tion include engineering stem cells with bioresponsive gene circuits that can sense inflammatory factors such as cytokines or reactive oxygen species and, in turn, induce the production of anti-inflammatory factors, allowing endogenous progenitors or transplanted cells to repair damage (*9*). Indeed, the beneficial effects of some stem cell therapies have been traced to immune-modulatory effects of the transplant, rather than the tissue-generating properties of the stem cells themselves. In a mouse model of cardiac ischemic injury, transplanting stem cells augmented cardiac function, not by production of cardiomyocytes but by activating macrophages that limit extracellular matrix (ECM) deposition and modulate the mechanical properties of an injured area to rejuvenate the heart (*10*).

Tempering the immune system presents a formidable challenge because the same factor can promote repair or inflict damage through inflammatory effects, depending on context (*11*). For instance, early in wounding, interleukin-17 (IL-17) enables hypoxia adaptation of damaged epithelium, but persistent IL-17 signaling potentiates pathology by recruiting damage-causing neutrophils (*11*). Synthetic biology provides opportunities to divorce the damage-causing effects of inflammation from those involved in repair. IL-22 induces the expression of proregenerative signal transducer and activator of transcription 3 (STAT3) and pro-inflammatory STAT1 transcription factors. Engineering IL-22 with altered receptor binding to only induce regenerative STAT3 boosted intestinal stem cell proliferation in a mouse model of radiation injury, without driving STAT1-mediated inflammatory outcomes (*11*).

A critical hurdle to regeneration is fibrosis, which rapidly plugs damaged tissue by haphazardly depositing ECM. Fibrosis profoundly compromises tissue mechanics and cellular interactions and physically obstructs organ function (*1*, *12*). Antiscarring therapies have been notoriously hard to achieve because profibrotic factors such as transforming growth factor–β (TGFβ) also have important functions in maintaining health. Alternatively, modulating mechanical signaling by inhibiting fibroblast Yes-associated protein (YAP), a mechanosensory transcription coregulator, prevented scarring during skin repair in mice (*12*). Notably, opposing fibrosis in this manner was sufficient to restore the skin's architecture and tensile strength. Similarly, using engineered chimeric antigen receptor (CAR) T cells to target conserved antigens on ECM-generating cardiac fibroblasts reduced fibrosis and revived heart function after ischemic injury (*13*). These studies indicate that adult organs may still possess molecular roadmaps to activate regenerative responses. A comparison of fibroblasts from regenerating reindeer antler skin and scarring back skin uncovered that inflammatory priming distinguishes the profibrotic state (*14*). Thus, precisely targeting inflammation may also ameliorate fibrosis and unlock latent regenerative capacity (*1*).

What was once considered the future of medicine is now becoming reality. But there is no magic pill for regeneration (yet). In addition to scientific and technological innovation, there are also practical considerations of cost and production. Innovations in regenerative therapies for complex diseases or damage involving multiple cell types have been hampered by the lack of appropriate preclinical models and a paucity of fundamental information on instructive signals to build tissues. Accordingly, efforts to systematically chart tissue repair over time, in different model systems, and after different types of damage are now underway (*14*). Rather than limiting therapies to the rules of mammalian physiology, radical strategies from nonvertebrate species and even the plant kingdom are surfacing. For example, nanosized plant photosynthetic systems that augment chondrocyte anabolism could limit cartilage degradation and osteoarthritis in mice (*15*). Finally, achieving regeneration in humans will require a rapid transition from rodent models to clinically relevant large animal and human studies. Ascending the summit of human regeneration demands an interdisciplinary effort that brings together biologists, biomedical engineers, and clinicians. The view from the top will reveal a transformed medical landscape that is able to seamlessly rejuvenate organs, ultimately extending human life span and health span. ■

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ECOLOGY

Past microbial stress benefits tree resilience

Soil microbiota from stressful environments provide an avenue for climate resilience

By **Michelle E. Afkhami**

By pushing environments to new extremes and exposing organisms to unprecedented levels of stress, anthropogenic changes are threatening biodiversity and ecosystem services. The substantial diversity and long evolutionary history of microorganisms provide a well of biological innovation that has the potential to relieve stress and increase ecosystem resilience (*1*). On page 835 of this issue, Allsup *et al.* (*2*) report that soil microbes can relieve climatic stress and enhance tree survival when the microbes have previous experience with that stress (drought or excess heat or cold). They also show that inoculated microbes, including beneficial mycorrhizal fungi, were still detectable in tree roots 3 years after planting in nature. These results suggest that management of soil microbiota, especially during restorations, could provide a valuable strategy for increasing forest resilience to climate change.

Microbial communities are fundamental to healthy, functioning environments around the globe. Soil microbiota underpin ecosystem services including nutrient cycling, decomposition, and carbon sequestration directly and through interactions with plants—the primary producers (autotrophs) that fuel food webs (*3*). Plants host diverse assemblages of fungi and prokaryotes (bacteria and archaea) that live on and inside roots, leaves, stems, and flowers. They can help plants withstand drought, high salinity, extreme heat and cold, low nutrients, heavy-metal pollution, and other challenging conditions (*4*). For example, the hyphal networks of mycorrhizal fungi in soils can access water and nutrients beyond the rhizosphere (the plant's rooting zone) to exchange for photosynthetic carbon, increasing fitness of both the fungi and plant.

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As communities face escalating and new stresses in the Anthropocene, plants must find ways to persist in changing environments or track habitable conditions to avoid extinction. Microbiota can ameliorate stressors in situ or new stress encountered during range expansion (*5*).

A legacy of stress can be good. Allsup *et al.* grew trees preinoculated with stress-experienced soil microbiotas from 12 sites across Wisconsin and Illinois in field and greenhouse common gardens for 3 years and evaluated tree survival, growth, and rhizosphere fungal composition. They demonstrated that soil microbiota experienced with climate stress—cold, hot, or dry conditions—are better able to promote tree survival under those specific conditions (e.g., warm-habitat microbiota ameliorate heat stress). If the stress legacy of microbiota enhancing their ability to promote tree health under that stress is a common phenomenon, this would provide a method for predicting when microbiota will facilitate climate resilience and for choosing the "correct" inoculates for use in restoration, management, and sustainable agriculture. Stress legacy effects have been supported in other systems, where only salinity-experienced microbiota ameliorated salt stress for mangroves (*6*, *7*). Further, the importance of stress legacy emphasizes that different habitats harbor distinct microbial communities that maximize benefits under those habitat conditions, contradicting the "everything is everywhere" adage. This highlights the need to consider how microbiota will migrate with climate change and whether active management of microbial communities is required for ecosystem health.

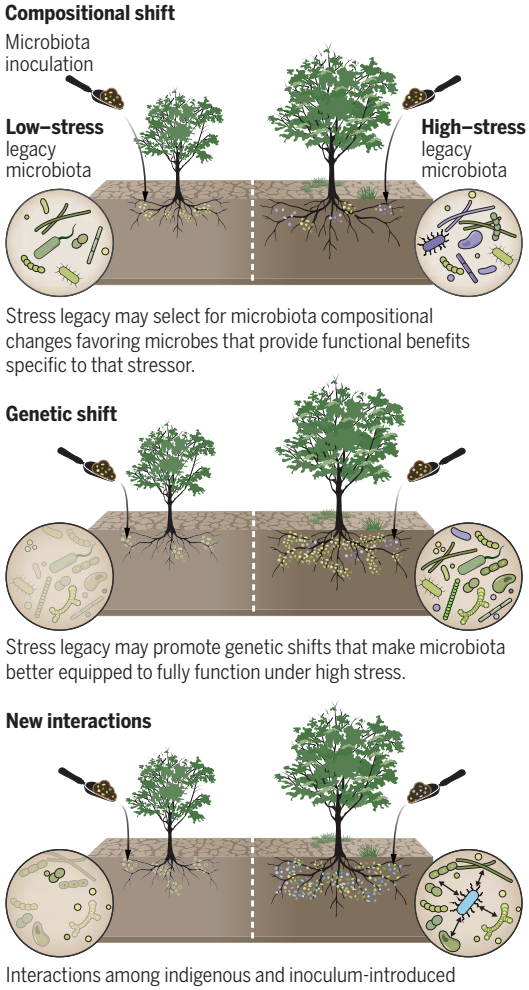
A key question moving forward is how stress primes the rhizosphere microbiota to ameliorate specific stresses in host plants (see the figure). One possibility is that stressful environments select for distinct groups of interacting fungi and prokaryotes that underpin functional benefits that are specific to that stressor, but which are absent when humans rapidly alter stress regimes. Another nonmutually exclusive explanation is that local adaptation of microbes to stressful conditions is crucial for microbes to maintain their own metabolic and physiological functions needed to produce and share benefits. Moreover, new interactions between indigenous and inoculum-introduced microbiota may allow better overall community functioning. For example, stress-tolerant microbes from inoculum could supply resources needed for indigenous microbiota health by replacing stress-sensitive species, or horizontal gene transfer could propagate stress-resistance adaptations within indigenous microbiomes. Future metagenomic and metatranscriptomic studies, ideally including single-cell sequencing, will be valuable for differentiating among these three possible mechanisms and for identifying how stress primes changes to function and dynamics in microbial communities.

It is notable that Allsup *et al.* found that inoculated microbes were still detectable in experimental trees' roots after 3 years. This is both a point of excitement and caution for restoration. That properties of inoculated microbial communities and their effects on host plants were retained across years points to preinoculation of plants during revegetation efforts as a feasible avenue for restoring microbial communities and function (*6*). However, it also raises concerns because unplanned microbial introductions from nursery plants are likely common, and even carefully considered inoculations of seedlings or soils may lead to unintended consequences. For example, the longevity of microbes in plantings could facilitate spread of new species that displace indigenous microbial diversity, and horizontal gene transfer among introduced and indigenous microbes could rapidly reshape genetic variation in local communities.

Interestingly, in their northern sites, which simulated the expanding forest range edge, Allsup *et al.* found that no single microbiota optimized survival of trees experiencing both winter cold and summer drought. By contrast, trees at this site that only experienced cold stress (i.e., no drought) benefited from cold-experienced microbial inoculates. This suggests that multidimensional stress can disrupt the positive effect of microbial stress legacy. Similarly, recent work on soil microbiota showed that increasing the number of anthropogenic stressors disrupts soil microbial multifunctionality and can generate synergistic negative effects that cannot be predicted from individual stressor effects (*8*, *9*). Although natural ecosystems are inherently stressful across multiple dimensions, the introduction of new stressors or rapid intensification of anthropogenic stressors may contribute to disrupted microbial services by generating particularly strong conflicting selection on microbial functions, dismantling the fail-safe of functional redundancy within microbial communities and/or causing the loss of influential microbes. For example, "keystone microbes," which structure soil communities and provide important ecosystem functions (*10*), may be especially stress-sensitive (*11*). The finding that stress-experienced microbiomes can ameliorate climate stress raises hope for ecosystem resilience, but a comprehensive gene-to-ecosystems understanding of microbial roles in climate change resilience is needed before active management of soil microbial communities can be undertaken. ■

How stress legacy of soil microbiota might increase tree resilience

Inoculations with soil microorganisms can help trees withstand stressful conditions, such as drought, high salinity, soil contamination, and extreme temperatures, especially when they have previous experience with that stress (high stress legacy). Several possible mechanisms might mediate these beneficial effects under high stress such as drought.



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