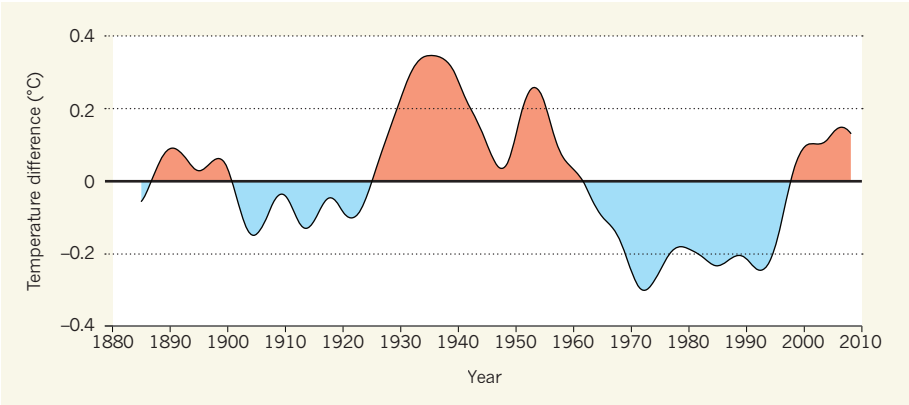

Figure 1 | Atlantic multidecadal variability. The difference between the average sea surface temperature of the North Atlantic Ocean and the average global sea surface temperature swings between cool (blue) and warm (red) phases, with a characteristic timescale of several decades. Although this phenomenon has been studied for more than 20 years, there is still uncertainty about what processes drive the interdecadal variability. (Data from ref. 18.)

The idea that external forcing could have the dominant role in driving AMV has been slow to gain traction, for at least three reasons. First, the internal and external mechanisms share many patterns of response, which means that separating their respective fingerprints in the observed temperature record is difficult. Second, doubts have been raised[6] about aerosol forcing because, in the study in which this was investigated[2], the aerosol levels obtained were linked to biases in simulated oceanic heat content. Although other climate models reproduce similar external forcing of AMV without such biases[11], this is not widely known.

Third, and perhaps most importantly, the majority of current models neglect aerosol–cloud interactions that have been shown to be a key factor in external forcing of AMV[2]. In the past decade, many estimates of external forcing have either used climate models that ignore these interactions[12] or focused headline results on the average over many models, of which only a minority included these interactions[13]. However, in analyses that have incorporated aerosol–cloud interactions, there is good agreement that external forcing has driven AMV over the past 50 years[13,14]. Where such analyses disagree is on whether external forcing had the leading role in driving AMV before the past half-decade, and it is here that there is greater potential scope for a dominant internal-variability role.

The responses of AMV to external forcing and internal variability are similar, but they differ in the tropics. Climate models that include key processes (such as low cloud, wind–evaporation–temperature and dust feedbacks) simulate surface-temperature gradients better than those that omit them, but such models reproduce observed gradients only when external forcing is also included[15]. The tropical AMV response is important because it drove historical changes in tropical rainfall and hurricane activity. Current climate-model simulations of AMV driven by internal variability cannot reproduce the magnitude of the historical rainfall shifts — they can match[15] or approach[16] the observed magnitude only when external forcing is also taken into account.

The idea that AMV must be driven either by external forcing or by internal variability is probably a false dichotomy, but separating their relative roles remains the biggest challenge. For instance, modelling suggests that Atlantic Ocean circulation responds to external forcing, either through decadal variations in surface radiative forcing[9,17] or through changes in the North Atlantic Oscillation[9].

The presence of these credible and competing explanations should force us to critically re-evaluate both scenarios. What do models suggest that the magnitude, period and latitudinal spatial coherence of internal variability should actually be? Models that simulate externally forced AMV should not escape similar scrutiny. External forcing could have only a minor role in AMV, given the current modelling uncertainties in the key processes involving cloud feedbacks and aerosol–cloud interactions. However, if internal variability did indeed dominate observed changes, I would find it a remarkable coincidence that these changes match the timing and magnitude of AMV that we would expect from models driven by external forcing. ■

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NEUROBIOLOGY

A bitter–sweet symphony

Information about taste sensations, such as bitter or sweet, is relayed from the mouse tongue to the brain through taste-specific pathways. It emerges that semaphorin proteins guide the wiring of these pathways. SEE LETTER P.330

JIEFU LI & LIQUN LUO

Our immediate delight at eating delicious food relies on taste sensations in the tongue being transmitted to the brain. An accurate perception of taste is essential for animal survival, because molecules that provoke a bitter taste usually warn of poisonous substances, whereas sweet-tasting molecules indicate nutritious foods. How is the taste system wired up to transmit such signals faithfully? On page 330, Lee *et al.*[1] identify two proteins of the semaphorin family that instruct the wiring of bitter and sweet taste pathways in mice.

The mouse tongue contains hundreds of

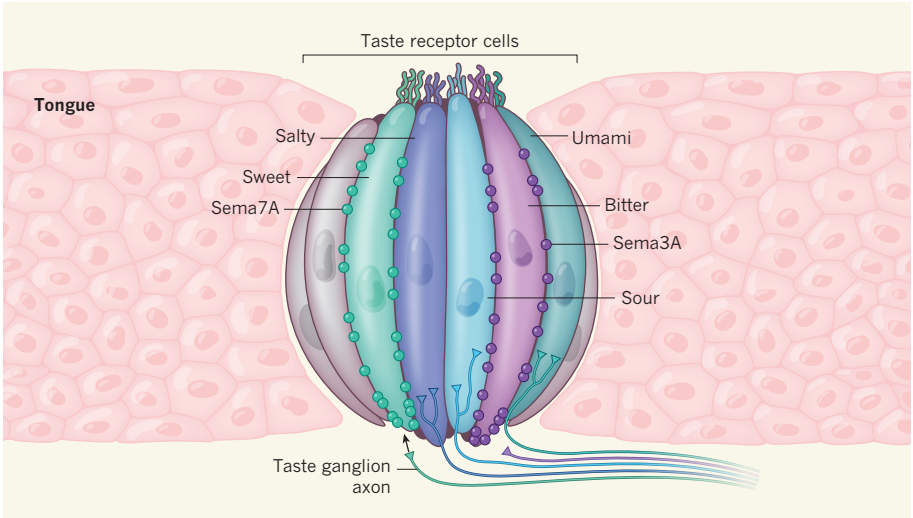

Figure 1 | Wiring the taste system in mice. Each taste bud of the tongue harbours dozens of taste receptor cells (TRCs), most of which are receptive to only one of the five taste qualities — bitter, sweet, sour, salty and umami. In mice, TRCs connect to neuronal projections called axons that originate from clusters of neurons called ganglia in the head that relay taste information, mostly in a type-specific manner (type-specific axons are colour-coded to match TRCs). For example, TRCs that respond to sweet tastes connect to axons from sweet-responsive ganglion neurons. Lee *et al.*[1] have shown that two proteins from the semaphorin family guide this pattern of wiring. Sema3A, produced by bitter TRCs, guides connections with bitter ganglion neurons. Sema7A has the same role but in the sweet taste pathway.

taste buds. Each houses dozens of taste receptor cells (TRCs), which can detect five basic qualities of taste: bitter, sweet, sour, salty and umami[2]. In most cases, each TRC relays information about only one of the qualities, dictated by the taste receptor that it expresses. Taste receptors are cell-surface proteins that bind to and are activated by molecules that stimulate taste sensations. To send information to the brain, TRCs are connected to neuronal projections called axons that originate from two clusters of taste-responsive neurons in the head — the geniculate ganglion and petrosal ganglion. These ganglia serve as the relay stations for taste cues en route to the brain[2].

Similar to TRCs, most ganglion neurons are tuned to single taste qualities[3], which suggests that taste information propagates to the brain primarily through specific pathways that are tuned to each taste. For instance, sweet TRCs faithfully connect to sweet-responsive ganglion neurons but not to bitter-responsive ones, and the converse is true of bitter TRCs. This raises a question: how do the axons of sweet ganglion neurons find the sweet TRCs to which they must connect, given that taste buds contain intermingled TRCs that are each receptive to one of the five qualities?

To address this question, Lee *et al.* examined the gene-expression profiles of bitter and sweet TRCs. They searched for molecules that are differentially expressed in different types of TRC, and that have the potential to serve as axon-guidance molecules. The authors identified the semaphorins Sema3A and Sema7A as candidates that were highly enriched in bitter and sweet TRCs, respectively (Fig. 1).

Semaphorins are secreted or membrane-anchored proteins that regulate cell motility and are known to be involved in axon guidance[4]. To test whether wiring of the bitter taste pathway requires Sema3A, Lee and colleagues made use of mice genetically engineered such that their geniculate-ganglion neurons fluoresced when active. This enabled the authors to determine which tastes evoked neuronal activation. When they deleted the gene that encodes Sema3A from the bitter TRCs of these mice, almost 50% of bitter-responsive neurons became tuned to respond not only to bitter tastes but also to other qualities — an increase from the 9% of bitter ganglion neurons that are doubly tuned in wild-type mice. The result indicates that removing Sema3A causes promiscuous wiring of bitter ganglion axons.

Lee and co-workers showed that the misexpression of Sema3A in sweet TRCs could also rewire taste pathways, redirecting the axons of some bitter ganglion neurons to sweet TRCs and increasing the proportion of neurons that are doubly tuned to respond to both bitter and sweet qualities. The authors then combined the removal of Sema3A from bitter TRCs with its misexpression in sweet TRCs, which resulted in 70% of bitter ganglion neurons being tuned to more than one taste quality. Accordingly, mice with such a modification showed severely weakened aversions to bitter substances.

Next, the authors performed similar experiments with Sema7A. Misexpression of Sema7A in bitter or sour TRCs led to increased numbers of bitter–sweet or sour–sweet doubly tuned ganglion neurons. This suggests that Sema7A functions in a similar way to Sema3A, but in the sweet taste pathway.

Together, Lee and colleagues' findings demonstrate that Sema3A and Sema7A are instructive cues for establishing the bitter and sweet taste pathways, respectively. Although Sema7A is anchored to the cell membrane, Sema3A is a secreted guidance molecule[4] — as such, its ability to guide the axons of ganglion neurons to specific cells in taste buds that are tightly packed with various types of intermingled TRCs is remarkable. This finding indicates that secreted guidance molecules can act locally with single-cell resolution, challenging the conventional wisdom that such cues diffuse across distances to exert their effects.

TRCs turn over rapidly, with a typical lifespan of less than three weeks. By contrast, the axons of ganglion neurons in the tongue last a lifetime. Thus, such axons must undergo rewiring frequently to connect with new partner TRCs. It seems likely that the axons permanently maintain this ability, in contrast to axons in many other systems — generally, connections with other cells are formed during development, and the genetic program that enables this wiring process is gradually switched off after neurons mature[5,6].

Although rewiring the bitter and sweet taste pathways altered their outputs strikingly, the taste system also exhibited superb robustness. Even when Lee *et al.* combined Sema3A removal from bitter TRC with its misexpression in sweet ones, 30% of bitter-responsive ganglion neurons remained singly tuned to molecules that stimulate bitter tastes, and the corresponding engineered mice still showed some aversion to bitter substances. Wiring signals that have been identified in other systems[7–9] might act in concert with the semaphorins, contributing to this fidelity. For instance, the authors found that the cell-adhesion proteins Dscaml1 and Pcdhgb7 are preferentially expressed in bitter TRCs — perhaps they have the potential to regulate wiring specificity in the taste bud.

Lee and colleagues have identified two signalling molecules expressed by TRCs, but the receptors for these signals on the axons of ganglion neurons remain undetermined. Because most of these neurons seem to be specifically connected to a single type of TRC, each type of ganglion neuron probably expresses one or more distinct receptors to match the signals made by their corresponding TRC. Identifying these receptors should substantiate our understanding of the development of the taste system. At the same time, they may provide a means to explore the function of ganglion neurons in a type-specific manner using genetic engineering, therefore enabling the examination of taste circuits between the ganglia and brain. ■

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CANCER GENOMICS

Human metastases under scrutiny

Sequences of the DNA and RNA of 500 human cancers that have spread from their primary site in the body take us a step closer to the convergence of basic science and patient benefit. **SEE ARTICLE P.297**

G. STEVEN BOVA

Most of the damage that cancer does is caused by the spread of cells from the primary cancer site to other regions of the body. These metastatic cancer cells accrue genomic changes beyond those found in the primary tumour, and some such changes allow the metastatic cancer to survive in the face of therapy. Molecular studies of metastatic cancer tissues can provide valuable insights into how this resistance might be overcome, but such studies have been relatively rare, mainly because of logistical and technical barriers. Robinson *et al.*[1] report on page 297 that they have extended work from earlier studies[2,3] to take detailed snapshots of genome sequences and immune responses in metastatic cancer tissues from 500 people, known as the MET500 cohort.

The authors enrolled patients whose metastases derived from 30 types of primary cancer (the most common were prostate, breast and soft-tissue-sarcoma metastases), and patients for whom the primary cancer was unknown. Female and male patients of different ethnicities were enrolled from 22 cancer centres across the United States, but most were from the University of Michigan Comprehensive Cancer Center. Tissue samples came from more than 20 organs.

Robinson *et al.* sequenced the protein-coding portion of the genome from metastatic tissue samples and compared these exome sequences with those from non-cancerous tissue from the same patient. Next, they sequenced messenger RNA from the metastases, and compared this with mRNA profiles from corresponding normal tissues taken from reference databases. Together, these analyses provided information about the genetic mutations and the altered gene-expression profiles that characterize the metastases and their supporting tissues. The analyses complement genomic studies of primary cancers, many of which have been conducted by two large consortia: The Cancer Genome Atlas (http://cancergenome.nih.gov) and the International Cancer Genome Consortium (http://icgc.org).

For people who have cancer, Robinson and colleagues' work is important on two levels. First, it demonstrates that a set of difficult challenges can be overcome in a clinical setting to biopsy metastatic cancers and obtain integrated exomic and mRNA data sets for each patient. These challenges include: logistical ones, such as obtaining biopsies from regions of the body that are difficult to access; technical challenges (metastasis biopsies are often tiny, and the fraction of tumour cells compared to healthy cells can be low); and ethical challenges for the patient, physician and researchers when assessing the risks and possible value of taking a biopsy — especially because the potential benefit for patients is not well defined.

"The analysis provides information about genetic mutations that could potentially be targeted by drugs."

Second, the work has produced a wealth of publicly available information (http://met500.path.med.umich.edu) that will help to guide future approaches to cancer treatment based on precision medicine. The integrated analysis of each patient's biopsy and matched normal tissue delivers a map of what is going on in each metastasis sampled. The analysis, therefore, provides information about genetic mutations that could potentially be targeted by drugs; about the immune response and other microenvironmental responses to the tumour, which could also point to therapeutic options; and about mutations present in the non-cancerous DNA from each patient, which might indicate the mutations that predispose them to cancer. The latter could have implications not only for the patient's treatment, but also for risk management in the person's family.

Notably, Robinson and colleagues identified mutations in germline DNA (that with which the patient was born) that could confer predisposition to cancer in 12.2% of the MET500 cohort. This striking finding is consistent with previous studies limited to people with metastatic prostate cancer[2] — some of whom may also have been included in the MET500 cohort. Studies involving larger numbers of people with metastasis are now needed to determine whether a diagnosis of metastatic cancer should trigger more-intense evaluation of familial cancer risk than currently occurs.

One of several interesting findings in Robinson and colleagues' study is that metastatic cancers fall into two main subtypes on the basis of their mRNA profiles — one associated with inflammation, and a second, proliferative subtype associated with increased metabolism and systemic stress signalling. If this pattern is found across multiple metastases in individual patients, it seems likely that where the metastatic cancer sits in this spectrum could strongly influence response to specific therapies.

Another finding of interest lies in the analysis of the magnitude of immune-cell infiltration in metastatic cancers (MImmScore[4]), which is a measure of how the body's immune system is responding to a tumour. This and other immune measures reported in the work could potentially help to select therapies and analyse patient responses in clinical trials of emerging immunotherapies, which modulate the body's immune response to target cancer. The highest average MImmScores were found in kidney cancer and certain cancers of the skin and thymus gland, and the lowest were in testicular cancers and cancers of the adrenal gland. However, each tumour type had outliers that had relatively high or low immune infiltration, and some (including metastatic pancreatic, lung, thyroid and liver cancers) had especially broad ranges of infiltration between people who had those metastatic cancer types.

Robinson and colleagues' study is the largest of its kind. Establishing the potential usefulness of this type of integrated genomic approach to improving cancer management and best practices will require many more well-curated cases, in addition to a record of outcomes, which was not included in the current study. Moreover, metastatic cancers evolve over time[5–10] and in response to therapy[11,12] — it remains to be seen when and how