found that introducing BCL-6 and MTA3 into plasma cells caused them to 'dedifferentiate' towards a B-cell state. The cells began to express numerous protein 'markers' of B cells. Conversely, they no longer expressed Blimp-1 or XBP1 (a key regulator of the ability of plasma cells to secrete antibodies[9]). Although this dedifferentiation is surprising, the potential for such plasticity is in fact built into double-negative regulatory networks[1].

An important caveat is that the dedifferentiation was accomplished with malignant plasma cells derived from a patient with multiple myeloma. The ability of BCL-6 and MTA3 to push these cells towards the B-cell state may have been helped by the fact that the cells are, abnormally, still dividing[10]. This is because they express *c-myc*, owing to a chromosomal translocation — an abnormal event in which segments of different chromosomes are swapped about, potentially affecting the expression of any genes involved, and often contributing to cancer. It will be interesting to conduct studies in which BCL-6 and MTA3 are overexpressed at various stages of normal plasma-cell differentiation, to see whether the same dedifferentiation results.

Turning a vice into a virtue, however, these experiments may help to explain some puzzling aspects of human lymphoid cancers. A cancer generally derives from one abnormal cell, which multiplies to produce a clone of malignant cells. In multiple myeloma, however, not all the cells in the so-called clonal population are alike: although most resemble plasma cells, a few lack plasma-cell proteins and instead express markers of B cells[11]. This minor population of cells may be more proliferative than the rest, and there is evidence that they form tumours more readily in immunodeficient mice[12]. This leads to the somewhat controversial notion that such cells are myeloma 'stem cells'[11,12] — a pool of cells that can both multiply themselves and produce different cell types (in this case, the cells that resemble plasma cells, perhaps). Meanwhile, the cells that resemble plasma cells might be less proliferative, but they might also be long-lived and accumulate because of survival signals that they receive from the bone-marrow microenvironment in which they grow.

In light of Fujita and colleagues' findings, it is conceivable that the myeloma 'stem cells' are produced through the dedifferentiation of the cells that resemble plasma cells back into the germinal-centre B-cell state. It will be fascinating to see whether the proliferation and 'tumorigenicity' of myeloma cells is affected when the balance between BCL-6 and Blimp-1 is experimentally perturbed.

The new results might also see use in the clinic. The importance of BCL-6 in human lymphomas is already known: it is the most frequently translocated gene in non-Hodgkin's lymphomas[13], and is characteristically expressed by certain lymphoma subgroups[14]. Manipulating the BCL-6–Blimp-1 circuit might be useful in treating lymphomas, given that inhibiting BCL-6 activity in cultured lymphoma cells causes them to differentiate into plasma cells and stop dividing[4]. And now that MTA3 is known to be important to BCL-6 function, another window of opportunity has opened: next, we need to identify small-molecule inhibitors of this interaction. Perhaps the plasticity inherent in a double-negative regulatory circuit can be harnessed to therapeutic effect. ■

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Climate

Wider connections for El Niño

William J. Randel

Data from Europe in 1940–42, and simulations of severe El Niño events, suggest that the effects of such events can be unexpectedly far-reaching. The stratosphere could be a key player in this behaviour.

Climate variations associated with the El Niño/Southern Oscillation (ENSO) cause droughts, floods and extreme temperatures over much of the tropics, and the effects are often felt in North America. Brönnimann *et al.*[1] (page 971 of this issue) now show that climate anomalies associated with the large El Niño of 1940–42 extended to much more of the Northern Hemisphere, including Europe. The atmospheric circulation anomalies also reached into the stratosphere, influencing the ozone layer. Similar results from climate-model simulations likewise suggest that the effects of extreme ENSO events may be more far-reaching than previously thought.

El Niño is characterized by a warming of the surface water in the eastern Pacific Ocean that occurs irregularly every 3–7 years. The warming is caused by anomalous ocean circulation in the tropical Pacific, which is in turn linked to systematic changes in winds and storms throughout the Pacific region. The associated variations in atmospheric circulation were originally termed the Southern Oscillation, hence the designation ENSO for the coupled ocean–atmosphere cycles[2].

The tropical Pacific storms associated with ENSO have their far-reaching effects through the generation of planetary-scale atmospheric waves. These result in coherent climate anomalies — 'teleconnections' — over distant regions of the globe, which are experienced locally as persistent wet or dry periods, or systematic changes in storms or hurricanes. Teleconnections for ENSO include droughts or floods over parts of Africa, South Asia, Australia and South America. They also extend to high latitudes, in particular influencing temperatures and precipitation over North America by the so-called Pacific–North American teleconnection pattern. But most previous studies have suggested that ENSO has a relatively

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Figure 1 **Europe, winter 1940 — a Pacific link?**

small (or highly variable) impact on European climate[3].

Enhanced planetary waves during ENSO events also propagate vertically and influence winter circulation in the stratosphere, although the effects are typically small compared with other sources of stratospheric variability. Systematic searches for ENSO effects in the stratosphere have shown only weak or variable signals[4].

Brönnimann *et al.*[1] began by analysing some of the earliest measurements of atmospheric ozone, extending back to the 1930s at several European stations[5]. The data show unusually high and persistent values between 1940 and 1942, although the observations were never explained at the time. This wartime period also saw the first systematic (but sparse) balloon-borne measurements of the upper atmosphere. These measurements have been used in statistical 'reconstructions' of meteorological conditions in the upper atmosphere, and detailed comparisons with the ozone measurements show that the period of anomalously high ozone was associated with persistent meteorological anomalies in the lower stratosphere during winter. In particular, the polar stratosphere was relatively warm and stratospheric winds were relatively weak, characteristics that are typically associated with high ozone values.

During 1940–42, exceptional climate conditions occurred around the globe, including a series of intensely cold European winters (Fig. 1) that had a significant influence on events during the Second World War. A prolonged ENSO event occurred during 1939–42, and the coincidence of these anomalies suggests a connection between ENSO, European climate and the stratosphere. Brönnimann *et al.* have isolated the hemispheric-scale climate signals for this period, and find features expected for ENSO, including the Pacific–North American teleconnection pattern. But the results also highlight a large response over the Atlantic–European region, and an extension into the stratosphere (hence influencing ozone, as observed).

The anomalies in European climate and stratospheric circulation during the 1940–42 El Niño could be a chance occurrence, but Brönnimann *et al.* show that similar patterns occur in model simulations of extreme ENSO events. They analysed the largest ENSO events that occur in a 650-year model simulation, which includes coupling between atmosphere and ocean, and produces ENSO events as a part of its natural variability. An ensemble of the stronger ENSO events in the model shows global teleconnections that strongly resemble the 1940–42 observations, with strong surface signals in the Atlantic–European region that extend into the lower stratosphere.

Both the spatial and temporal characteristics of the model events are a reasonable match for the observed anomalies. Although ozone does not vary in this model, the stratospheric meteorology is consistent with large ozone anomalies. The overall agreement between the model and observations suggests that the 1940–42 climate anomalies corresponded to a recurring, extreme state of the climate system that was associated with El Niño and encompassed the troposphere and stratosphere.

So, might the stratosphere have an active role in extreme ENSO dynamics? Recent studies have highlighted a dynamical coupling between the stratosphere and troposphere during winter, with stratospheric pressure and wind anomalies at middle and high latitudes often being linked with surface anomalies of the same sign[6]. This coupling sometimes occurs in the form of downward-propagating anomalies, suggesting that the stratosphere can influence weather patterns at the surface[7,8]. The amplitudes of the surface-pressure anomalies are often largest in the Atlantic region, where the north–south see-saw patterns contribute to a teleconnection structure known as the North Atlantic Oscillation, which in turn is strongly coupled to European climate[9]. Thus, a plausible connection is that large ENSO events affect winter stratospheric circulation at high latitudes, these anomalies in turn being communicated to the surface and having an especially strong influence in the Atlantic–European region.

This apparently cogent picture is marred by the absence of similar European and stratospheric anomalies for the large ENSO events of 1982–83 and 1997–98. This is not unexpected, however, given that the sample is so small. Each ENSO event is different in detail, and other factors are known to influence stratospheric circulation (such as the eruption of the El Chichon volcano in Mexico, in 1982). So although Brönnimann and colleagues' study is suggestive of a consistent chain of connections, the large variability between the handful of observed large ENSO events highlights the complexity of the troposphere–stratosphere climate system. ■

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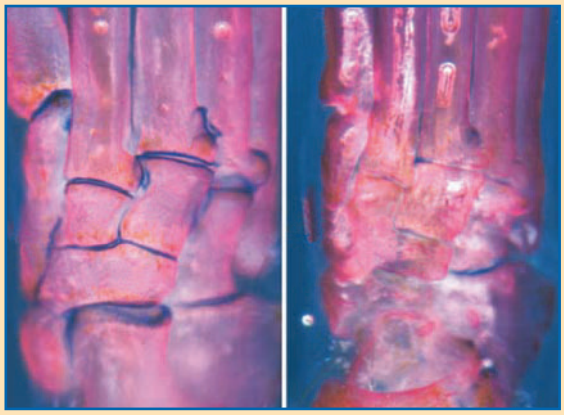
Physiology

Joint approach



These photographs show what happens when a certain protein is inactivated in the ankle joints of developing mice. Particular joints completely fail to form. Elsewhere in the body, joints do form, but they are not maintained. Both conditions are evident from the lack of blue staining in the right-hand image. The photographs appear in a paper by David M. Kingsley and colleagues (*PLoS Biol.* **2,** e355; 2004), and the findings bear on our understanding of human osteoarthritis.

In healthy joints, where two bones meet, the ends of the bones are covered in cartilage, helping to reduce friction. In people with osteoarthritis, however, the cartilage wears away, so that the underlying bones are exposed and rub together painfully. To investigate the molecular mechanisms involved, Kingsley and colleagues built on the knowledge that certain proteins of the bone morphogenetic protein (BMP) family are involved in joint formation. Using a complex genetic system, they generated mice in which a BMP receptor, the BMPR1a protein, is selectively inactivated in the joints.

In these mice, some joints did not form at all; others did form, but the cartilage gradually wore away, producing the physical and behavioural characteristics of osteoarthritis. The authors suggest that signalling pathways activated by BMPR1a are needed to maintain the production of components of the cartilage extracellular matrix. And they propose that mutations in BMPR1a might account for some of the genetic variation that is known to contribute to human osteoarthritis. **Amanda Tromans**