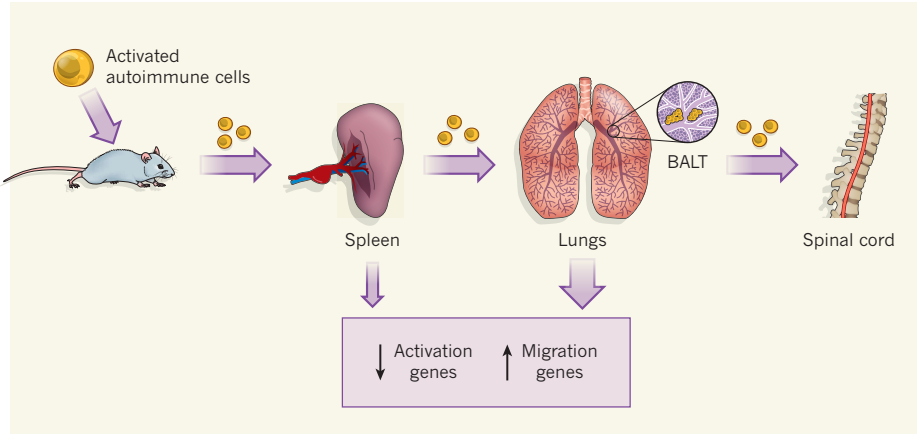

Figure 1 | Autoimmune cells transit the airways. In a commonly used rat model of multiple sclerosis, it takes four to five days following injection of disease-causing autoimmune cells into the bloodstream for signs of disease to appear. Equally puzzling is the fact that the autoimmune cells do not cause disease if they are injected directly into the cerebrospinal fluid. It was previously shown[3] that cells injected into the bloodstream move to the spleen, where they begin to downregulate the expression of proliferation- and activation-related genes and to upregulate the expression of genes involved in cell migration. Odoardi and colleagues now demonstrate[1] that the cells then move to the lungs, where they accumulate in bronchus-associated lymphoid tissue (BALT; clusters of immune cells near the walls of the lung's air passages). Here, the changes in gene expression are consolidated, and the authors propose that this 'licensing' step allows the cells to migrate to the spinal cord, where they begin to cause disease.

encephalitogenic T cells 48 hours earlier, and then monitored the arrival of the cells in the CNS of each animal. They found this to occur at approximately the same time in both rats, suggesting that the CNS of the rat that had received the cells earlier was not preconditioned to harbour an inflammatory reaction.

The researchers next sought to identify where the transferred cells reside before arriving in the CNS. Surprisingly, the two-photon microscopy experiments revealed the vast majority of the T cells to be in the rats' lungs. The cells were initially located in the lung bronchi (air passages) and alveoli (terminal air sacs), before accumulating in dense immune-cell clusters known as bronchus-associated lymphoid tissue (BALT; Fig. 1). The authors also show that, unlike encephalitogenic T cells injected into the bloodstream, T cells injected into the lungs' bronchi by means of the trachea can rapidly leave the lungs and cause disease. This finding suggests that the time the T cells spend in the lung environment 'licenses' them in a way that allows them to move to the CNS. They found, for example, that the changes in gene-expression profile previously observed in these cells were accentuated during the time spent in the lungs.

Importantly, the authors also found encephalitogenic T cells in BALT of rats that had been injected with the cells 2–3 months earlier, as newborns, and that had not developed signs of disease. When the researchers stimulated these dormant T cells by introducing MBP as an aerosol into the rats' tracheas, the cells became activated and accumulated in the CNS, causing disease.

Interpretation of this latter finding is assisted by considering the concept of tissue-resident immune memory cells, an idea stemming from the immune system's remarkable ability to mount an accelerated response to a pathogen to which it was previously exposed even decades before. Although it has long been known that memory T cells circulate through blood and lymphoid tissues, it is now clear that vast numbers of memory T cells also persist in other tissues, particularly those exposed to the outside world, such as the skin, gut and lung[9]. Not surprisingly, the distribution of tissue-resident memory cells mirrors sites of pathogen predilection; for example, influenza-specific memory cells are found mainly in the lungs.

Odoardi and colleagues have now shown that tissue-resident immune memory cells are not limited to pathogen-responsive populations but also include autoimmune cells, which can be activated to emigrate and mediate disease in a distant organ. Although the relevance of these findings to human disease remains speculative, distinct possibilities are evident. For example, healthy humans lack substantial BALT, but cigarette smoking, which is a potent risk factor for developing multiple sclerosis, is also known to induce BALT formation[10–12]. Furthermore, disease activity in patients with multiple sclerosis can be triggered by respiratory infections[13]. Both of these observations might be explained by a process in which myelin-specific autoimmune cells transit the lungs before establishing disease in the CNS, with some of these cells forming a resident lung population that can be subsequently reactivated. ■

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OCEAN SCIENCE

Ancient burial at sea

A study reveals cyclic changes in the rate of burial of biogenic calcium carbonate at the Pacific ocean floor 43 million to 33 million years ago, as Earth exited a warm 'greenhouse' state to become an ice-capped planet. SEE ARTICLE P.609

HEATHER STOLL

From the highest mountains to the coastal plains, rocks are continually dissolved by rain and washed into the sea. The resulting dissolved ions are used by calcifying organisms in the ocean to make shells; when these organisms die, their shells 'rain' down on the sea floor, forming great piles of calcium carbonate. On page 609 of this issue, Pälike *et al.*[1] provide a record of the accumulation of calcium carbonate in the Pacific Ocean over the past 53 million years, based on sedimentary cores drilled out of the sea floor (Fig. 1). This reveals the dramatic shifts in carbonate burial over this period in a new level of detail, and also their relationship with climate.

During periods when more mountains dissolve, calcium carbonate accumulates at progressively deeper regions of the ocean floor, ensuring a balance between the rate at which ions are added to and removed from

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Figure 1 | Cores for thought. Pälike *et al.*[1] have drilled cores of sediment from the floor of the Pacific Ocean. The image shows part of one such core, which was taken from a water depth of 4,000 metres. The muds change from dark (older, deeper sediments) to pale (younger, upper sediments), reflecting the surge of white calcium carbonate that has been deposited from 33 million years ago. The section shown is 450 centimetres in length.

the ocean. The burial of this carbonate at the bottom of the ocean removes carbon dioxide from the atmosphere, cleaning up the CO_2 that is continuously leaked into the atmosphere by volcanoes. But if the burial rate of carbonate outpaces the rate of CO_2 addition, atmospheric levels of CO_2 drop, which causes the climate to cool.

The authors show that about 33 million years ago, calcium carbonate began to accumulate in much deeper parts of the ocean than had been the case previously, suggesting that rocks on land were dissolving much faster. This could have been because of the major collision that occurred between India and Asia at around this time. The collision shoved up high-elevation mountains[2] in the reaches of the tropical rain belt, and this has long been surmised to have fuelled a greater rate of rock dissolution[3]. At the same time, the climate plunged into an 'icehouse' phase — a cool period characterized by the presence of continental ice sheets. The abrupt onset of glaciation on Antarctica lowered sea levels[4] and diverted some of the calcium carbonate that would have accumulated in shallow coral reefs into the deep ocean.

Pälike and colleagues' second key finding is that surprisingly large and geologically rapid oscillations (with a period of 1 million to 2 million years) occurred in the depth of calcium carbonate accumulation on the Pacific sea floor during the 10 million years before the icehouse plunge. However, it is difficult to explain these oscillations by invoking changes in the supply of solutes (dissolved ions) from continents to the ocean — mountains are not built and unbuilt in a day, or even in a million years. Furthermore, ice caps had not reached sufficient size to significantly lower sea level at this time.

Another possible explanation is that cyclic increases in atmospheric CO_2 and temperature periodically accelerated the dissolution rate of rocks. But if this had occurred, the additional solutes supplied at peak dissolution times would have remained dissolved in the ocean, because the higher concentration of atmospheric CO_2 would have made the ocean more acidic. In other words, there would have been no change in the depth at which carbonate accumulated on the sea floor. So what could explain the seemingly indecisive entry into the icehouse implied by the oscillations?

Pälike *et al.* propose an answer that involves the scores of hungry microbes that feast on the remains of algae raining down into deep water from the sunny ocean surface. These microbes respire CO_2, which, in turn, dissolves the calcium carbonate in the shells descending from the surface before it can accumulate on the sea floor. The authors suggest that, if this microbial CO_2 production had been curbed periodically (either by a shift in the composition of algal populations to types that are more resistant to microbial degradation, or by a cooling of the ocean that slowed this degradation[5]), then algal remains would have been buried rather than converted into CO_2. The result would have been a periodic accumulation of carbonate in the deep ocean, as observed.

To substantiate this proposed mechanism, future studies must explore the causes of the proposed synchronous global changes in marine ecology and/or identify evidence that global temperature oscillations affected respiration rates. Because the suggested mechanism could act as positive feedback for climate cooling by removing CO_2 from the atmosphere at faster rates during cold periods, mechanisms that could explain the reversal of the cycle on million-year timescales must also be found.

Alternatively, there may be ways in which the delivery of solutes to the ocean can be rapidly increased without relying on increases in CO_2 and temperature. For example, rates of rock dissolution are also strongly enhanced by intense rainfall. In tropical regions, the amount of rainfall for a given hemisphere increases when Earth's orbit is highly elliptical and the summer season coincides with the perihelion for that hemisphere (the point of the orbit at which the hemisphere is closest to the Sun). In the Irrawaddy River system[6] in southeast Asia, weathering intensity has been shown to increase with these precipitation cycles, rather than with global temperature. During the interval from 55 million to 35 million years ago, when highly soluble rocks in India were entering the tropical rainfall belt[7], modulation of the monsoon system due to changes in the ellipticity of Earth's orbit (which have a long periodicity of 1.2 million to 2.5 million years[8]) could have contributed to intense variations in solute flux.

Still, large changes in ocean ecology or solute fluxes are required to explain the oscillations in the Pacific record only if those oscillations are representative of changes also occurring throughout the Atlantic and other oceans. The global current in the deep ocean accumulates CO_2 from microbial respiration along its flow path, and therefore curtails carbonate accumulation in the ocean basin at the 'end of the line'. So, if the direction of the current reverses, carbonate accumulation becomes shallower in ocean basins close to the end of the current's path, and deeper at basins close to the start. It is therefore important to determine in upcoming drilling expeditions whether the rapid cycles in Pacific carbonate burial also occurred in the Atlantic at precisely the same time. If the cycles are opposite to each other, that would suggest that the same quantities of solutes were precipitating from the global ocean throughout the period concerned, but the precipitation was alternating between the basins, as has occurred during the glacial cycles of the past million years.

Verifying that ancient carbonate-accumulation events are globally synchronous on timescales of a million years or so requires precise correlations of sediments from one ocean to the next, necessitating careful integration of geochemical, sedimentological and palaeontological data. This is exactly the kind of detailed, interdisciplinary collaboration on which the international Integrated Ocean Drilling Program — of which Pälike and colleagues' study was a part — is based. So I, for one, am optimistic that the answer to this question is close at hand. ■

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