electrostriction must therefore be tuned through careful material design. Most existing materials that exhibit a large electrostriction coefficient (the property that quantifies the effect) contain lead, which is toxic, so lead-free compounds displaying pronounced electrostriction are highly sought after[3].

Aside from polymeric materials[4], tailored oxide substances, such as compounds containing gadolinium and cerium[5] and some bismuth-based materials[6], are particularly promising candidates. Now, Zhang *et al.* have shown that electrostriction can be enhanced in such oxides by engineering them to contain artificial interfaces. The resulting materials have electrostriction coefficients that are approximately 1,500 times larger than those reported previously for these oxides.

In his Nobel lecture in 2000, physicist Herbert Kroemer argued that "the interface is the device", in reference to the key role of interfaces in structures built from inorganic semiconductor materials (see go.nature.com/3bhbsjs). This sentiment now seems more relevant than ever: interfaces in certain oxide compounds have already been shown to induce unexpected piezoelectricity[7], and new physical phases have started to emerge at these interfaces[8]. Zhang and colleagues' success takes these concepts to another level and is the next chapter in this story.

The authors engineered artificial structures by layering oxide films as thin as approximately one nanometre (Fig. 1). The films alternated between one kind of oxide and another, and the number of interfaces was shown to influence the structural and electrostrictive properties of the material. By varying the thickness of the layers, and thereby tuning the number of alternating oxide interfaces, the authors succeeded in achieving an extremely large electrostriction coefficient.

Through a powerful combination of structural characterization and molecular-dynamics simulations, Zhang *et al.* found evidence to suggest that the thickness of pairs of oxide films was key to the enhanced electrostriction. Specifically, reducing this thickness gave rise to atomic processes in the materials that couple mechanical and electrical effects. Their simulations showed that, as the thickness was decreased, atoms at the interfaces were less likely to be fixed in space. This gave them a freedom that distorted the local structure of the material, inducing a strain that was detected in the authors' experiments.

This strain, in turn, had a pronounced effect on the electric dipoles in the material, because it induced them to become stronger and to adopt a spatial configuration that made it easier to orient them in an external electric field (Fig. 1). This configuration effectively gave rise to the extraordinary electrostrictive effect observed in Zhang and colleagues' oxides. The findings therefore provide key insights into the interplay between subtle, interface-induced structural changes and the behaviour of electric dipoles in materials comprising ultrathin oxide layers.

It is tempting to compare the structural distortions observed by Zhang *et al.* with symmetry-breaking phenomena that can occur in bulk materials, far away from interfaces. A pertinent example arises in halide perovskite materials, which also exhibit pronounced electrostriction and are promising candidates for converting solar energy into electricity. Local fluctuations in the arrangement of atoms in these materials are thought to underlie some of their fascinating physical properties[9], so investigating the role of fluctuations that potentially occur at interfaces, and how they couple to symmetry-breaking phenomena and strain variations, could well inform our understanding of both systems.

Although Zhang and colleagues' study focuses on a single model system, the authors attempted to apply their design strategy to other materials — with encouraging results. This demonstrates that tuning electrostriction through the engineering of atomic-scale interfaces in oxide materials is a promising route to the fabrication of compounds with advanced electromechanical functionalities. Potential future applications of materials of this kind include nanometre-scale sensors and actuators, which could be used in biomedical technologies or in sonar devices for marine navigation, for example.

Implementation of these structures on a scale that is large enough to be commercially viable remains as fascinating as it is challenging. One particularly thought-provoking issue concerns the stability of the materials and their interfaces, because Zhang *et al.* found that chemical intermixing at the oxide interfaces (indicating a loss of stability) coincided with decreased electrostriction. This effect will be particularly relevant for future efforts to integrate electrostrictive structures into actual devices. Wiring these multilayered compounds to other materials will create even more interfaces than they contain alone, and the intermixing effect could pose a problem. Then again, as Kroemer would no doubt remind us, such interfaces are also 'the device', so perhaps integration will be yet another chance to improve performance.

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Pharmacology

Two-drug trick to block systemic toxicity

Matthias P. Wymann & Chiara Borsari

When combined, two drugs alter the activity of a protein complex called target of rapamycin complex 1 such that it is inhibited in the brain but not the body, enabling the treatment of brain tumours in mice without systemic toxicity. **See p.822**

Medicinal chemists and pharmacologists dream about how drugs might be directed specifically to selected organs. A particularly challenging target is the brain: many drugs do not pass easily through the blood–brain barrier (BBB), or are actively pumped out of the brain. The situation is complicated further when a drug to be delivered also shows body-wide (systemic) adverse effects. One such drug is rapamycin, which blocks tumour growth, but is also used as an immunosuppressant during organ transplantation[1]. Rapamycin and its semi-synthetic derivatives, dubbed rapalogs, inhibit a protein complex called target of rapamycin complex 1 (TORC 1). On page 822, Zhang *et al.*[2] present an innovative chemical approach to confine the action of rapalogs to the brain, and thereby eliminate undesirable systemic effects such as immunosuppression. They combine a high-affinity rapalog (RapaLink-1) with a newly developed molecule (RapaBlock) that prevents TORC1

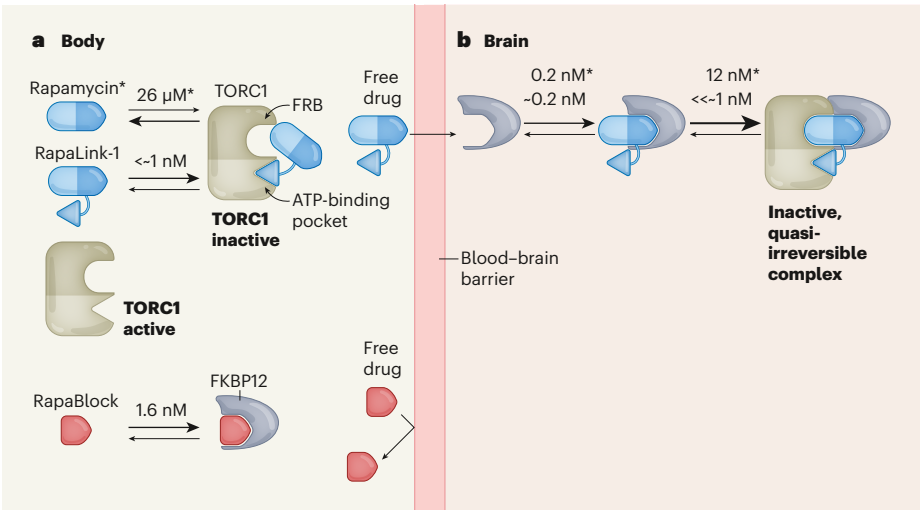

Figure 1 | Drug targeting to the brain. a, The drug rapamycin is used to inactivate signalling of the TORC1 enzyme complex (shown without accessory proteins). When used to treat brain diseases, rapamycin and its synthetic derivatives, such as RapaLink-1, can have adverse systemic effects. RapaLink-1 contains two motifs that bind to TORC1: one, shared with rapamycin, binds to the enzyme's FRB domain; the other binds to its ATP-binding pocket (numbers above the arrows reflect dissociation constants, with asterisks denoting the values for rapamycin. Arrow thickness indicates the ligand's propensity for binding or dissociation.) This interaction can temporarily inhibit TORC1, but to stably inhibit the complex, RapaLink-1 must also bind to the protein FKBP12. Zhang *et al.*[2] have developed a molecule called RapaBlock that binds tightly to FKBP12 in the body, preventing its association with the TORC1–RapaLink-1 complex. **b**, RapaBlock cannot cross the blood–brain barrier, so a quasi-irreversible TORC1–RapaLink-1–FKBP12 complex forms in the brain, inactivating TORC1.

inhibition systemically, but cannot enter the brain.

TORC1 regulates many fundamental biological processes, including cell proliferation, autoimmunity, metabolism and cancer. Rapalogs have been used successfully to slow tumour growth[1], as well as to treat disorders of the central nervous system[3].

To stably inhibit TORC1, rapamycin must form a complex with a cellular protein called FKBP12 and the rapamycin-binding domain (the FRB domain) of a protein called mechanistic target of rapamycin (mTOR), which is part of TORC1. This happens through the initial formation of either an FKBP12–rapamycin or an FRB–rapamycin complex. The RapaBlock molecule developed by Zhang and colleagues is a high-affinity ligand (a binding molecule) for FKBP12, and blocks its association with rapamycin. Because the FKBP12–rapamycin complex is much more stable than the FRB–rapamycin complex[4] (with a dissociation constant (K_d) of about 0.2 nanomolar, as opposed to 26 micromolar), RapaBlock prevents the formation of a 'quasi-irreversible' tripartite FKBP12–rapamycin–FRB complex, and thus keeps TORC1 largely free to function (with some being temporarily bound and inactivated by RapaLink-1; Fig. 1).

How did Zhang *et al.* design the RapaBlock molecule? They built two structurally diverse chemical libraries of molecules based on a synthetic ligand of FKBP12 called SLF, and the higher-affinity natural ligand (FK506). The authors then tested the resulting molecules for their ability to block the inhibition of TORC1 either by rapamycin or by its derivative RapaLink-1. RapaLink-1 is composed of rapamycin linked to an mTOR kinase inhibitor (which binds to mTOR's catalytic ATP-binding pocket[5]). By engaging both the FRB domain and the ATP-binding site, RapaLink-1 binds to TORC1 exceptionally tightly.

Zhang *et al.* found that rapamycin could be impeded by the low-affinity SLF derivatives, but that RapaLink-1 was substantially intercepted only by the higher-affinity FK506 derivatives. They therefore selected an FK506 derivative as RapaBlock, which integrates three key properties: first, it has a high affinity for FKBP12 (a K_d of 1.6 nM); second, it cannot enter the brain; and third, it cannot bind to the calcineurin protein (which binds to the FK506–FKBP12 complex, triggering immunosuppression)[6,7]. These features allow RapaBlock to sequester systemic FKBP12 in the body, blocking the activity of RapaLink-1 and preventing its interference with immunity. Because RapaBlock does not penetrate the BBB, RapaLink-1 action is not suppressed in the central nervous system.

Delivering compounds to the brain is demanding, and a number of tools have been developed to predict whether a chemical will be able to penetrate the BBB. One widely used example is the multiparameter optimization (MPO) algorithm, which incorporates six key physico-chemical properties (including a molecule's topological polar surface area, lipophilicity and molecular weight). An MPO score of 4 or higher predicts a good equilibration of drug levels in the blood and brain[8]. Newer versions of mTOR inhibitors (such as mTOR kinase inhibitors, which are structurally and functionally unrelated to rapamycin) have been optimized for access to the brain: PQR620, for instance, has an MPO of 3.8, and reaches brain–blood ratios of 1–1.5, depending on the dose[9,10].

The MPO scores of rapamycin (1.25), RapaLink-1 (1.0) and RapaBlock (1.25) predict very low brain penetration[8]. This has been confirmed for rapamycin and its derivative, everolimus, which reach maximum brain–blood ratios of around 1:100 (ref. 10). Nonetheless, rapamycin and everolimus can reduce epileptic seizures in individuals with tuberous sclerosis complex (a condition that is caused by hyperactivation of TORC1 in the brain). The actions of rapamycin, its derivatives and RapaLink-1 therefore seem to be dominated by a sink effect that traps the small amount of compound reaching the brain in a quasi-irreversible tripartite FKBP12–rapamycin–TORC1 complex.

In keeping with this model, Zhang *et al.* found that combining RapaLink-1 and RapaBlock prolonged survival in two mouse models of glioblastoma brain tumours, and also reduced tumour growth in one of the models. Moreover, a previous study[11] showed that the combination of RapaLink-1 and RapaBlock could also be successfully applied in a mouse model of alcohol abuse. Co-administering the two drugs prevented TORC1 signalling in the brain's nucleus accumbens, reduced alcohol craving and consumption and protected against RapaLink-1-induced liver toxicity, glucose intolerance and loss of body weight[11].

Zhang *et al.* have also modelled the RapaLink-1–RapaBlock and rapamycin–RapaBlock interactions and brain penetration. They predict a need for a blood-plasma concentration of around 1 μM of RapaBlock to intercept rapamycin, and roughly 10 μM of RapaBlock to substantially protect TORC1 signalling from inhibition by RapaLink-1. These concentrations will be difficult to reach in therapeutic settings, so properties such as pharmacological kinetics and the affinity of RapaBlock for FKBP12 will need improvement.

Finally, the authors claim that combining drugs that act intracellularly (such as protein kinase inhibitors) with an FK506-derived FKBP12-binding module would yield other programmable inhibitors that could be directed to the brain rather than to the body by means of RapaBlock. The molecules used by the authors do accumulate intracellularly, but their penetration of the BBB still needs to be demonstrated. In general, there is no 'on-target trap' akin to the tripartite FKBP12–rapamycin–TORC1 complex for the proposed programmable drugs. But, with further studies and refinements, Zhang and colleagues' impressive chemical strategy should open up new routes to organ-specific drug targeting.

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Developmental biology

A stressful start for human embryos

Tommaso Cavazza & Melina Schuh

Analysis of early human embryos reveals that DNA duplication after fertilization is highly inefficient. This causes DNA damage, chromosome breaks and abnormal numbers of chromosomes, impairing embryo development.

Fertilization of human eggs brings a mother's and a father's DNA together into one cell. It is crucial that this parental DNA is transferred accurately and without damage to the trillions of daughter cells that will eventually develop from the fertilized egg. Writing in *Cell*, Palmerola *et al.*[1] show that the accurate transfer of DNA often fails very early in development, directly after fertilization, owing to inefficient and incomplete copying of the parental genomes before the first division of the embryo.

The unification of the parental genomes in a fertilized egg, also called a zygote, involves several steps that are unique to this stage of life. For instance, the maternal and paternal chromosomes are initially enclosed in two separate nuclei, which must come together. After fertilization, the chromosomes need to be extensively modified through the addition and removal of molecular groups, and copied through DNA replication, to ensure that two complete genomes are available when the zygote divides into two cells. All of this happens in the absence of transcription. Whether human zygotes can replicate and transfer parental genomes efficiently and without DNA damage despite these unusual circumstances has been unclear.

Palmerola and colleagues studied parental genomes in human zygotes before and after DNA replication. They noticed that DNA damage was undetectable directly after fertilization, but present in about 50% of zygotes after DNA replication was completed. Further investigation revealed signs of DNA replication stress — a phenomenon involving the slowing or stalling of structures called replication forks, which form when the DNA duplex unwinds to enable replication, and which move along the strand as replication proceeds.

Strikingly, the authors found that replication forks moved along DNA much more slowly in zygotes than in cells at later stages of embryo development. This prompted them to investigate whether some zygotes fail to complete DNA replication before they divide. This would be dangerous, because incompletely replicated chromosomes can break, causing the loss of a piece of a chromosome[2,3] — a condition called segmental aneuploidy[4,5]. This condition affects 15–25% of human embryos, and has been suggested to cause embryonic failure[4].

When the authors blocked DNA replication shortly before zygotes divided, they observed a prominent increase in chromosome breakages, compared with cells in which replication was unperturbed. This indicated that some DNA regions are indeed replicated only shortly before a zygote divides. Might these regions sometimes fail to replicate before division? To test this hypothesis, the authors examined unperturbed embryos, and found that chromosomes often broke in gene-poor regions, which replicate late. The break sites overlapped with those induced by blocking DNA replication. These data strongly suggest that replication stress causes segmental aneuploidy in human embryos.

DNA replication stress can also cause entire chromosomes to distribute incorrectly during cell division[2]. This leads to a condition called whole-chromosome aneuploidy, in which cells have an incorrect number of chromosomes. More than 50% of human embryos contain this type of aneuploid cell, which is considered to be a leading cause of embryonic failure and miscarriage[6]. Palmerola *et al.* therefore investigated whether DNA replication stress in human zygotes contributes to whole-chromosome aneuploidy. They used a similar experimental approach to that used before, but inhibited DNA replication over a longer period. After

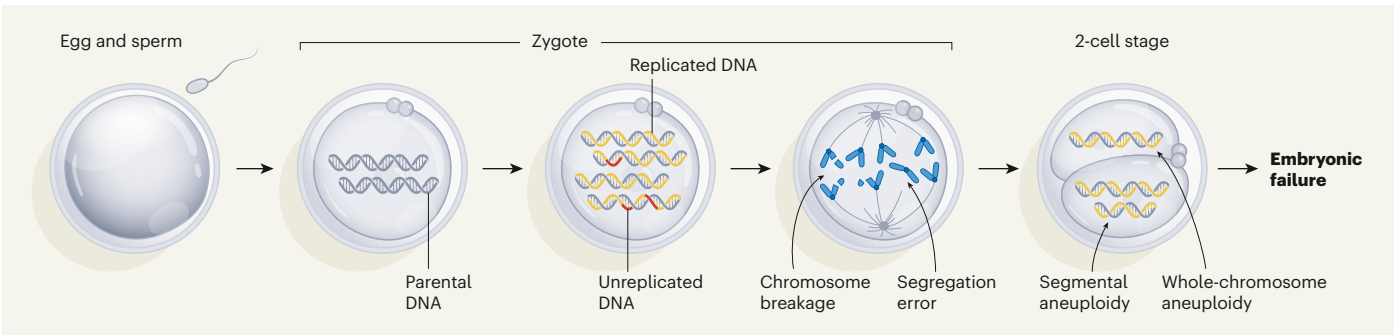

Figure 1 | DNA-replication errors at the beginning of human embryo development. Fertilization of an egg by sperm generates a zygote — the first cell of the embryo. Before the zygote divides into two cells, the parental DNA derived from the egg and sperm must be duplicated through DNA replication. Palmerola *et al.*[1] report that, in human zygotes, DNA replication is slow and erratic (a phenomenon known as replication stress) and is sometimes not completed before cell division. Incomplete DNA replication leads to chromosome breakages, and can also cause errors during segregation of the duplicated chromosomes into daughter cells. These defects respectively cause phenomena called segmental aneuploidy (in which parts of chromosomes are missing from the 2-cell embryo) and whole-chromosome aneuploidy (in which whole chromosomes are missing). The aneuploidies can lead to embryonic failure.