From the archive

The wonders of life contained in the soil beneath our feet, and the sociability of cats.

100 years ago

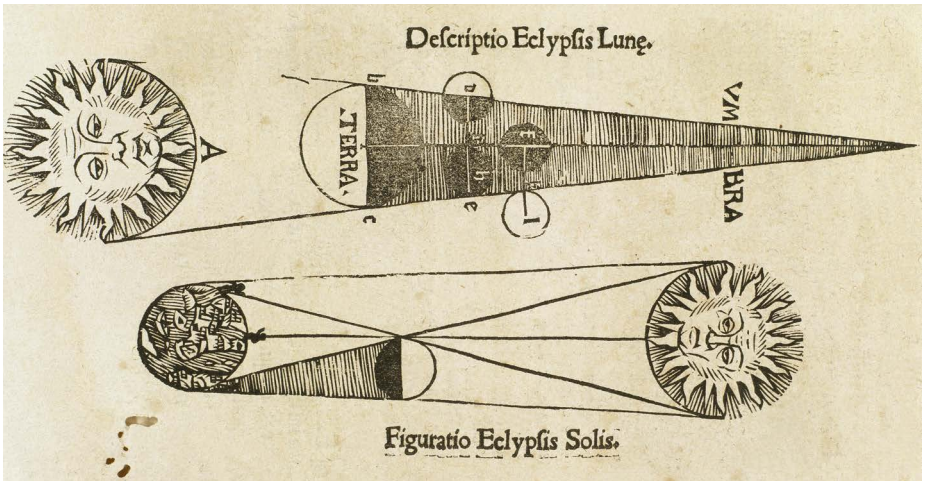
The number of organisms in one single gram of soil — no more than a teaspoonful — often well exceeds 40 millions. This looks big, but it is difficult to form an idea of its immensity. If each unit in the whole array could be magnified up to the size of a man and the whole caused to march past in single file, they would go in a steady stream, every hour of the day and night for a year, a month and a day, before they had all passed. We must think then of the apparently lifeless soil which we tread beneath our feet as really throbbing with life, changing daily and hourly in obedience to some great laws which we have not yet discovered; pulsating with birth, death, decay, and new birth. And if the wonder were not sufficient, we know that in some way these lowly organisms are preparing the food for our crops … It is possible … that our attempts to learn something of this wonderful population may lead to some degree of control which would have valuable economic results. But even if this never happened the work would still be justified because it shows to the countryman something of the abounding interest of his daily task and of the infinite wonder of the soil on which he spends his life.

From *Nature* 7 April 1923

150 years ago

It may prove of interest to naturalists to record the following curious instance of the social habits of cats :— I once had two she cats that were upon very intimate terms with each other, always together, and never appeared to have quarrelled. At one time, one of them being about to add an increase to their number, the other very kindly nursed it, and even performed the function of a midwife, and actually attended to the necessary offices that are in ordinary cases attended to by the parent of the progeny. … I carefully watched my pets, and can therefore vouch for the truthfulness of this extraordinary manifestation of feline sociability.

From *Nature* 3 April 1873



PRIMA ARCHIVO/ALAMY

Figure 2 | A diagram of solar and lunar eclipses, from a printed edition of Johannes de Sacrobosco's astronomical text (around 1220).

of the Moon was therefore out of step with the calendars of major religious institutions.

Church chroniclers faced a dilemma. Some saw a darkening of the Moon as a clear sign of an eclipse, whereas others interpreted it differently. The problem was exacerbated by the fact that a given eclipse might be more clearly visible in some parts of Europe than others, and that information took time to be transmitted between regions. For these reasons, the lack of agreement between medieval chroniclers on the timing of total eclipses of the Moon should not be seen as the result of religious censorship or ignorance – they were simply days out of sync. In this context, Guillet and co-workers' accomplishment in overcoming this problem to link historical sources to climate events is all the more impressive.

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The authors declare no competing interests.

Tumour biology

Cancer cells remodelled to resist chemotherapy

Stephanie Panier

Cancers that arise from epithelial cells often contain tumour cells that have acquired the characteristics of another cell type – a mesenchymal cell. A mouse model of skin cancer offers insights into why such cells resist treatment. **See p.168**

Modern therapeutic approaches for cancer, such as 'targeted' drugs or therapies that harness the immune system, have greatly advanced the treatment options for many types of tumour. However, chemotherapy failure is a key limiting factor in treatment success. On page 168, Debaugnies *et al.*[1] provide some reasons for why such treatment resistance can occur.

In cancers that arise from epithelial cells (which line the surfaces of the body), treatment resistance is closely associated with a process called the epithelial–mesenchymal transition (EMT). During EMT, cancer cells of epithelial origin progressively lose their epithelial characteristics and acquire those of another cell type – a mesenchymal cell (Fig. 1). These newly gained characteristics enable the

cancer cells to invade surrounding tissues and spread elsewhere in the body[2].

Cancers containing cells that have undergone EMT are associated with a poor clinical prognosis[3], which is often driven by chemotherapy resistance[4]. Although distinct molecular mechanisms by which EMT supports the spread of cancer have been identified, the role of EMT in promoting treatment resistance is not well understood.

EMT is essential for normal embryonic development, and has a key role in wound healing. But epithelial cancer cells can use their innate ability to undergo EMT to become mobile and escape the initial (primary) tumour site. During EMT, the cells undergo extensive shape changes, losing their characteristic asymmetry along one axis of the cell (apical–basal polarity) and their inter-cell contacts[2]. Their metabolic and transcriptional properties also undergo striking changes. Many studies indicate that this EMT-driven rewiring can favour resistance to cancer drugs, for example by upregulating genes needed for drug resistance or for cell-survival pathways[4]. However, a limitation of many of these studies is that they were carried out *in vitro*, and it is often unclear whether the cellular mechanisms identified also drive EMT-associated therapy resistance in primary tumours *in vivo*.

To address this problem, Debaugnies and colleagues investigated why EMT cells in primary skin tumours resist chemotherapy *in vivo*. The authors used a combination of the chemotherapeutic drugs cisplatin and 5-fluorouracil to treat mice that had been genetically engineered to develop skin tumours. This drug combination is currently the standard chemotherapeutic approach for people with an advanced stage of this type of skin cancer[5], and it acts by inducing DNA damage that can kill cancer cells[6]. The authors found that 32% of the skin tumours failed to respond to this treatment, and that most of these resistant tumours (70%) were composed exclusively of cells that had undergone EMT and that were intrinsically resistant to drug-induced cell death.

Debaugnies *et al.* identified a protein called RhoJ as the main culprit of EMT-associated chemotherapy resistance in their studies. RhoJ belongs to a family of enzymes called Rho GTPases, which function as molecular switches. They control the dynamic reorganization of a subset of fibres called actin filaments, which form part of the cell's internal architecture (the cytoskeleton)[7]. The remodelling of these filamentous protein polymers is central to many of the cell-shape changes associated with EMT. Although numerous Rho GTPases were previously shown to be deregulated during cancer-associated EMT and to have roles in cancer progression and spread (metastasis)[8], the involvement of RhoJ was not previously known.

The authors show that RhoJ is expressed at a higher-than-normal level specifically in mouse skin tumour cells that have undergone EMT. RhoJ helps EMT tumour cells to resist the lethal DNA damage inflicted by chemotherapeutic drugs.

Debaugnies and colleagues carried out a wide array of biomolecular analyses to clarify the molecular mechanism by which RhoJ drives chemotherapy resistance. One of their most striking findings is that RhoJ promotes the repair of DNA damage and the activation of 'dormant origins' of DNA replication in EMT tumour cells after chemotherapy. Dormant origins are back-up start sites for the cellular machinery that replicates the genome. They ensure the timely duplication of DNA when the DNA-replication machinery encounters obstacles, for example, those induced by drugs such as cisplatin and 5-fluorouracil.

"One of the authors' most striking findings is that the RhoJ protein promotes the repair of DNA damage."

Accordingly, treatment with these drugs resulted in higher levels of DNA damage in EMT tumour cells that lacked RhoJ than in cells containing this enzyme, and induced multiple signs of dysfunctional DNA replication (also known as replicative stress) and associated problems. The findings are of note for future RhoJ-based treatment approaches, because they suggest that RhoJ promotes therapy resistance by enabling tumour cells to repair DNA damage and to tolerate replication problems that would otherwise kill them.

How does RhoJ, a signalling protein that regulates actin-filament dynamics, achieve such therapy resistance? Considerable data have implicated nuclear actin filaments as having a role in guiding the dynamics of DNA repair[9]. Consistent with this, Debaugnies and colleagues show that RhoJ-mediated DNA repair and replicative-stress tolerance do indeed depend on the enzyme's ability to induce the formation of nuclear actin filaments.

The authors' finding firmly connects RhoJ-dependent actin-filament remodelling to mechanisms of genome maintenance in therapy-resistant EMT tumour cells. However, the precise molecular details of how such actin filaments support DNA repair and activate extra replication origins remain to be elucidated. Possible, and not mutually exclusive, scenarios include the actin-dependent relocation of sites of DNA damage and dysfunctional DNA replication to repair-competent areas in the nucleus, particularly the nuclear periphery[10], and actin-mediated loading of replication and DNA-repair factors onto the DNA[11].

Debaugnies and colleagues' study is a remarkable demonstration of the power of *in vivo* cancer models to dissect the molecular

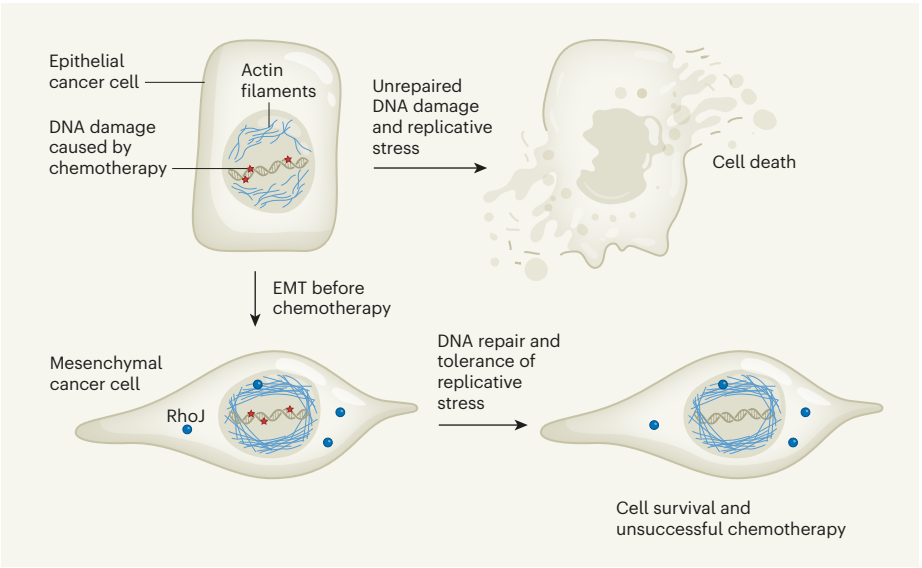

Figure 1 | The RhoJ protein and chemotherapy failure. In cancers that arise from the epithelial cells that line the surfaces of the body, failure of chemotherapy is closely associated with a process called epithelial–mesenchymal transition (EMT), during which epithelial cells progressively lose their epithelial characteristics and acquire properties associated with mesenchymal cells. Many chemotherapeutic approaches work by driving DNA damage and causing replicative stress (defects in DNA replication) — effects that activate signalling pathways to kill the cancer cells. Debaugnies *et al.*[1] report that the protein RhoJ is expressed at higher-than-normal levels in mouse tumour cells that have undergone EMT. The authors show that RhoJ counteracts chemotherapy-induced DNA damage by triggering the formation of long filaments of actin protein in the nucleus. Together, RhoJ and these filaments (through mechanisms that are not fully understood) promote DNA repair and the ability to overcome replicative stress, ensuring cell survival.

biology underlying cancer therapy resistance, particularly that involving EMT. However, a limitation of cancer models can be the genetic diversity of cancers and the fact that they have different cellular origins, which often precludes mechanistic generalizations being made regarding their biology.

For example, RhoJ is also highly expressed in melanoma skin cancer cells, in which it promotes therapy resistance to DNA-damage-inducing agents through an alternative mechanism: that is, it disables DNA-damage sensing and, as a consequence, averts cell death induced by the transcription-factor protein p53 (ref. 12). The skin cancer model used by Debaugnies and colleagues lacks p53, and this might explain the different RhoJ-associated therapy-resistance mechanism uncovered by the authors.

These findings highlight the challenge of dealing with the range of molecular tumour subtypes encountered in the clinic. Future studies should address whether RhoJ-dependent DNA repair and replicative-stress tolerance drive resistance to DNA-damage-inducing chemotherapeutics in other EMT-associated cancers.

Given the prominent roles of cytoskeleton remodelling in cancer progression and metastasis, Rho GTPases such as RhoJ constitute promising chemotherapeutic targets, especially for cancers that are resistant to current treatments[13,14]. Although the identification of clinically effective inhibitors that target Rho GTPases or their downstream proteins has proved challenging, several compounds and lead drugs are showing promise[13]. Their development should continue to be a goal of basic and clinical cancer research.

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The author declares no competing interests.
This article was published online on 22 March 2023.

Fisheries

Blue foods brought to the table to improve policies

Nanna Roos

What are the benefits of a fish-rich diet, not only for nutrition and health but also for the environment, economies and sustainability? A new framework offers a way to assess the benefits and trade-offs on national and global scales. **See p.104**

Fish is one of the most nutritious types of food and is recommended as part of a healthy diet. But how nutritious it is depends on the fish chosen. The environmental sustainability of aquatic foods, also known as blue foods, varies, but it is generally better than that of terrestrial livestock. Yet, remarkably, blue foods are often absent from the agenda for developing sustainable, healthy food systems.

To help policymakers fill this gap, the Blue Food Assessment (BFA) initiative (see go.nature.com/3z6x5ff) has conducted a series of thematic analyses on the global contribution of blue foods to nutrition, health, the environment, climate and social justice[1–4]. As part of this endeavour, Crona *et al.*[5] present on page 104 a synthesis of this analysis as a framework of four ways that blue foods can contribute to a healthy and sustainable food system.

Why is this work timely? For a start, the diversity of aquatic foods available is staggering. The numbers provided by Crona *et al.* show that more than 2,200 animal species are fished from the deep-water ocean, inland rivers and lakes, for example; and around 600 species are farmed. From small-scale subsistence fishers to industrial-scale aquaculture enterprises, the livelihoods of an estimated 800 million people rely on the sector.

Although the economic importance is undeniable, the nutritional significance of aquatic foods has long been a neglected area in policies[6]. Even in places where malnutrition is high and seafood is abundant, such as Cambodia (Fig. 1), using fish as an alternative to milk to help malnourished children is not mainstream practice, despite its obvious potential[7]. Stakeholders, in Cambodia and elsewhere, need to wholeheartedly embrace and invest in developing solutions that integrate blue foods into nutrition and health policies and strategies.

Crona and colleagues' framework provides a measure for how relevant blue foods are to achieving defined policy objectives. The framework's four objectives are: ensuring supplies of crucial nutrients; providing healthy alternatives to terrestrial meat sources; reducing environmental footprints associated with food; and safeguarding blue-food contributions to nutrition, economies and livelihoods under a changing climate. The framework is unique because it addresses the potential co-benefits as well as the unavoidable trade-offs between these four policy areas, which have fundamental implications for lives and societies.

The BFA group identified the key dimensions of blue foods in food-system transformation that are outlined in the group's thematic analyses[1–4]. A stepwise approach defined the policy objectives and the principles for assessing the blue-food relevance to each objective. By using a method based on logic formulae (true or false for predefined threshold values), the group assessed the relevance of blue-food policy objectives for individual nations. For example, reducing red-meat consumption is meaningful only if the nation's consumption is above a threshold, and increasing the supply of crucial nutrients is of interest only when these are deficient in a certain proportion of the population. The outputs of this analysis classified whether blue-food policies addressing each of the four objectives were 'less relevant', 'relevant' or 'highly relevant' for each nation.

For nutrition, the policy objective was to reduce nutrition deficiencies, but was narrowed down to deficiencies of two nutrients: vitamin B_{12} and omega-3. The authors identified these as relevant nutrients that can be deficient in diets across nations and of which blue foods are a key source, according to the original analysis[3] underlying the framework.

The original analysis also found that other crucial nutrients, such as iron and vitamin A, had little relevance in relation to blue foods globally. However, an estimated 16% of the total calcium available for consumption across nations originates from blue foods[3]. Calcium is present in fish bones, but the nutritional