請仔細閱讀每一篇短文，用中文將最關鍵大意寫出，字數不要超過 300 字，也不要逐字翻譯
共四題 每題 25 分

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Heart regeneration has been intensely investigated, and extremely controversial, for more than 150 years1. In pursuit of this subject, the heart has been stabbed, snipped, contused, cauterized, coagulated, frozen, injected with toxins, infected and infarcted, in species ranging from marine invertebrates to horses2,3. Why has this proven to be such a difficult challenge? The heart is one of the least regenerative organs in the body, so if there is a regenerative response, it is small in comparison to that seen in many other tissues, such as liver, skeletal muscle, lung, gut, bladder, bone or skin. For most investigators, the question is about whether there is no regeneration, which is intrinsically difficult to prove, or whether it occurs but at very low rates, which is not easy to detect but possible using highly sensitive approaches.

This is more than an academic argument. Heart failure is a burgeoning public health problem, and some predict that it will reach epidemic proportions as our population ages. Cardiomyocyte deficiency underlies most causes of heart failure. The human left ventricle has 2–4 billion cardiomyocytes, and a myocardial infarction can wipe out 25% of these in a few hours4. Disorders of cardiac overload such as hypertension or valvular heart disease kill cardiomyocytes slowly over many years5, and ageing is associated with the loss of ~1 g of myocardium (about 20 million cardiomyocytes) per year in the absence of specific heart disease6. If the human heart has even a small innate regenerative response, it may be possible to exploit this therapeutically to enhance the heart's function. This fundamental motivation has kept investigators pursuing rare events for more than a century.

Over the past 15 years, researchers have taken a more interventional approach to the injured heart, creating the field of cardiac repair. The ultimate goal of cardiac repair is to regenerate the myocardium after injury to prevent or treat heart failure. This interdisciplinary field draws from advances in areas such as stem cells, developmental biology and biomaterials in an attempt to create new myocardium that is electrically and mechanically integrated into the heart. Cardiac repair has moved rapidly from studies in experimental animals to clinical trials involving thousands of patients. In this Review, we summarize the evidence for heart regeneration in animal models and humans. We discuss the status of research using adult stem cells and pluripotent stem cells for cardiac repair in experimental animals,

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and explore the promises and problems of cellular reprogramming and tissue engineering. Clinical trials will be covered only briefly, owing to space limitations, so we refer interested readers to recent reviews on this topic7,8.

Heart regeneration in amphibia and fish

Unlike humans, many amphibia and fish readily regenerate limbs, appendages and internal organs after injury. There is a long history of research on amphibian heart regeneration9; more recently, the zebrafish has proven to be a particularly useful model, given its substantial regenerative capacity and amenability to genetic manipulation10. The zebrafish heart fully regenerates after the surgical amputation of the cardiac apex — an injury that corresponds to a loss of approximately 20% of the total ventricular mass10. In the low-pressure zebrafish heart, this large wound is effectively sealed by an initial fibrin clot, which is gradually replaced by de novo regenerated heart tissue rather than by scar tissue10,11,12,13.

Not surprisingly, this regenerative response involves a substantial amount of cardiomyocyte proliferation. Even at baseline levels, zebrafish cardiomyocytes show a much higher degree of cell-cycle activity than equivalent cells from their mammalian counterparts. A recent study showed that approximately 3% of cardiomyocytes in the compact myocardium of uninjured adult zebrafish hearts incorporate the thymidine analogue bromodeoxyuridine (BrdU) during a seven-day pulse-labelling experiment. Two weeks after amputation of the cardiac apex, the fraction of BrdU-positive cardiomyocytes had increased by tenfold, and this parameter remained as high as 20% as late as one month after injury10.

Initial experiments suggested that undifferentiated progenitor cells were the principal source of regenerating cardiomyocytes in zebrafish11, but two recent genetic fate-mapping studies unambiguously demonstrated that pre-existing committed cardiomyocytes are instead the main source12,13 (Box 1). The two groups independently generated transgenic zebrafish in which the cardiomyocyte-specific cmlc2 (also known as myl7) promoter drives the expression of tamoxifen-inducible Cre recombinase. These animals were crossed with a reporter line, in which Cre-mediated excision of a loxP-flanked stop sequence induces constitutive expression of green fluorescent protein (GFP). In the offspring of this cross, all pre-existing cardiomyocytes and their progeny can be induced to express GFP by tamoxifen treatment. If the regenerated myocardium were derived from undifferentiated progenitor cells, the new ventricular apex should be GFP–. Instead,

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both groups found that the vast majority of the newly regenerated cardiomyocytes were GFP+ (refs 12, 13). Thus, heart regeneration in zebrafish is principally mediated by the proliferation of pre-existing cardiomyocytes, rather than the generation of new cardiomyocytes from stem cells.

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The microbiome may yield a new class of psychobiotics for the treatment of anxiety, depression and other mood disorders

The notion that the state of our gut governs our state of mind dates back more than 100 years. Many 19th- and early 20th-century scientists believed that accumulating wastes in the colon triggered a state of "auto-intoxication," whereby poisons emanating from the gut produced infections that were in turn linked with depression, anxiety and psychosis. Patients were treated with colonic purges and even bowel surgeries until these practices were dismissed as quackery.

The ongoing exploration of the human microbiome promises to bring the link between the gut and the brain into clearer focus. Scientists are increasingly convinced that the vast assemblage of microfauna in our intestines may have a major impact on our state of mind. The gut-brain axis seems to be bidirectional—the brain acts on gastrointestinal and immune functions that help to shape the gut's microbial makeup, and gut microbes make neuroactive compounds, including neurotransmitters and metabolites that also act on the brain. These interactions could occur in various ways: microbial compounds communicate via the vagus nerve, which connects the brain and the digestive tract, and microbially derived metabolites interact with the immune system, which maintains its own communication with the brain. Sven Pettersson, a microbiologist at the Karolinska Institute in Stockholm, has recently shown that gut microbes help to control leakage through both the intestinal lining and the blood-brain barrier, which ordinarily protects the brain from potentially harmful agents.

Microbes may have their own evolutionary reasons for communicating with the brain. They need us to be social, says John Cryan, a neuroscientist at University College Cork in Ireland, so that they can spread through the human population. Cryan's research shows that when bred in sterile conditions, germ-free mice lacking in intestinal microbes also lack an ability to recognize other mice with whom they interact. In other studies, disruptions of the microbiome induced mice behavior that

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mimics human anxiety, depression and even autism. In some cases, scientists restored more normal behavior by treating their test subjects with certain strains of benign bacteria. Nearly all the data so far are limited to mice, but Cryan believes the findings provide fertile ground for developing analogous compounds, which he calls psychobiotics, for humans. "That dietary treatments could be used as either adjunct or sole therapy for mood disorders is not beyond the realm of possibility," he says.

Personality shifts

Scientists use germ-free mice to study how the lack of a microbiome—or selective dosing with particular bacteria—alters behavior and brain function, "which is something we could never do in people," Cryan says. Entire colonies of germ-free mice are bred and kept in isolation chambers, and the technicians who handle them wear full bodysuits, as if they were in a biohazard facility. As with all mice research, extrapolating results to humans is a big step. That is especially true with germ-free mice because their brains and immune systems are underdeveloped, and they tend to be more hyperactive and daring than normal mice.

A decade ago a research team led by Nobuyuki Sudo, now a professor of internal medicine at Kyushu University in Japan, restrained germ-free mice in a narrow tube for up to an hour and then measured their stress hormone output. The amounts detected in the germ-free animals were far higher than those measured in normal control mice exposed to the same restraint. These hormones are released by the hypothalamic-pituitary-adrenal axis, which in the germ-free mice was clearly dysfunctional. But more important, the scientists also found they could induce more normal hormonal responses simply by pretreating the animals with a single microbe: a bacterium called Bifidobacterium infantis. This finding showed for the first time that intestinal microbes could influence stress responses in the brain and hinted at the possibility of using probiotic treatments to affect brain function in beneficial ways. "It really got the field off the ground," says Emeran Mayer, a gastroenterologist and director of the Center for Neurobiology of Stress at the University of California, Los Angeles.

Meanwhile a research team at McMaster University in Ontario led by microbiologist Premsyl Bercik and gastroenterologist Stephen Collins discovered that if they colonized the intestines of one strain of germ-free mice with bacteria taken from the intestines of another mouse strain, the recipient animals would take on aspects of the donor's personality. Naturally timid mice would become more exploratory,

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whereas more daring mice would become apprehensive and shy. These tendencies suggested that microbial interactions with the brain could induce anxiety and mood disorders.

Bercik and Collins segued into gut-brain research from their initial focus on how the microbiome influences intestinal illnesses. People who suffer from these conditions often have co-occurring psychiatric problems such as anxiety and depression that cannot be fully explained as an emotional reaction to being sick. By colonizing germ-free mice with the bowel contents of people with irritable bowel syndrome, which induces constipation, diarrhea, pain and low-grade inflammation but has no known cause, the McMaster's team reproduced many of the same gastrointestinal symptoms. The animals developed leaky intestines, their immune systems activated, and they produced a barrage of pro-inflammatory metabolites, many with known nervous system effects. Moreover, the mice also displayed anxious behavior, as indicated in a test of their willingness to step down from a short raised platform.

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Bacterial Quorum sensing (QS) involves self-produced extracellular chemical signals, which can accumulate in a local environment to levels that are required to activate transcription of specific genes2,3,4. The first hints about QS came in the late 1960s and early 1970s, when investigators showed that genetic competence in Streptococcus pneumoniae5 and luminescence in two species of marine bacteria6,7 required the production of extracellular molecules. Cell–cell signalling via these molecules was proposed as a form of chemical communication, but these early publications were met with scepticism and generally ignored for the next 10–20 years. The 1980s brought two landmark discoveries: (i) the luminescence (lux) genes from the marine bacterium Vibrio fischeri were identified, and the genes required for what is now called quorum control of luminescence, luxI and luxR, were show to control lux gene transcription8,9; and (ii) the QS signal from V. fischeri was determined to be N-3-oxohexanoyl-L-homoserine lactone (3OC6-HSL)10 (Fig. 1a). The luxI gene codes for the autoinducer synthase that is required for 3OC6-HSL production, and luxR codes for a 3OC6-HSL-responsive transcriptional activator of the lux genes (Fig. 1a).

General interest remained muted for another decade. In the 1990s, DNA sequencing and comparative sequence analysis became everyday laboratory procedures, and gene pairs with homology to luxR and luxI began to attract the curiosity of some

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investigators. This led to an explosion of findings that other bacterial species controlled genes for conjugation, exoenzyme production and antibiotic synthesis with luxI–luxR-like systems2. A common theme emerged; the LuxI homologues catalysed synthesis of an acylated homoserine lactone (AHL) and the LuxR homologues all showed specificity for their cognate AHL. This convergence of discoveries led to the concept of QS (Fig. 1a); that the diffusible AHLs served as a proxy for cell density and allowed a bacterial species to produce costly extracellular public goods only when there was a sufficient biomass to benefit from the public goods4. Shortly thereafter, the QS signal from S. pneumoniae (often referred to as a pheromone) was shown to be a small peptide11, and Staphylococcus aureus was shown to use small cyclic peptide pheromones to activate genes for the production of extracellular toxins12. Quorum sensing was therefore shown to occur in both Gram-positive and Gram-negative bacteria via diverse chemical signals (Fig. 1b). An early study showed that a luminescent marine bacterium called Vibrio harveyi could sense a self-produced signal and also a signal or signals produced by other bacterial species to induce light production7. This phenomenon is considered to be a type of QS, in which cells of many species in a mixed microbial community sense the general bacterial population density via a molecule termed autoinducer-2 (AI-2)13,14. The strengths and weaknesses of this concept are discussed later in this Review. Further studies also described QS-like systems in eukaryotic microbes (the pathogenic fungi Candida and Histoplasma)15,16 and recently in viruses17, thus providing clear examples of convergent evolution. Some QS signals are volatile, for example the diffusible signal factor (DSF) and 3-hydroxy palmitic acid methyl ester (PAME) signals shown in Fig. 1b, and there is some evidence that volatile signalling can occur in a local atmosphere18. Functional studies followed the discovery of many of these systems and revealed that, for many plant and animal pathogens, QS mutants showed greatly reduced virulence12,19,20. The early connection between QS and pathogen virulence led to excitement about the idea of targeting QS as a novel approach to treat bacterial infections (Box 1).

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A global cooling trend known as the "little ice age" ended centuries ago, but it lives on in the deepest parts of the Pacific Ocean, researchers reported here last week at a meeting of the American Geophysical Union. What's more, this oceanographic time capsule could be helping blunt some of today's human-driven warming, at least for now.

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The oceans are a massive heat reservoir, absorbing some 90% of the warming from human-caused climate change. But this modern heat doesn't penetrate evenly—or quickly—into their vast depths. As part of a network of global ocean currents called the thermohaline circulation, chilled surface waters in the North Atlantic Ocean dive into the deep and, over the course of many centuries, wind their way to the deep North Pacific, which is in many ways Earth's cold storage locker.

That means the deep waters of the Pacific, unlike the relatively young Atlantic depths, should reflect surface temperature trends that are hundreds of years old. "From 1350 to the present day [those depths are] expected to be cooling," says Jake Gebbie, a physical oceanographer at the Woods Hole Oceanographic Institution in Massachusetts, who presented the work. "Cooling—despite the fact that the surface is warming."

A host of models of reconstructed global surface temperatures show that centuries ago, the world was unusually cold—as paintings of the frozen Thames River attest. After the "medieval warm period" ended in the 1400s, a cooling trend of a few tenths of a degree set in, ending only when human-driven warming began in the 1800s. By priming an ocean model with these historical surface temperatures, Gebbie and his co-author, Peter Huybers, a climate scientist at Harvard University, were able to predict where in the depths these trends would reveal themselves.

To test their model, they needed evidence of long-term temperature change from the deep ocean. But records below 2000 meters are sparse, produced only every decade or so during research cruises. And they're seemingly nonexistent prior to the 20th century. But not entirely.

In the 1870s, a British research ship, the HMS Challenger, spent half a decade recording ocean temperatures during a grand scientific tour across the globe, making 760 readings below 2000 meters with thermometers lowered by rope. The duo compared the Challenger's readings to measures taken from the 1970s onward, and tried to account for potential biases from that era, such as the stretchiness of hemp ropes and the behavior of early mercury thermometers under extreme pressure. After calibrating the old and modern data, "We see exactly what we see in the simulation," Gebbie said, "deep Pacific cooling and deep Atlantic warming."

In effect, the deep ocean acts as a filter, one that wipes out short-term temperature fluctuations and keeps the long-term trend. And this signal seems to persist despite

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large-scale phenomena, such as eddies, that can mix up the oceans. Assuming Gebbie's model is correct, the deep Pacific will continue to cool for decades as the little ice age water arrives.

"This is fantastic," says Yair Rosenthal, a paleoceanographer at Rutgers University in New Brunswick, New Jersey, who is impressed that Gebbie could trace the cooling flow of little ice age water to the deep Pacific. "If you caught a fish today in the deep Pacific and asked it what it thought about global warming," Rosenthal says, "it'd think that we are talking about the medieval climate."

But Greg Johnson, an oceanographer at the National Oceanic and Atmospheric Administration's Pacific Marine Environmental Laboratory in Seattle, Washington, cautions that the researchers used a coarse model of the ocean, which may not adequately simulate real conditions. They also did not consider how decadeslong variations in North Atlantic currents could influence the trends they see. "It is an interesting result, but I am skeptical," says Johnson, who is developing a program to regularly sample deep ocean temperatures with deep-diving robotic floats.

If real, this slow drop in deep ocean temperatures is a boon to a warming planet. If the little ice age hadn't cooled the oceans, they'd likely be absorbing less heat from the atmosphere today, and surface warming would be much worse than it already is. "It's buying us time," Rosenthal says. "It's buying us time."

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