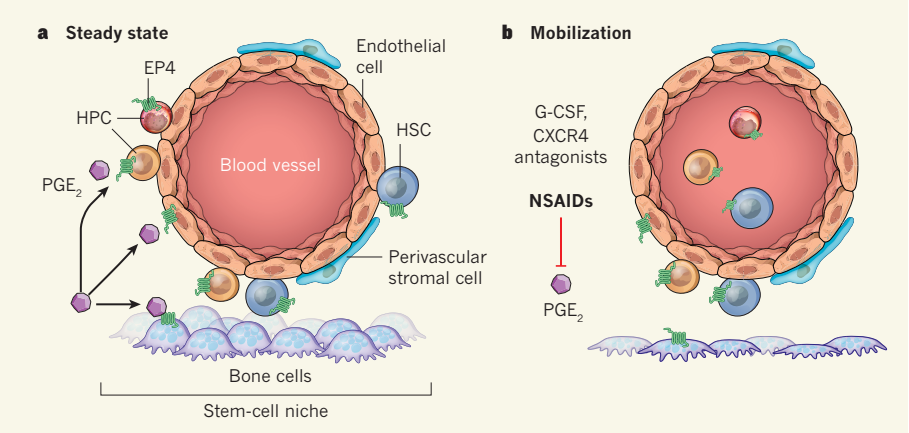

Figure 1 | NSAIDs are gatekeepers of the haematopoietic microenvironment. **a**, Prostaglandin E_2 (PGE_2) can bind to its receptor EP4 on the surface of haematopoietic stem and progenitor cells (HSCs/HPCs), as well as on the surface of niche cells within the HSC/HPC microenvironment, which include perivascular stromal cells, endothelial cells that line blood vessels and cells of the bone lineage. The signalling cascade initiated by PGE_2–EP4 interaction inhibits mobilization of HSCs/HPCs into the circulation. **b**, Hoggatt *et al.*[1] show that NSAIDs, by inhibiting PGE_2–EP4 interactions and in part by thinning of the bone cells, can synergize with the mobilizing agents G-CSF and CXCR4 antagonists. This promotes egress of HSCs/HPCs into the circulation by weakening their tethering to the niche cells.

blood vessels; by subsets of haematopoietic cells; and most probably by perivascular cells, which occur in peripheral blood vessels. Hoggatt *et al.* show that treatment with NSAIDs results in thinning and loss of the cells of the bone lineage, diminishing their capacity to retain HSCs/HPCs within the bone marrow. Moreover, they find that NSAIDs decrease bone-derived osteopontin, a molecule that regulates mobilization of haematopoietic cells. These painkillers might therefore primarily target bone cells to decrease the tethering of HSCs to stromal cells.

Nonetheless, PGE_2 might also induce mobilization by directly affecting perivascular and endothelial cells. Notably, sinusoidal endothelial cells line small blood vessels called sinusoids. The sinusoids, which form branching structures in much of the bone-marrow vasculature, are not mere passive conduits for delivering oxygen and nutrients, but rather represent specialized blood vessels that form an instructive 'vascular niche' in the haematopoietic organs. Normally, activated endothelial cells produce defined blood-related growth factors (angiocrine factors) to balance the self-renewal and differentiation of HSCs[9–16]. One angiocrine factor is PGE_2, through which endothelial cells could modulate HSC/HPC trafficking. Indeed, during recovery from myeloablative therapy, the induction of angiocrine factors — including PGE_2 — in endothelial cells regulates trafficking and regeneration of HSC/HPCs[11–14]. Unravelling the mechanism by which PGE_2 polices the trafficking of HSCs/HPCs within the complex network of intertwined niche cells will require the deletion of EP4 in specific niche cells, including endothelial cells, perivascular cells and cells of the bone lineage.

Notwithstanding the potential benefits of NSAIDs, these drugs may act as a double-edged sword during haematopoietic recovery. Because activation of PGE_2–EP4 signalling promotes blood-vessel formation, NSAIDs might interfere with the regeneration of endothelial cells, thus impairing haematopoietic reconstitution. These complex issues could also be addressed by differentially deleting EP4 in various bone-marrow stromal niche cells, specifically endothelial cells during recovery from myeloablation. In addition, selective deletion of prostaglandin-E synthase enzymes in various niche cells will define the specific niche cells that functionally deploy PGE_2 to activate HSCs/HPCs.

The present findings are relevant to whether NSAIDs can restore the mobilization of HSCs/HPCs in patients who are resistant to treatment with G-CSF and CXCR4 antagonists. It is plausible that resistance to these factors is not due to intrinsic HSC/HPC defects, but rather reflects impaired instructive functions of haematopoietic niche cells. Thus, NSAIDs could pave the way for defining alternative routes to safely mobilize HSCs/HPCs through manipulation of haematopoietic niche cells. These observations also shed light on the mechanism by which NSAIDs may contribute to protection against cardiovascular disorders, by mobilizing haemangiocytes — HPCs that promote organ-specific formation of functional blood vessels[17]. ■

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EARTH SCIENCE

Mainly in the plain

The finding that global mass loss from landscapes is dominated by physical erosion and chemical weathering from flat terrain, rather than from mountains, challenges our understanding of how Earth's surface evolves.

JAMES W. KIRCHNER & KEN L. FERRIER

Inexorably, everything falls apart. As individuals, we humans last only some decades or so. Our most Ozymandian creations crumble into oblivion over hundreds or thousands of years. And on million-year timescales, even the landscapes on which we build our civilizations will disappear, gradually consumed by physical erosion and chemical dissolution. How quickly these processes transform Earth's surface has been a question of great interest to geologists and geochemists.

But they may have mostly been looking for the answer in the wrong places, Willenbring *et al.*[1] report in *Geology*. Geologists love mountains, and have focused their attention on steep terrain, where rapid erosion is thought to drive rapid chemical weathering[2]. However, Willenbring *et al.* say that, on a global basis, there is just not enough mountainous terrain to account for much of the global flux of sediment (from erosion) or solutes (from chemical weathering) reaching the oceans.

This argument is likely to arouse interest, and some measure of controversy, because

it concerns not only the evolution of Earth's surface, but also its long-term climate. When calcium and magnesium are dissolved from silicate minerals and later deposited as carbonates on the ocean floor, carbon dioxide is removed from the ocean–atmosphere system. This mechanism may stabilize global climate over the long term if the climatic shifts that accompany higher atmospheric CO_2 levels also accelerate global erosion and weathering fluxes.

Willenbring and colleagues' analysis is based on a global compilation of what geologists term denudation rates: these are rates of mass loss, or of equivalent surface lowering, from landscapes as a result of physical erosion and chemical weathering. Long-term denudation rates can be inferred from cosmogenic nuclides — rare isotopes that are produced inside mineral grains by cosmic-ray bombardment[3]. Measuring the concentrations of these nuclides is technically demanding, but the effort is worthwhile because they intrinsically reflect average denudation rates over thousands or tens of thousands of years. And when they are measured in handfuls of river sand, they reflect the average denudation rate of the entire contributing drainage basin. In the nearly 20 years since this technique was proven to work[4], more than 1,000 such measurements of basin-scale denudation rates have been published.

Using their global compilation of cosmogenic-nuclide measurements, Willenbring *et al.* show that roughly half of the worldwide variation in denudation rates can be explained by a simple exponential function of average basin slope. This implies that other factors such as climate, rock type and vegetation must be of secondary importance. Another recent compilation of cosmogenic-nuclide data[5] is consistent with this exponential relationship, as are other, smaller data sets covering different spatial scales, timescales and measurement methods[4,6,7]. This exponential relationship implies that denudation rates do not decline to zero as slope approaches zero; instead, they converge to a constant value of roughly 0.01–0.1 millimetres per year.

These rates are slower than those in steep mountainous terrain by an order of magnitude or more, but gentle landscapes are so abundant that they dominate the global denudation budget. Willenbring and co-workers calculate that landscapes with slopes of less than 100 metres per kilometre account for more than nine-tenths of Earth's land surface and eight-tenths of the global denudation flux, even when the faster rates in steeper terrain are taken into account. The implication is that understanding how Earth's topography and climate have co-evolved over geological time — and how they will co-evolve in the future — will require much better data on erosion and weathering processes in flat terrain.

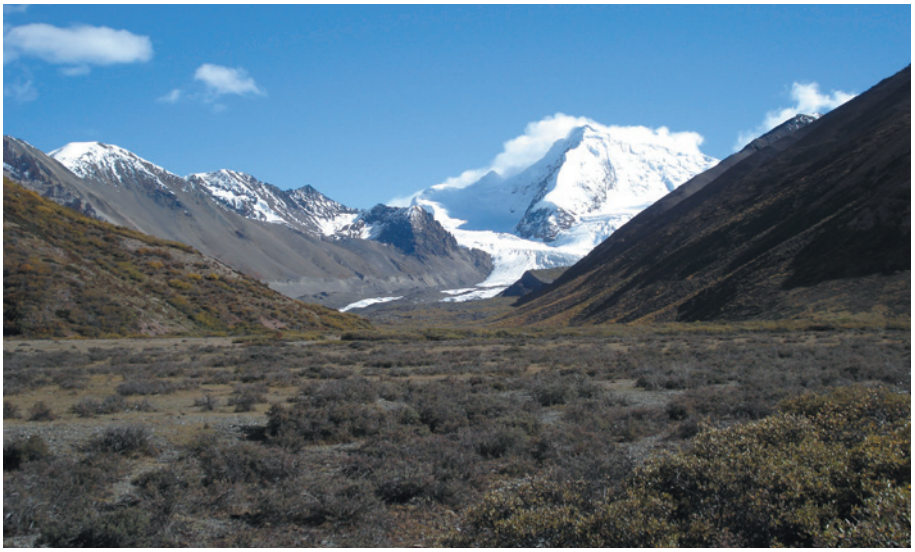
Getting those data will be a challenge. We currently have far fewer measurements of long-term denudation rates in gentle terrain than in steep terrain[8]. Not one of the nearly 1,000 denudation-rate measurements in Willenbring and colleagues' database comes from a landscape with a slope of less than 10 m km^{-1}, even though such landscapes account for roughly half of Earth's land surface[1].

There are details in the paper that one can argue over. For example, measurements of topographic slope are scale-dependent; widely spaced elevation measurements straddle valleys and ridges and thus underestimate topographic gradients, potentially by a lot. Therefore, Earth may not be nearly as flat as one would infer from the global topographic data set used by the authors, which has a spatial resolution of only 1 km.

More fundamentally, a lot of gentle terrain consists of depositional landforms such as basins, deltas, fans and playas, where sediment accumulates, rather than erodes, over the long term. Cosmogenic nuclides can say nothing useful about the denudation rates of depositional landscapes (which are, strictly speaking, negative). Therefore, cosmogenic nuclides are typically measured only in the subset of gentle landscapes that are actively eroding, and not in those that accumulate sediment. This will lead to a systematic upward bias in the inferred average denudation rate of gentle terrain, and so to an upward bias in the importance of gentle terrain in Willenbring and colleagues' global denudation budget. The magnitude of this bias is unknown.

Nonetheless, the authors' analysis does suggest that more geologists should climb down from the mountains that they love so much, to explore the erosion and weathering of the surrounding lowlands (Fig. 1). When they get there, however, they will find that many of these landscapes have been utterly transformed by human activities, which have greatly accelerated soil-erosion rates — to the point that they rival or exceed natural erosion rates in some of the steepest mountains on Earth, and threaten the long-term future of our food supply[8].

This is not a new problem: the crumbling relics of many vanished civilizations bear mute witness to the fate of those who squander their soil resources[9]. What is new, this time around, is that we know we are destroying our soil, and we know how to stop. The scientific basis for soil conservation has been understood for decades. What remains to be discovered, in many cultural landscapes, is the will to implement it. ■



J. W. KIRCHNER

Figure 1 | Lowland flat, mountain high. Flat terrain surrounds towering peaks in the eastern Tibetan Plateau. Willenbring and colleagues' analysis[1] suggests that geologists need to focus on gently sloping terrain, rather than mountains, if we are to understand the denudation processes that transform Earth's surface.

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