given population of reprogrammed cells and the methods used for their reprogramming or propagation. Hussein *et al.*[1] provide some evidence that CNV occurred more frequently at sites prone to replication stress. It is not clear, however, whether this stress is unique to the reprogramming process, or whether it would be common to any experimental situation in which a cultured cell is subjected to strong selection and replication pressures *in vitro*.

Despite extensive evaluation of recurrent genetic change in a vast number of cell lines, we are only slightly closer to identifying which particular genes within the larger chromosomal regions that are commonly subject to duplication in iPSCs and ESCs might be under selection. Years of cytogenetic studies of germ-cell tumours have also identified large genomic regions that are commonly over-represented in these cancers, but the identification of the specific genes involved in the transformation of these pluripotent cells has remained elusive[6]. A possible interpretation of the data on the genetics of germ-cell tumours is that multiple genetic regions, or large regulatory regions, are crucial to the process of oncogenesis *in vivo*. Perhaps a similar mechanism is in play during *in vitro* adaptation of ESCs or iPSCs.

With regard to evaluating the safety of ESCs and iPSCs, a key issue is the biological significance of the changes that these studies[1–5] report. Clearly, aneuploid cell lines would not be used in therapy (although they might be useful for research into the basis of genetic disorders associated with anomalies in chromosome number or other genetic abnormalities). Cell lines bearing mutations of established functional consequence in oncogenes or tumour suppressors, or in genes associated with Mendelian disorders (those usually due to a single gene), could equally not be used therapeutically. However, the many sub-chromosomal changes, CNVs or point mutations that are not obviously associated with known disease-related genetic abnormalities pose challenges to interpretation. This is because it is unclear how best to assess the effects of new genetic lesions on the growth, differentiation, tumorigenicity and functionality of pluripotent stem cells or their differentiated progeny. High-throughput functional genomics will probably be required to answer these questions. Pluripotent cells themselves will provide the most promising platform for such studies. ■

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CLIMATE CHANGE

Rethinking the sea-ice tipping point

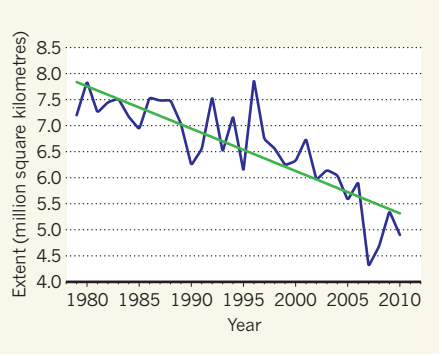
Summer sea-ice extent in the Arctic has decreased greatly during recent decades. Simulations of twenty-first-century climate suggest that the ice can recover from artificially imposed ice-free summer conditions within a couple of years.

MARK C. SERREZE

Will the Arctic's floating cover of sea ice pass a critical threshold, or tipping point, beyond which a rapid, irreversible slide occurs to a seasonally ice-free Arctic Ocean? The question is a pertinent one bearing on the adaptability of Arctic marine life[1], how ice loss influences atmospheric circulation and precipitation patterns within and beyond the Arctic[2], and prospects for resource extraction and marine shipping[3]. According to a new study by Tietsche and colleagues[4], and other recent work[5], concerns over a tipping point may be unfounded.

That the Arctic is moving towards a seasonally ice-free state is clear. Over the period of satellite observations (1979 onwards), linear trends in the decline of sea-ice extent have been recorded for all months. The trends are smallest in winter and largest in September, the end of the melt season. When referenced to a 1979–2000 mean, the rate of decline in sea-ice extent for September is about 12% per decade; Fig. 1). A key driver of this seasonal asymmetry in trends is that spring ice cover is increasingly dominated by relatively thin ice that formed during the previous autumn and winter, with less of the generally thicker ice that has survived at least one summer-melt period[6]. Because less energy is required to melt out thin ice, with other factors equal, the thinner the ice in spring, the lower the ice extent at the end of summer. Thin spring ice also strengthens the seasonal albedo feedback, whereby dark (low albedo) open-water areas are exposed to the Sun earlier in the melt season, leading to stronger seasonal heating of the upper ocean that, in turn, helps to melt more ice, exposing even more of the dark ocean.

Concern over a tipping point stemmed from a modelling study[7] by Holland and colleagues published in 2006. They found that, as the climate warmed and the spring sea-ice cover thinned in response to rising greenhouse-gas levels, a strong kick from natural climate variability could more easily induce a reduction in sea-ice extent sufficiently large to set the albedo feedback process into high gear. As a result, the path of a general downward trend in summer ice cover would be interrupted by sudden plunges spanning a decade or more, hastening the slide to a seasonally ice-free ocean. The concern was fuelled in 2007 by a record September minimum in sea-ice extent — 23% below the previous record set in 2005 — driven by a combination of several decades of sea-ice thinning and a highly unusual summer weather pattern.



SOURCE: NATIONAL SNOW & ICE DATA CENTER

Figure 1 | September sea-ice extent in the Arctic for 1979–2010. Satellite data (blue) show that September sea-ice extent is decreasing in the Arctic, and that, relative to the 1979–2000 mean, the rate of decline is about 12% per decade; green line represents the best fit to the satellite data. Tietsche and colleagues' simulations[4] indicate that the extent can recover from artificially imposed ice-free summer conditions within two years.

Specifically, a combination of especially high atmospheric pressure over the Beaufort Sea, north of Alaska, in conjunction with low pressure over Siberia, drew warm air into the Arctic, hastening melt, while at the same time helping to transport some of the remaining thick ice out of the Arctic into the North Atlantic Ocean[6]. Was this the kick initiating a rapid, irreversible decline in ice extent? Although there was widespread speculation over this

possibility, the Septembers of 2008 and 2009 instead saw successively higher sea-ice extent.

One interpretation of this apparent short-term recovery is that the spring ice cover needs further thinning for a tipping point to occur[8]. An alternative is that there is no true tipping point. Tietsche *et al.*[4] do not argue against the mainstream view that a seasonally ice-free Arctic Ocean is inevitable if greenhouse-gas concentrations continue to rise. The issue is how we get there — with or without a tipping point.

Tietsche and colleagues performed a series of reference simulation runs with a global climate model driven by the middle-of-the-road Intergovernmental Panel on Climate Change A1B greenhouse-gas emissions scenario for the twenty-first century. In these simulations, the September ice cover typically disappears by the year 2070 and beyond. The authors then performed perturbation runs, whereby every 20 years they artificially removed the entire sea-ice cover on 1 July. Instead of maintaining ice-free conditions, ice extent in September recovered to values typical of the reference runs within a couple of years, even in the later parts of the century.

The crux is winter. Initially, with ice-free summers, the ocean picks up a great deal of extra heat, delaying autumn ice growth. If there was a tipping point, this summer heat gain would lead to ice cover the following spring being thin enough to completely melt out over the following summer. Instead, so much ocean heat is lost during the darkness of the polar winter that enough ice grows to survive the next summer's melt.

Although the paper by Tietsche and colleagues[4] brings a more optimistic view of the Arctic's future, the troubling interpretation from other recent modelling studies is that periods of rapid twenty-first-century sea-ice loss, hastening the evolution to ice-free summers, don't need to be preceded by a critical threshold of sea-ice thickness, greenhouse-gas concentration or combination of factors that lie at the heart of the tipping-point argument[5]. As we move through the coming decades and the climate warms, the ice cover will simply become more vulnerable to triggers that cause rapid loss events. So although the tipping-point argument can perhaps be laid to rest, we may nevertheless be looking at ice-free summers only a few decades from now. ■

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MOLECULAR BIOLOGY

The expanding arena of DNA repair

The protein Sae2 mediates the repair of double-strand breaks in DNA. It emerges that Sae2 activity is controlled by both its modification with acetyl groups and its degradation by the process of autophagy. SEE ARTICLE P.74

CATHERINE J. POTENSKI & HANNAH L. KLEIN

Cells use myriad ways to regulate the complex processes involved in their function. To control protein activity and stability, for example, an oft-used mechanism is post-translational modification of the protein. On page 74 of this issue, Robert *et al.*[1] report one such modification that links the seemingly unrelated processes of DNA-damage repair and autophagy. Their observations simultaneously highlight the depth of cellular ingenuity and the immense interconnectedness of biological pathways.

The authors began by examining the effect of a specific post-translational modification — protein acetylation, in which an acetyl group is added to a protein. They used the drug valproic acid (VPA) to inhibit histone deacetylase (HDAC) enzymes, thereby causing hyperacetylation of histone proteins and reduced HDAC activity[2]. This treatment had no effect on cells, but after exposure to various DNA-damaging agents, the apparently normal VPA-treated cells were unable to activate the typical response to DNA damage.

50 Years Ago

The Birds of Borneo. By Bertram E. Smythies — This is a very unusual bird book. The main body of the work (about 460 pages) consists of a detailed systematic account of all the 549 species of birds that have been found in Borneo … But it is the hundred pages that precede this excellent treatise that put this book in a class apart … Lord Medway's chapter gives a fascinating account of the cave swiftlets, the saliva-built nests of which are the edible birds' nests of commerce, and which echo-navigate in the darkness of the caves where millions congregate to breed. [Mr. Tom] Harrison remarks that Governments "by some complicated zoo-geology, claim the guano as a mineral and allow extraction (for fertilizer) under licence. Thus what comes out of the swiftlets' mouth as spit is succinctly dissociated from what comes out of the other end".
From *Nature* 4 March 1961

100 Years Ago

In the Prussian Diet of February 18, Prof. Kirchner … is reported to have said that, during the last few weeks, three cases of plague had occurred in London, the infection being conveyed by ship-rats. This statement has been officially denied … With regard to rat infection, three rats which had probably escaped from a ship were examined at the London Docks in November last, and two of them were found to be suffering from plague, but at present there is no evidence of the existence of a plague epizootic among rats in the London Docks area. The destruction of rats … is still carried out at the London Docks, and careful precautions are being taken to prevent rats in ships from infected ports from escaping ashore, and possibly initiating an epizootic among the shore rats.
From *Nature* 2 March 1911