

rium prausnitzii down-regulates intestinal inflammation, which is associated with the production of specific metabolites, such as butyrate and salicylic acid derived from host cells or bacteria in the intestine and peripheral blood (12). Clearly, molecular characterization of intestinal *Akkermansia*, *Faecalibacterium*, and *Bifidobacterium* strains from cancer patients is needed to fully understand how they influence the tumor microenvironment and synergize with immune checkpoint blockade. These studies could lead to the isolation and characterization of microbial components that are responsible for the beneficial effects. For example, administration of Amuc_1100, a protein isolated from the outer membrane of *A. muciniphila*, reproduces the beneficial effect of the bacterium on diabetes in pre-clinical models (13).

The relationship between microbial communities and antitumor drug responses are complex. On the one hand, depletion of selective bacterial taxa by means of antibiotic exposure or other stressor conditions may diminish immunotherapy responses. On the other hand, the presence of specific microorganisms in local or distant sites may interfere with treatment through metabolic activities (14). For example, bacteria of the Enterobacteriaceae family, such as *Escherichia coli* strains, decrease efficacy of the chemotherapeutic agent gemcitabine by metabolizing and deactivating the active form of the drug, thereby negatively interfering with tumor response (15). Therefore, the presence of specific strains of bacteria may be able to modulate cancer progression and therapeutics, raising the possibility that precision medicine directed at the microbiota could inform physicians about prognosis and therapy. One could view the microbiota as a treasure trove for next-generation medicine, and tapping into this network may produce new therapeutic insights. ■

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OCEANS

Mind the seafloor

Research and regulations must be integrated to protect seafloor biota from future mining impacts

By Antje Boetius^{1,2,3} and Matthias Haeckel⁴

As human use of rare metals has diversified and risen with global development, metal ore deposits from the deep ocean floor are increasingly seen as an attractive future resource. Japan recently completed the first successful test for zinc extraction from the deep seabed, and the number of seafloor exploration licenses filed at the International Seabed Authority (ISA) has tripled in the past 5 years. Seafloor-mining equipment is being tested, and industrial-scale production in national waters could start in a few years. We call for integrated scientific studies of global metal resources, the fluxes and fates of metal uses,

“To be economical, any single operation would have to mine several hundred square kilometers of deep seafloor per year...”

and the ecological footprints of mining on land and in the sea, to critically assess the risks of deep-sea mining and the chances for alternative technologies. Given the increasing scientific evidence for long-lasting impacts of mining on the abyssal environment, precautionary regulations for commercial deep-sea mining are essential to protect marine ecosystems and their biodiversity.

REMOTE AND UNKNOWN

The seabed covers 70% of Earth's surface and is home to a virtually uncharted diversity of marine life. The ocean floor, at an average depth of 4 km, is characterized by pressures of several hundred bars, temperatures around the freezing point of water, and no sunlight for photosynthetic productivity. For humans, this environment is inhabitable, barely accessible, and extreme.

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et, the relatively stable environmental conditions of the deep sea have promoted a vast biodiversity of taxa that are not found in shallow waters or on land.

Because of its remoteness and the technical challenges associated with reaching the deep seabed, much less than one-thousandth of its area has been studied (1). As a result, little is known about how much deep-sea species contributed to the evolution of life and biodiversity on Earth, how they can tap into unusual energy sources, how the sparse populations maintain enough standing stock in this vast realm, and how they adapt to perturbations. No country sustains the necessary amount of deep-sea observations required to answer such questions. The lack of long-term ecological time series is particularly problematic, making it difficult to decipher natural dynamics and anthropogenic perturbations (2). Recent findings suggest a tight coupling between the dynamics of surface and deep-sea processes and confirm that effects of climate change and pollution propagate quickly. But little is known about the resilience and recovery of deep-sea communities in the context of activities such as mining (3).

HAZARDS OF DEEP-SEA MINING

Critical metal resources in the deep sea include arsenic, copper, cobalt, nickel, lithium, platinum, tellurium, zinc, and many rare earth elements (4). The exploitable resources of the potentially prolific, 40-million-km² deep-sea area (5) could be worth \$20 trillion to \$30 trillion, considering current metal prices. However, these resources are not renewable, because polymetallic nodules and crusts grow very slowly over millions of years. Furthermore, mining is highly invasive, damaging the surface seafloor and entailing considerable risks for deep-sea life (6, 7). Even in shallow seas, there is no efficient governance for monitoring, managing, and protecting the oceans. The extensive seafloor damage caused by benthic trawling or by accidents such as the 2010 *Deepwater Horizon* oil spill in the Gulf of Mexico shows that ecological impacts on the deep sea remain literally out of sight in ocean resource management. Even in national waters, no system is in place to repair, restore, and compensate for loss of seafloor habitat.

On land, metal mining is highly destructive to the environment and can put the

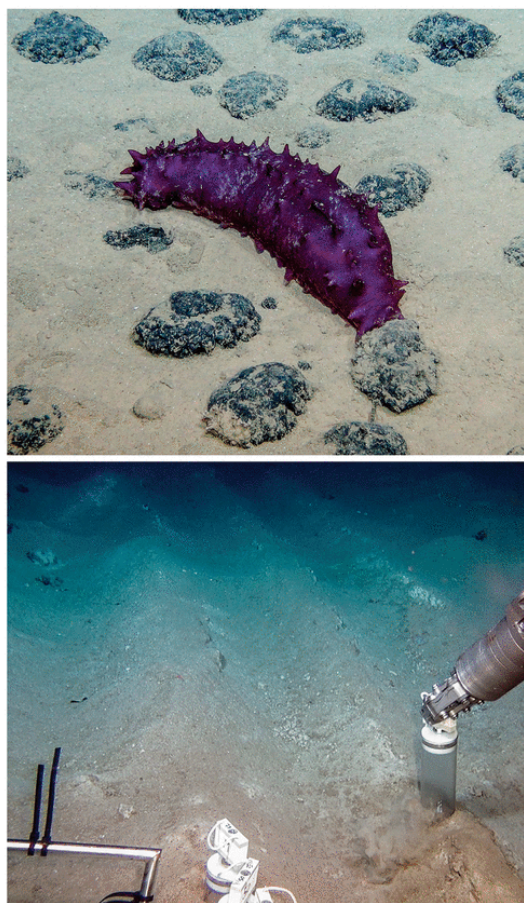
health of miners and local communities at risk, if not carefully regulated and managed. Mitigation actions such as habitat compensation, restoration, and adaptive management are expensive, but can minimize the damage to biodiversity and help to restore terrestrial landscapes within a few decades. However, it remains questionable whether any land-based mitigation mechanisms can serve as a blueprint for regulations of deep-sea mining (8). The high economic costs of ecological impact on land (9) are often used as an argument for deep-sea mining. Yet, such a “not-in-my-backyard” drive toward seafloor uses would violate the internationally affirmed precautionary approach, as reflected in principle 15 of the 1992 Rio Declaration on Environment and Development.

The ISA, which is responsible for controlling the exploitation of mineral resources in international waters, adopts this principle in its draft regulation, published on 8 August 2017 (10). However, concrete environmental objectives for protecting and conserving the deep-sea environment, including its biological diversity and ecological integrity, have not been agreed upon yet. To be economical, any single operation would have to mine several hundred square kilometers of deep seafloor per year, but this estimate does not include the costs of environmental management. At the anticipated scale of seafloor damage, monitoring, compensation, and restoration techniques would be extremely expensive to implement. But without such measures, the use of deep-sea mineral resources to sustain further global economic growth would endanger the deep sea’s genetic resources, which are a long-term target for biotechnology and medicine (11).

THE RESEARCH BASIS

Several countries are currently funding a range of activities connected to deep-sea mining, from developing technologies for deep-sea raw materials extraction to researching the ecological consequences of deep-sea mining, but there is no central synthesis platform to bring together arising knowledge.

The MiningImpact project (a part of the Joint Programming Initiative Healthy and Productive Seas and Oceans) has brought together 11 European countries to study the



(Top) Holothurian in a polymetallic nodule field of the Clarion-Clipperton Fracture Zone of the Pacific Ocean. (Bottom) ROV Kiel 6000 push coring disturbed surface sediment of the 26-year old plow track of the DISCOL experiment in the Pacific Peru Basin.

environmental impacts of seafloor mining, with a focus on polymetallic nodules. The researchers revisited benthic impact experiments in the Pacific Peru Basin and in ISA contract areas in the Clarion-Clipperton Fracture Zone in the Pacific Ocean (see the photos). Some of these experiments were initiated up to 40 years ago and have now been studied with state-of-the-art methods (12). Key conclusions were that deep-sea ecosystems associated with polymetallic resources support a diverse fauna with high spatial and temporal variability and largely unknown connectivity; that the loss of seafloor integrity by mining reduces population densities and ecosystem functions for many decades; and that sediment plumes will likely blanket the seafloor up to several tens of kilometers outside the mined area

(13). On the basis of current scientific knowledge, the long-term risks of industrial-scale deep-sea mining to the marine environment seem unmanageable from both the economical and the ecological perspective.

However, predicting impacts on the basis of small-scale benthic impact experiments is associated with many uncertainties. Benthic trawling provides a rough analog for large-scale impact on seafloor integrity. In shelf seas, recovery of seafloor communities from benthic trawling can take less than a decade depending on the substrate (14), but decades to centuries are needed in deep-water habitats (15). In 2016, the European Union banned seabed trawling on continental slopes below 800 m to reduce risks for deep-sea life.

Dark, cold, energy-poor deep-sea ecosystems are particularly vulnerable to mechanical disruption of the surface seafloor, which contains most of the food and microbial communities on which benthic fauna depend. Biogeochemical investigations as part of the MiningImpact experiments confirm that even the soft sediment seafloor would take many decades to hundreds of years to recover from the disturbance caused by nodule removal (13). The nodules and crusts themselves, which provide habitats to many deep-sea species, would need millions of years to grow back (4).

CAREFUL OCEAN GOVERNANCE

Strict environmental regulations need to be formulated by the ISA as they finalize their regulations (10). Before any industrial activities could begin, long-term studies with realistic analogs to mining technologies would be needed. Conservation areas must closely match ecosystem characteristics of mined areas to safeguard abyssal biodiversity. Technologies for baseline studies and monitoring need to be standardized and regularly revised to reflect state-of-the-art science. Indicator sets for deep-sea ecosystem status and threshold values for harmful effects must be defined. Environmental management plans need to address uncertainties of sediment-plume dispersal. Finally, transparent and independent international scientific assessment of environmental management plans needs to be in place before any deep-sea mining

PHOTOS: GEOMAR, KIEL

operations can start. Transparency also needs to be increased in the ISA's decision-making process for issuing contracts, as has become obvious by the latest approval of a 10,000-km² claim at the Mid-Atlantic Ridge (16) that includes the hydrothermal-vent systems of Lost City, Trans-Atlantic Geotraverse, and Broken Spur, which are key scientific research sites.

Before taking any risk to destroy deep-sea habitats and endanger marine species, metal resources on land could be fully mapped and explored. Technological and social innovations could improve the way metals are used and recycled, and international politics could foster metal-market stability. In all of this, holistic science projects and stakeholder dialogue could help in finding solutions to the development of metal resources, uses, and fates. This would also provide the necessary time to valorize ocean life and its genetic resources (17). A new kind of international deep-sea science and policy, in which knowledge and governance of mineral and genetic resources as well as other ocean ecosystem services are integrated and channeled into international policy, would allow humanity to sustain the full range of options for the deep sea. ■

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IMMUNOLOGY

Lung inflammation originating in the gut

Parasite infection in the intestine can lead to inflammatory immune cells in the lung

By Jenny Mjösberg^{1,2} and Anna Rao¹

Innate lymphoid cells (ILCs) are a type of immune cell that are considered to be tissue-resident gatekeepers situated in mucosal membranes, where they contribute to both homeostasis and pathology (1). In healthy individuals, ILCs are involved in tissue repair, but ILCs have also been shown to participate in several types of inflammation, including allergy and asthma. Whereas ILCs can be found at low frequencies in the blood circulation, mucosal barriers such as the intestine and airways are enriched for ILCs (1). However, whether ILCs are in fact tissue resident in the sense that they self-renew without substantial replenishment from other organs has been a topic of debate. The mechanisms of ILC circulation are important for understanding various

“...ozanimod and related drugs might interfere with the ILC gut-lung axis and be beneficial in chronic lung inflammation...”

types of inflammatory conditions and how they can be treated. On page 114 of this issue, Huang *et al.* (2) demonstrate that ILC2s are not obligate tissue-resident cells because they can be recruited from the gut to the lung and other organs in response to inflammatory signaling.

ILC2s contribute to so-called “type 2 immunity” in which they are typically activated by the cytokines interleukin-25 (IL-25) and IL-33 to produce large amounts of IL-5 and IL-13, which are key players in this type of inflammation. In 2015, Huang *et al.* (3) described a population of lung ILC2s characterized by high expression of killer cell lectin-like receptor subfamily G member 1

(KLRG1) and the IL-25 receptor, IL-17 receptor-β (IL-17Rβ), but low expression of the IL-33 receptor, ST2 (KLRG1^{high} ST2^{low} ILC2s). In contrast to natural ILC2s (nILC2s), which reside in the lungs during homeostatic conditions, KLRG1^{high} ST2^{low} ILC2s were termed inflammatory ILC2s (iILC2s) as they arise in the lungs only after type 2 immunity induced by IL-25 exposure or gastrointestinal infection with the parasitic worm *Nippostrongylus brasiliensis*. Now Huang *et al.* (2) extend their observations using a model to study circulation of blood-borne cells between two surgically connected (parabiotic) mice to show that iILC2s accumulate in the lungs during these conditions because they are rapidly recruited within 3 to 5 days. These data challenge the existing view established following the seminal paper by Gasteiger *et al.* (4), who did not observe replenishment of ILC2s until day 15 after *N. brasiliensis* infection in parabiotic mice. The discrepancy in timing of ILC2 recruitment between these two studies might be due to different conditions in which mice were housed. Gasteiger *et al.* kept their mice on antibiotic treatment, whereas Huang *et al.* (2) did not. It is therefore possible that the intestinal microbiota might play an important role in ILC2 circulation.

Huang *et al.* (2) identify the intestine as the critical origin of iILC2s recruited to the lung upon IL-25 administration, revealing a striking ILC2 gut-lung recruitment axis (see the figure). Supporting the intestine as the major source of iILC2s in the lung, transcriptional analysis demonstrates that lung iILC2s are more similar to small intestine ILC2s (siILC2s) than to lung nILC2s.

The recruitment of iILC2s in the lung is a transient phenomenon. Twelve days after IL-25 administration, iILC2s are undetectable in the lung. However, parabiosis experiments reveal that 10% of nILC2s in the lung and 40% of ILC2s in the intestine originate from the donor mouse, suggesting that lung iILC2s can return to the intestine or display plasticity and convert into nILC2-like cells in the lung (see the figure). Because these nILC2-like cells in the lung are derived from activated iILC2s, it is possible that they make up tissue-resident

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