and burns mainly sugar, rather than the sugar and lipid combination processed by most thermogenic fat. Its discovery could open up new therapeutic possibilities for weight loss.

Thermogenic fat cells are currently classified as either brown or beige[4]. Unlike brown fat, beige fat cells are found interspersed in white fat. The production of beige fat cells can be triggered in response to cold by activation of the β-adrenergic-receptor proteins on the surface of precursor cells in white-fat tissue depots. These receptors are stimulated by the β-adrenergic signalling pathway, which originates in the nervous system.

Extensive efforts have been made to target thermogenic fat for weight loss, but no successful drug has been developed so far. This is due partly to the fact that the amount of active brown fat varies between individuals, and decreases with age. In addition, current strategies to induce the formation and activation of beige fat typically involve simulating cold responses, and are thought to act through β-adrenergic signalling. This inevitably affects other organs, because the β-adrenergic receptors are widely expressed across various tissues[5] — and such a lack of specificity raises safety issues. Thus, other ways of inducing the formation and activation of thermogenic fat would be very valuable.

Chen *et al.* set out to identify alternative pathways by which to activate thermogenic fat using a mouse model called the β-less mouse, which lacks all three β-adrenergic receptors. They confirmed previous reports[6,7] that some beige fat cells were still produced under these conditions (Fig. 1).

Where do these cells come from? Chen *et al.* performed an in-depth characterization of gene expression in the fat tissues of the β-less mice, which revealed that genes involved in muscle development were more highly expressed in fat tissues lacking β-adrenergic receptors than in those of control animals. The authors genetically engineered mice so that cells expressing one such gene, *Myod* (which encodes the protein MyoD and is normally expressed in muscle-cell precursors), were indelibly labelled with a fluorescent protein. They then blocked β-adrenergic signalling using a drug and exposed the mice to mild cold, before tracking the fate of MyoD-expressing cells and their descendants. This lineage-tracing experiment revealed that some MyoD-expressing cells give rise to a subset of beige fat cells, suggesting that muscle-cell precursors can be reprogrammed to turn into specific beige fat cells.

When they analysed the gene-expression profiles of the cells, Chen *et al.* found that this subset of beige fat differs from that of conventional beige fat. The subset expresses higher levels of many genes involved in sugar and carbohydrate metabolism and glycolysis — the process by which energy is produced from glucose. On the basis of this profile, the authors dubbed the cells glycolytic beige fat (g-beige fat). The data indicated that the transcription factor GABPα drives the differentiation of MyoD-expressing progenitors into g-beige fat cells. The authors confirmed this supposition *in vitro*, showing that overexpression of GABPα in muscle progenitors leads to their differentiation into fat.

Chen *et al.* next demonstrated that g-beige fat has a physiological role in mice, mainly burning sugar to produce heat. G-beige fat was generated in wild-type animals subjected to prolonged, harsh cold conditions. Moreover, animals engineered so that they could not produce g-beige fat showed reduced glucose uptake and oxygen consumption in fat compared with controls; their ability to control their body temperature in response to cold was also impaired.

The authors' findings are exciting for several reasons. First, this study reinforces the idea that mature fat is composed of various cell types[8,9]. It is plausible that other subpopulations of brown, beige and even white fat cells exist. These cell types might have different roles in regulating body-wide metabolism. Furthermore, it is possible that the g-beige fat cells have functions besides thermogenesis. For example, in recent years it has become evident that brown fat communicates with other tissues by secreting specific signalling molecules[10] — perhaps g-beige fat similarly modulates hormone signalling in the body to promote cross-talk with other fats or other tissues.

Second, g-beige fat is induced through a previously unknown pathway, which might be targeted specifically to improve glycolytic control — a key factor in the treatment of type 2 diabetes. And if these cells are also present in humans, their characterization might pave the way for new approaches to activating thermogenic fat cells. For such approaches to be successful, researchers would first need to determine how g-beige fat is induced, including which receptors and subsequent signalling cascades trigger GABPα-mediated differentiation.

In light of the current obesity epidemic, efficient and safe approaches are required to regulate excess body weight. The discovery of g-beige fat could provide a sweet way to do just that. ■

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EARTH SCIENCE

Experiments cast light on mantle mineralogy

A technically challenging analysis has revealed the physical properties of a mineral at pressures and temperatures as high as those in Earth's mantle. The findings have implications for our understanding of Earth's deep interior. SEE LETTER P.218

JOHANNES BUCHEN

The movement of tectonic plates carries parts of Earth's crust back into the deep interior of the planet. Earlier in Earth's history, processes that preceded the present regime of tectonic motion might also have forced crustal rocks to sink into Earth's mantle[1]. The fate of crustal material recycled in the mantle, however, is unknown. On page 218, Gréaux *et al.*[2] present measurements of the speed of sound in one of the minerals that are thought to form in recycled crustal rocks, at pressures and temperatures that resemble those in Earth's mantle. The findings promise to facilitate the use of seismic waves to track crustal rocks in the mantle.

Beneath the oceans, Earth's crust consists mainly of a rock called basalt. When exposed to high pressures as a result of tectonic processes, basalt transforms into an assemblage of minerals that is denser than the rocks of the underlying mantle. Basaltic rocks can therefore sink into the mantle, where they are exposed to rising pressures and temperatures that drive further mineral transformations[3,4]. One of these reactions produces the mineral calcium silicate perovskite (CaPv).

The crystal structure of CaPv has cubic symmetry at temperatures greater than about

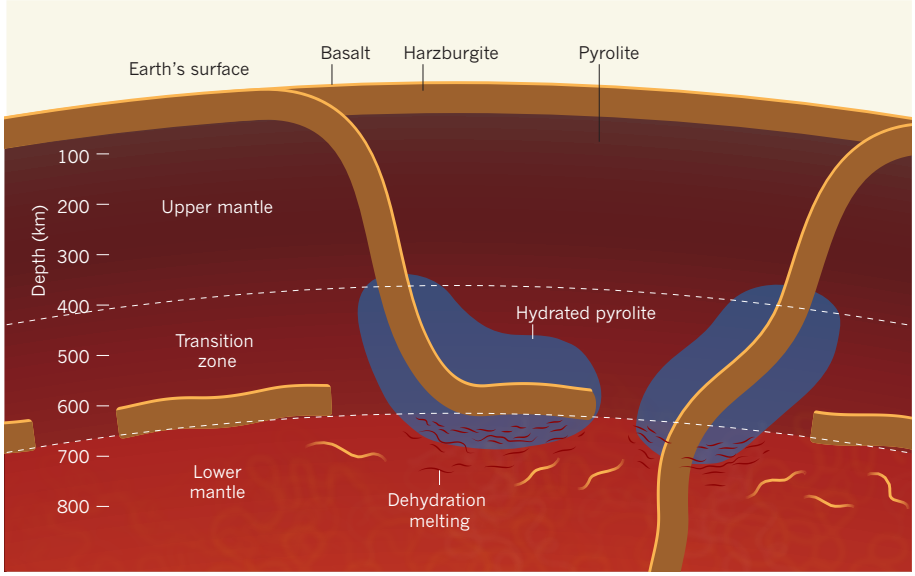

Figure 1 | Current theories for the recycling of oceanic crust in Earth's mantle. Slabs of oceanic crust (which is formed mainly of a rock called basalt) and underlying mantle rocks (harzburgite) sink into Earth's mantle, which is often modelled as being formed from a hypothetical rock called pyrolite. Basalt accumulates within and beneath the transition zone between the upper and lower mantle. In downwelling regions, hydrated rocks in the transition zone are pushed into the lower mantle, where they release water bound in their minerals. The resulting aqueous fluids can trigger melting. This dehydration melting could explain[10,11] why seismic waves have low velocities in some regions at depths greater than 660 kilometres. Gréaux *et al.*[2] report that basaltic rocks in the mantle will also have slow seismic waves. The presence of basaltic rocks at depths greater than 660 km could therefore be an alternative explanation for the low seismic-wave velocities in these regions.

600 kelvin, and this cubic form is probably adopted at the high temperatures present in the mantle. However, the crystal structure of CaPv spontaneously distorts to a tetragonal form at lower temperatures. CaPv must therefore be held at high temperatures and pressures to determine the physical properties of the cubic phase.

In their experiments, Gréaux *et al.* synthesized CaPv, and analysed both the cubic and the tetragonal forms at high pressures and temperatures in a high-pressure apparatus. They measured the time taken for ultrasonic waves to travel through the CaPv at different pressure–temperature combinations, and irradiated the samples with intense X-rays to generate images and diffraction patterns. By combining these measurements, the authors derived sound-wave velocities and elastic moduli (which quantify the resistance of a solid material to small, non-permanent deformations) for CaPv.

Gréaux and colleagues found that the shear modulus of cubic CaPv, which specifically measures the resistance of the mineral to reversible deformation caused by distortions (shear deformation), is substantially lower than estimates[5,6] calculated using first-principle computations. The difference reflects the fact that the computed sound-wave velocities were significantly higher than those measured in the experiments. The experimental findings highlight the importance of assessing the elastic and acoustic properties of mantle minerals at relevant pressures and temperatures that, in the case of CaPv, would stabilize the cubic form. The authors went on to use the new data for cubic CaPv to improve estimates of the velocities of seismic waves travelling through rocks in Earth's mantle.

The boundary between Earth's upper and lower mantle is marked by steep gradients in density and seismic-wave velocities at depths of around 660 kilometres. The pressures and temperatures thought to prevail at this depth coincide with major changes in the mineral assemblage of pyrolite — the hypothetical rock that is often used as a model for the rocks that constitute the bulk of the mantle. These mineral transformations increase the density of pyrolite, so that basaltic materials become buoyant at depths of between 660 km and 750 km (refs 4, 7, 8). Geodynamic simulations[9] show that the sequence of density changes in this region can effectively trap recycled oceanic crust.

Gréaux and colleagues' results suggest that seismic waves travel much more slowly through recycled oceanic crust than through pyrolite at depths of between 660 km and 770 km. Consequently, the authors propose that the presence of trapped basaltic rocks could explain the reduction of seismic-wave velocities that has been observed locally at these depths (Fig. 1). The reduction was previously attributed[10,11] to deep dehydration melting — the process in which water is released from the crystal structures of hydrous minerals, causing melting. The report last year of the discovery[12] of a fragment (an inclusion)

50 Years Ago

Later this year, in November, *Nature* will be a hundred years old. For much of the century, the journal has contributed in several unrelated ways to the development of science. From the beginning, of course, it has been a professional journal, but at the beginning it was most especially a means by which the still small and informal profession of science could be kept aware of events within and of pressures from outside. The early volumes of *Nature* contain an entirely readable mixture of opinion, news — particularly the doings of universities, learned societies and observatories — and occasionally of argument … For a great many years, the correspondence from readers was largely concerned with natural curiosities … Only by the turn of the century did the correspondence columns become a vehicle for the announcement of important discoveries in science.

From *Nature* 11 January 1969

100 Years Ago

The Saxon State Railways are now submitting their engine-drivers and other responsible train officials to certain tests in their psychometric laboratory at Dresden … [T]he tests comprise strength of will and endurance, and fatigue where there is physical strain. The Dubois ergograph is used for the purpose, the object being to trace a fatigue curve. The forearm rests on the table; over the middle finger is run a catgut loop, which passes over a pulley, the other end of the gut supporting a weight of from 4 to 8 kg., according to the suitability of the subject. When the middle finger is bent the weight is raised, and when relaxed again the weight is dropped, the process of this motion being traced on a recording drum … The system has been said to give satisfactory results as regards the selection of men for the proper posts.

From *Nature* 9 January 1919

of CaPv in diamonds that formed in the deep mantle supports Gréaux and colleagues' hypothesis. However, inclusions of a hydrous mineral[13] and of pressurized ice[14] in two other diamonds point to the presence of water-containing fluids at similar depths, in support of the alternative hypothesis.

Global-scale geodynamic simulations[9] indicate that oceanic crust descending into the mantle accumulates to form a layer that is enriched in basaltic rocks, centred at a depth of around 600 km — that is, at shallower depths than would be inferred from experimentally derived rock densities alone[4,7,8]. Gréaux and colleagues' results show that, in basalt, the velocities of the two types of seismic wave (known as shear (S) waves and compressional (P) waves) remain lower than global average seismic velocities at that depth, although the reduction in velocity is less than the reduction that occurs at depths greater than 660 km. It is known that P waves are converted to S waves at depths of around 600 km by globally distributed zones that have below-average S-wave velocities[15]. The idea that a layer of basaltic rocks scatters seismic waves at around 600 km depth could reconcile the seismic observations with the geodynamic predictions and with Gréaux and colleagues' models derived from the measured physical properties of minerals.

Further seismological studies are necessary to map zones that have low seismic velocities through a range of depths, and to better constrain their characteristics — for example, to measure differences in the velocities of P and S waves relative to the surrounding mantle. Measurements of sound-wave velocities in single crystals of CaPv (rather than in polycrystalline samples, as studied by Gréaux *et al.*) would also reveal how such velocities depend on the direction of passage through the crystal lattice. The effect of the crystal lattice might give rise to an observable direction dependence of seismic-wave velocities in the mantle. Devising models that combine seismological data with constraints derived from geodynamic simulations and data for the physical properties of minerals will aid the search for recycled oceanic crust in Earth's mantle. ■

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IMMUNOTHERAPY

Immune cells track hard-to-target tumours

Clinical trials reveal that personalized vaccines can boost immune-cell responses to brain tumours that don't usually respond to immunotherapy. The findings also point to how to improve such treatments. SEE LETTERS P.234 & P.240

NEEHA ZAIDI & ELIZABETH M. JAFFEE

Instructing the immune system to recognize and kill tumours, an approach termed cancer immunotherapy, has transformed the clinical treatment of certain types of malignancy. Prominent among these therapies are immune-checkpoint inhibitors, which block the action of proteins that dampen immune-cell responses against tumours. For example, antibodies can be used to interfere with the inhibitory protein PD-1, which is present on T cells, a type of immune cell that attacks tumours. Immune-checkpoint inhibitors have been most successfully used to treat cancers, such as melanomas, that are well infiltrated by T cells and have a large number of genetic mutations[1,2]. A subset of these mutations might generate neoantigens — altered protein sequences that are uniquely produced in cancer cells and are recognized as foreign by the immune system[3].

Most cancers, however, including brain tumours called glioblastomas, do not respond to immune-checkpoint therapy. These non-responsive tumours typically have a low level of mutations and express few neoantigens; that is, they have an immunosuppressively 'cold' tumour microenvironment . They therefore fail to attract T cells that can infiltrate the tumour. Finding ways to boost an immune response to such tumours is an ongoing challenge. Keskin *et al.*[4] (page 234) and Hilf *et al.*[5] (page 240) report their progress in this area, and present the results of separate phase I clinical trials in which people with glioblastoma were treated with a personalized vaccine containing neoantigens that were specific to the individual's own tumour (Fig. 1).

Keskin *et al.* gave eight people who had undergone surgery to remove their tumour, and had received radiotherapy, a vaccine containing up to 20 protein fragments corresponding to neoantigens expressed in the person's tumour. These neoantigens were chosen by analysing the tumour material removed during surgery. Analysis of blood samples from the people who had been vaccinated then revealed whether types of T cell called helper $CD4^+$ T cells and killer $CD8^+$ T cells were responding to these neoantigens.

The authors found that the vaccine failed to elicit a robust T-cell response in the participants who had also been treated with the drug dexamethasone, which is a potent steroid immunosuppressant used to decrease swelling around the brain. The two people who had not received dexamethasone exhibited a neoantigen-specific T-cell response consisting of predominantly $CD4^+$ T cells as well as $CD8^+$ T cells. Notably, these neoantigen-specific T cells secreted proteins called cytokines, which are involved in killing tumour cells. These two people had T cells that expressed surface proteins known to be a hallmark of T cells that have acquired memory status — a characteristic that enables a faster and more robust immune response to a particular neoantigen if it subsequently re-emerges. However, all the vaccinated patients, even the two who responded, ultimately died of the cancer.

One key finding of this study relates to the T cells present in surgically removed samples of recurring tumour growth in one of the responders' tumours. In this case, the neoantigen-specific T cells in the tumour expressed proteins indicating that the cells had entered a dysfunctional state termed exhaustion. This state corresponds to a decreased ability to recognize and kill cancer cells. Exhausted T cells can sometimes be reinvigorated using immune-checkpoint inhibitors.

Hilf *et al.* tested a strategy that used two types of vaccine. One of these, similar to the one used by Keskin and colleagues, consisted of a personalized neoantigen vaccine. The other vaccine consisted of non-mutated protein fragments corresponding to tumour-associated proteins present on cancer cells. This latter vaccine was not personalized to match each individual's proteins — the tumour-associated proteins were