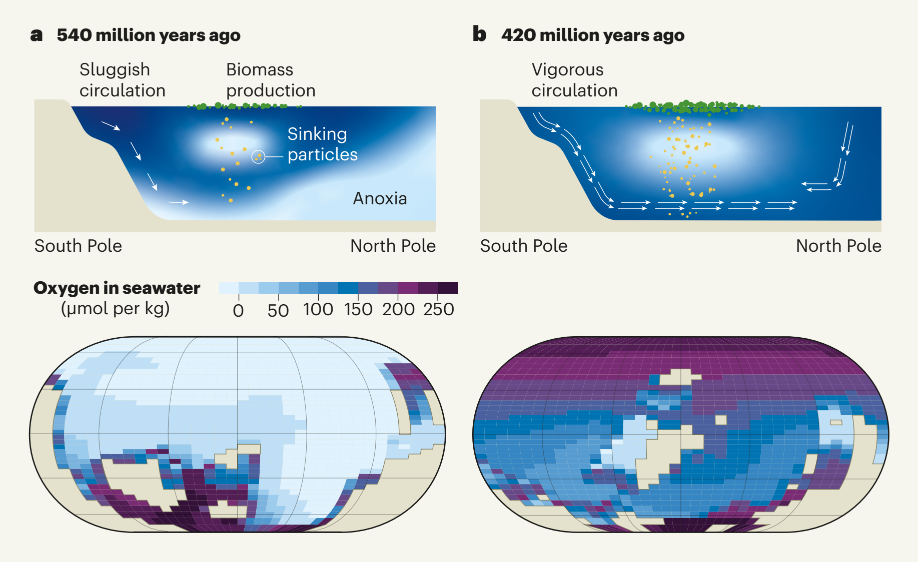

Figure 1 | The effects of continental configuration on ocean circulation and oxygenation. Pohl *et al.*[1] simulated the state of the global ocean at 28 time points spanning the past 540 million years, and find that continental configuration exerts large effects on circulation and oxygen levels. **a**, During the early Palaeozoic, 540 million to 460 million years (Myr) ago, ocean circulation was weak, leading to very low oxygen levels (anoxia) in the deep ocean (simulated data[1] for the deep ocean 540 Myr ago are shown in the lower panel). Low-oxygen regions also formed at subsurface depths (around 90–190 metres) as a result of microbial decomposition of organic particulates sinking from biomass produced at the surface. **b**, By contrast, circulation in more recent periods could be vigorous, oxygenating the deep ocean (lower panel shows simulated data for 420 Myr ago). Higher rates of biomass production at the surface might have produced larger subsurface low-oxygen regions during some periods. The cartoons of ocean circulation and oxygenation indicate broad trends, and are not quantitative.

surface leading to high oxygen consumption at the subsurface. Changes in the deep ocean (depths greater than 1,000 m) are mostly driven by the strength of the circulation, with sluggish circulation leading to low oxygen levels and vigorous circulation to higher oxygen levels. Although these results are not surprising, Pohl and colleagues' study is the first systematic analysis of circulation changes, and the associated changes in oxygenation, over such a long time span.

The authors' simulations show that the continental configurations of the early Palaeozoic era, 540 million to 460 million years ago, lead to weak deep-ocean ventilation (renewal of deep waters by surface waters) and very low bottom-water oxygen levels (Fig. 1). This is interesting, because ocean models usually struggle to simulate stable ocean states that have sluggish circulation over long time spans.

Under certain configurations, the model used by the authors becomes unstable, and starts flushing the deep ocean with well-oxygenated surface waters every few thousand years. These self-sustained oscillations make the ocean switch between the anoxic state characteristic of the early Palaeozoic and a more oxygenated state, representative of more-recent periods. Such oscillations might be an artefact of the relatively simple, highly diffusive physical model of the ocean used in Pohl and colleagues' study, but have also been observed in higher-resolution models (see ref. 7, for example). Whether they occur in the real world is unknown, although the observation of millennium-scale climate oscillations during the past glacial period (115,000–11,700 years ago) hints at such behaviour in the Southern Ocean[8,9].

There are several caveats to the results in this study. Even state-of-the-art climate models struggle to simulate ocean oxygen levels realistically, especially in low-oxygen regions[6]. The model used by Pohl *et al.* is of very coarse resolution, and certainly cannot be expected to realistically represent small-scale mixing processes that are important in such poorly ventilated regions. Moreover, the mechanisms that are responsible for the changes in circulation on which the authors' conclusions rely still need to be identified and verified.

Another limitation is that the nutrient inventory is kept constant in the simulations, and nutrient-related feedback mechanisms that exist in the real world are ignored. For example, when oxygen levels are extremely low, marine microbes start to use nitrate for respiration instead of oxygen, resulting in a net loss of this nutrient from the ocean[10]. By contrast, the nutrients phosphate and iron are increasingly released when marine sediments become anoxic, leading to an excess of phosphate and iron relative to nitrate. Such conditions might increase the fixation of nitrogen by cyanobacteria, resulting in an overall increase in the ocean's inventory of growth-limiting nutrients (nitrate, phosphate and iron). This, in turn, could lead to an increase in biological production and subsequent further enhancement of oxygen consumption, constituting a positive-feedback loop.

The study also poses a challenge to the way in which modelling of the geological past is approached. If even relatively small changes in the configuration of Earth's topography can lead to substantial differences in the simulated biogeochemistry of large parts of the ocean, then any assumptions about sea level, ocean area and depth distribution must be carefully stated. Moreover, the results might depend on the model's spatial resolution and numerical representation of water transport. The identification of multi-millennial internal oscillations in some of Pohl and colleagues' simulations raises questions about the robustness of results inferred from single simulations carried out over a few millennia or less, with single choices of initial and boundary conditions.

Pohl and co-workers' study highlights the complexity of the processes that can affect ocean oxygenation — a complexity that is not well represented in models. This is demonstrated, for example, by the fact that state-of-the-art climate models simulate only about half of the decrease in global ocean oxygen content that has been observed over the past few decades[5,6]. Pohl and colleagues' results support the idea that circulation changes are key drivers of variations in ocean oxygen levels. An improved understanding of all the underlying mechanisms is urgently needed, because the under-appreciated phenomenon of marine oxygen loss might pose severe problems for ocean ecosystems and human societies in the near future[11].

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