diminished when ice caps retreated around 10,000–15,000 years ago.

Today, the annual journeys of the tracked populations happen within their own climate niches — individuals from the same population experience the same conditions, but conditions differ between the populations. This might be one reason why individuals seem to keep consistently to the same routes and use the same population-specific wintering grounds in temperate and tropical regions.

The authors' analysis suggests that the gene *ADCY8* might have a role in aiding the migratory behaviour of peregrine falcons. From the comparison of DNA sequences between the different bird populations, Gu and colleagues found that this particular gene is highly divergent between the different populations and is probably under some type of selection. This gene might also be functionally linked to aiding the long-term memory that could be particularly important for the populations that have to undertake longer-distance journeys. Learning probably has a role in successful migration, and Gu *et al.* focused on identifying inherited genetic components that might enable learning through memory formation. Other work[6] has also investigated the role of genes that are possibly linked to long-term memory in the context of bird migration.

Gu and colleagues' work provides a prime example of how interdisciplinary approaches and sophisticated statistics can be used to infer the evolutionary history of population sizes. Their research also shows how the timing of splits in divergent populations can be used to infer patterns in an ecological–evolutionary framework. Such insights enable the modelling of community dynamics across large time spans, including past and future scenarios. Gu *et al.* notably conclude that the Arctic-breeding populations that migrate to Europe will experience dramatic future changes as a consequence of global warming, and that this will require specific behavioural adjustments, including adaptations for shorter migratory distances.

The interdisciplinary nature of Gu and colleagues' research could provide a blueprint to motivate similarly holistic approaches. Migratory species that have a wide diversity of migratory strategies are ideal model systems to consider for such efforts. For example, some subspecies of the white crowned sparrow (*Zonotrichia leucophrys*) in North America undergo a long-distance migration, whereas others are non-migratory[7]. The Eurasian blackcap (*Sylvia atricapilla*) has large migratory variations, particularly regarding the orientation and routes taken by members of this species[8].

Furthermore, and particularly in the context of investigating memory formation in relation to migrations, it is probably inevitable that studies similar to that carried out by Gu *et al.* will be undertaken to compare the first migration of juvenile birds with the routes they take as experienced adults. Species in which routes are taught to the juveniles by adults, such as in crane families[9], should also be investigated. The data should then be compared with analysis of some of the many shorebird or passerine species in which juveniles on their first migratory journey either manage migration on their own or even choose different routes from those of the adults[10]. Such comparative approaches and the complementary strengths of various study systems might pave the way to characterizing the genetic architecture of migratory behaviour and provide proof of causal factors.

There is arguably a thin line that separates oversimplifications within one discipline from the combining power provided by interdisciplinary research. However, Gu and colleagues' study is yet another example of the value of taking an interdisciplinary path that places the evidence from different fields in context to offer new insights and push scientific boundaries. More of this will be needed to understand complex behavioural processes such as migration. It will also provide the toolbox necessary for effective conservation work to preserve a natural phenomenon that awes and inspires us, and that is integral to many of Earth's ecosystems.

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Immunology

Cancer aided by greasy traitors

Caroline Perry & Ulf H. Beier

Cancer can evade destruction by the immune system if aided by immunosuppressive regulatory T cells. These cells depend on a lipid-production pathway in the tumour environment, a vulnerability that might be used to target them. **See p.306**

Immune cells called regulatory T cells (T_{reg} cells) are a subset of T cells that selectively dampen immune responses. They do this by suppressing the activation of inflammation-promoting T cells, and also by secreting anti-inflammatory factors[1]. Such blunting of an immune response is valuable because it prevents the immune system from turning on a person's own body — a type of malfunction that occurs in autoimmune disease. However, T_{reg} cells can benefit tumours by suppressing cancer-attacking immune cells, such as CD8 T cells (also known as killer T cells). On page 306, Lim *et al.*[2] identify a metabolic dependency of T_{reg} cells in the tumour microenvironment, a finding that reveals how the cells operate there.

Immunotherapy is used in the clinic to overcome a tumour's evasion of killer T cells. The approach can include treatments such as antibodies that target T_{reg} cells[3]. Although such therapy boosts anticancer immune responses, it can have a negative effect on T_{reg} cells elsewhere in the body that help to keep the immune system in balance. As a result, people receiving such treatments often develop autoimmune disease[4]. A major unmet need is therefore immunotherapy that targets only the 'bad' T_{reg} cells in the tumour vicinity while leaving the beneficial T_{reg} cells untouched.

To find a way to single out the unwanted T_{reg} cells, Lim and colleagues used mice that had a type of tumour called melanoma. They compared the gene-expression profiles of T_{reg} cells extracted from the tumour vicinity with those taken from elsewhere in

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the animal's body. Only tumour-associated T_{reg} cells expressed genes whose expression is controlled by a group of transcription factors called sterol regulatory element binding proteins (SREBPs). These proteins drive the expression of genes encoding enzymes that produce lipids[5], such as fatty acids and cholesterol (Fig. 1), which are needed for processes including cellular signalling and the construction of cell membranes.

To test whether this lipid-producing transcriptional signature is functionally important, Lim and colleagues used genetically engineered mice in which the SREBP-mediated gene-expression pathway was switched off specifically in T_{reg} cells. The authors monitored the growth of tumour cells transplanted beneath the animals' skin, and found that this interruption of SREBP resulted in much better antitumour immune responses in two forms of cancer than occurred in animals that had functional SREBPs.

Mice that did not receive tumour transplants but lacked SREBP-mediated gene expression showed no signs of autoimmune disease. This indicates that T_{reg} cells outside the tumour environment were functioning normally without the need for SREBP-mediated gene expression. Even when these animals were manipulated to develop an autoimmune brain disease similar to human multiple sclerosis, they had the same level of disease severity as did mice with normal T_{reg} cells. That result demonstrates that SREBP-mediated gene expression is needed for T_{reg} cells in the tumour environment but can be dispensable for other T_{reg} cells.

Why is SREBP-mediated lipid production needed for tumour T_{reg} cells? Cancers extract lipids from their surroundings and use these molecules to fuel their energy and growth[6]. In theory, a scarcity of lipids around tumours might mean that tumour T_{reg} cells must make their own lipids. But there is more to this requirement for SREBPs than just to satisfy the cell proliferation and energy needs of T_{reg} cells.

Lim and colleagues identify two key roles for SREBPs (Fig. 1a, b). First, they show that tumour T_{reg} cells need SREBPs to generate fatty-acid synthase, an enzyme involved in fatty-acid synthesis. If this enzyme is missing, tumour T_{reg} cells do not become fully mature, losing effectiveness and showing a diminished ability to blunt immune responses compared with T_{reg} cells that have this enzyme.

Second, Lim *et al.* demonstrate that, for T_{reg} cells to carry out their usual anti-inflammatory role in the tumour environment, they rely on what is called the mevalonate pathway (Fig. 1b). This SREBP-dependent pathway produces cholesterol, as well as other molecules, including geranylgeranyl pyrophosphate (GGPP). GGPP becomes bound to proteins through a process called prenylation. The addition of GGPP changes the target protein's chemical properties, in much the same way that other types of protein modification, such as phosphorylation and acetylation, alter the modified protein.

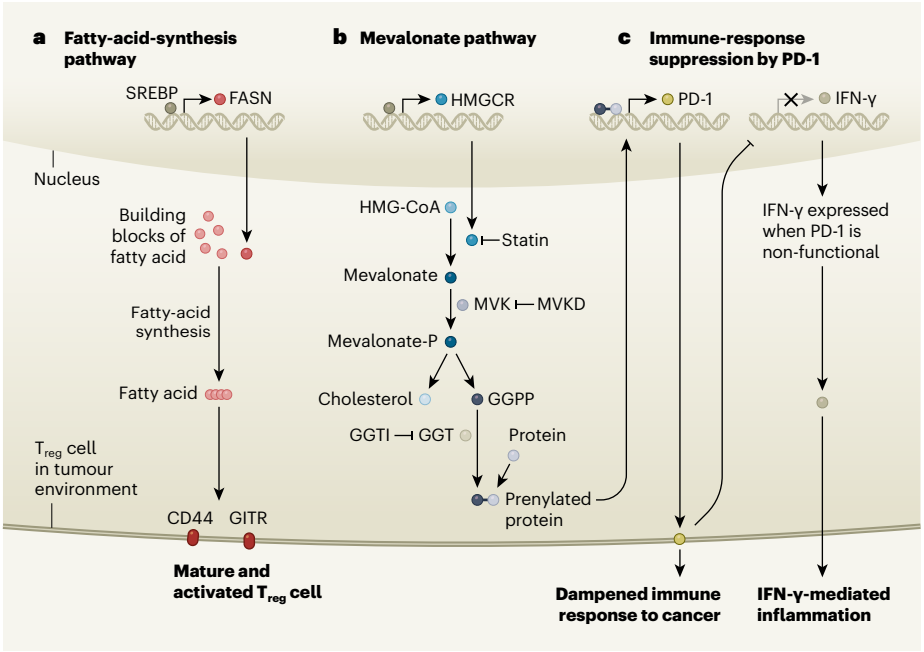

Figure 1 | Key pathways for a regulatory T cell (T_{reg} cell) in the tumour microenvironment. Lim *et al.*[2] report that two lipid-synthesis pathways operate when T_{reg} cells of the immune system are close to a tumour. **a**, One pathway produces fatty acids and requires SREBP transcription-factor proteins, which promote the expression of the enzyme fatty-acid synthase (FASN). This pathway enables T_{reg}-cell activation and maturation, which depend on the membrane proteins CD44 and GITR. **b**, The other pathway, called the mevalonate pathway, also requires SREBPs. An enzyme called HMG-CoA reductase (HMGCR) in this pathway is the target of cholesterol-lowering statin drugs. The pathway enzyme mevalonate kinase (MVK), which adds a phosphate group (P) to mevalonate molecules, is mutated in the autoinflammatory disease mevalonate kinase deficiency (MVKD). Geranylgeranyl pyrophosphate (GGPP) molecules made in this pathway are joined to proteins in a step called prenylation. This is catalysed by the enzyme geranylgeranyl transferase (GGT), which can be targeted by an inhibitor (GGTI). **c**, Expression of the protein PD-1 presumably requires a prenylated protein (because GGPP is needed for PD-1 expression). PD-1 hinders other immune cells from targeting the cancer and blocks expression of the pro-inflammatory protein interferon-γ (IFN-γ).

Lim and co-workers provide evidence linking GGPP production through the mevalonate pathway to the expression of a gene that encodes an immunosuppressive protein called PD-1. The prenylated protein that is presumably required for PD-1 expression is unknown; however, the authors demonstrate that, without GGPP, tumour T_{reg} cells did not upregulate the gene encoding PD-1. They show that PD-1 is required to 'stabilize' tumour T_{reg} cells: treatment of the tumour-bearing mice with an antibody that blocks PD-1 function leads to the expression of genes not normally associated with T_{reg} cells, such as a gene that encodes the pro-inflammatory protein interferon-γ (Fig. 1c). T_{reg} cells that produce interferon-γ can't shield a tumour from attack by the immune system[7].

The fact that a T_{reg}-cell population found in the context of cancer is metabolically vulnerable is a profound revelation. It might point the way towards the development of less toxic immunotherapies that selectively target damaging T_{reg} cells. With hundreds of clinical trials currently under way that are examining how anticancer immune responses might be boosted, attempts to destabilize tumour T_{reg} cells by targeting the pathways highlighted by Lim and colleagues will undoubtedly be of interest.

Drugs that specifically inhibit the mevalonate pathway are already in clinical use to combat cardiovascular disorders. For example, statins are a class of cholesterol-lowering drug that has been used by millions of people since the 1980s. Indeed, mortality is lower in people with tumours who are taking statins — a finding observed for cancers that include multiple myeloma[8], oesophageal cancer[9] and pancreatic cancer[10]. The idea of interrupting the mevalonate pathway as a way of treating cancer is gaining support because it has been observed that, compared with normal cells, some tumour cells have an increased demand for molecules generated downstream of this pathway[11]. It is fascinating to speculate that T_{reg} cells might have contributed to these earlier clinical observations. Perhaps inhibitors of the mevalonate pathway or inhibitors of GGPP-mediated prenylation will play a part in future anticancer therapies.

The key role of fatty-acid synthase in tumour T_{reg}-cell function is an interesting discovery,

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given that other research[12] indicates that inhibition of the enzyme acetyl-CoA carboxylase 1 (which functions one step upstream of fatty-acid synthase in the same pathway) boosts the formation and function of T_{reg} cells in the same autoimmune brain disease mouse model as that used by Lim and colleagues. These findings suggest that the effects of disrupting T_{reg}-cell function by interrupting SREBP-dependent fatty-acid synthesis is context dependent. Outside the tumour environment, disrupting fatty-acid synthase had no effect, whereas inhibiting acetyl-CoA carboxylase 1 actually conferred benefits on T_{reg}-cell function[12].

Lim and colleagues' study has implications beyond the realm of cancer. A rare autoinflammatory disease called mevalonate kinase deficiency is caused by a mutation in the gene encoding the enzyme mevalonate kinase, which acts in the mevalonate pathway. The disease is thought to be driven by defective protein prenylation, but the lack of a clear mechanistic understanding of the underlying cause has hampered efforts to develop an effective treatment[13]. Lim and colleagues' evidence raises the question of whether PD-1 or T_{reg} cells might be linked to this disease. The possibility warrants further investigation.

The research by Lim *et al.* reinforces the need to understand the relationship between metabolic pathways and the regulation of immune-system function. As this work shows, such insights could be vital in efforts to treat cancer.

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Astroparticle physics

Icy window on the physics of cosmic neutrinos

Carla Distefano

Evidence of a rare neutrino-interaction process called the Glashow resonance has been observed by a detector buried deep in the Antarctic ice — opening up a way to probe neutrino formation in astrophysical sources. **See p.220**

Neutrinos are the most elusive of the fundamental particles, and come in three types: the electron neutrino, the muon neutrino and the tau neutrino. Almost massless and lacking electric charge, they interact with matter only through a fundamental force known as the weak interaction, which is mediated by force-carrying particles called W and Z bosons. In 1959, the theoretical physicist Sheldon Glashow used the standard model of particle physics to predict[1] that negatively charged W bosons (W^- bosons) can be formed in the collisions between an electron and an electron antineutrino (the antimatter version of an electron neutrino). This process is now called the Glashow resonance, and occurs for electron antineutrinos that have energies of about 6.3 petaelectronvolts (1 PeV is 10^{15} eV).

The Glashow resonance has not been observed in laboratories, because the antineutrino energy required is beyond the range of currently available particle accelerators. However, naturally occurring antineutrinos that are produced in cosmic processes can reach energies up to tens of PeV (ref. 2). On page 220, the IceCube Collaboration reports the detection of an event produced by an antineutrino from an astrophysical source, which could be the first observation of the Glashow resonance[3].

When a neutrino interacts with matter, charged particles are produced. These emit light known as Cherenkov radiation when they travel through a transparent medium (such as ice or water) at a speed greater than the speed of light in that medium. High-energy astrophysical neutrinos can thus be observed by instruments that detect Cherenkov radiation in such a medium. Because the expected fluxes in the number of astrophysical neutrinos at the energy levels of interest are low, and these fluxes are thought to decrease rapidly as the energy of neutrinos increases[2], large volumes of the transparent medium are needed.

The IceCube Neutrino Observatory is a neutrino detector buried in the deep ice near the Amundsen–Scott South Pole Station in Antarctica (Fig. 1). Its main goal is to observe neutrinos produced from the most powerful astrophysical sources in the Universe, such as active galactic nuclei and γ-ray bursts, or from cataclysmic phenomena such as exploding stars and mergers of black holes or neutron stars. IceCube can detect all flavours of astrophysical neutrino, at energies beyond the exaelectronvolt range (1 EeV is 10^{18} eV). It consists of 5,160 digital optical modules (DOMs; devices capable of detecting faint light signals), arrayed over one cubic kilometre of Antarctic ice, buried at depths of 1,450–2,450 metres. The DOMs are attached to 86 vertical strings spaced 125 metres apart in the ice, deployed on a hexagonal grid.

Cherenkov radiation detected by the DOMs is used to reconstruct the properties of the neutrino that triggered it — such as its energy, and the direction from which it arrived. The topology of the radiation burst can also be instructive. For example, when a muon neutrino interacts with matter, it can create a muon particle that travels several kilometres[4]. This produces an elongated, luminous trajectory in the ice called a track. Other neutrino flavours produce cascades of secondary particles within a spherical region just 10 metres in diameter[5]. The spatial and temporal features of detected light signals thus contain information about the neutrino flavour, and about the interaction channel (the process by which the neutrino interacted with matter; the Glashow resonance is one type of interaction channel).

Antineutrinos that interact with matter through the Glashow resonance are expected to produce characteristic events in which the resulting W^- boson decays into a cascade of secondary particles, including particles called hadrons. Roughly 5% of the neutrino energy in these events is expected to be taken up by secondary particles that are neutral or don't have enough energy to produce Cherenkov radiation[5], limiting the amount of energy that can be observed to about 6.0 PeV. Moreover, low-energy muons are expected to be

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