A glassy material is rigid too, but the arrangement of its molecules is aperiodic ('amorphous'), and does not minimize the energy of the structure[2]. But we can still understand rigidity in amorphous arrangements in the absence of molecular motion (that is, at a temperature of absolute zero) by appealing to mechanical analogues. A random packing of particles with a density above a certain value — a pile of sand, for example — can be rigid. A less-dense collection of particles, in which each element is held to its neighbours by springs, also cannot change its shape if the number of constraints exceeds a critical value. But even with such pictures in mind, fundamental questions remain. Why have amorphous arrangements been adopted at low temperatures in glassy materials? Why not take on the configuration with the lowest energy?

The structures of real (as opposed to computer-modelled) glasses are not known beyond the shortest length scales. Yet it is precisely at longer distances that the consequences of 'ill-condensation' during the cooling process are reflected — and where the answers to these questions, and an understanding of the relationships between different materials, lie.

Salmon *et al.*[1] compare detailed measurements of the atomic arrangements of two simple binary glass-formers — zinc chloride ($ZnCl_2$) and germanium selenide ($GeSe_2$) — out to large inter-atomic separations, and demonstrate strong similarities between them. This is remarkable for two reasons. First, the nature of the interatomic interactions in the two materials is expected to differ, because $GeSe_2$ is more strongly covalent than $ZnCl_2$. Second, the two materials seem, from the temperature dependence of their viscosities (see ref. 3 and references therein), to approach the transition to the rigid glassy state in characteristically different ways. $ZnCl_2$ is the less 'fragile' liquid — its approach to rigidity is more continuous than that of $GeSe_2$, and similar to that of the silica of window glass. One might expect this difference to be correlated with a structural difference in the glasses at longer length scales.

Compared with a crystalline structure, the molecules in a normal liquid will be found at any given instant in a disordered, high-energy configuration — although at the level of the nearest neighbours the structure is almost always similar to that adopted in the solid. At high temperatures, the crystalline state, which minimizes energy, is not favoured because the number of disordered configurations, which give the liquid a higher entropy, is far greater. If a liquid is cooled slowly, the transition between the two states occurs at a sharply defined temperature (the freezing point), where the tendencies to maximize entropy and minimize energy are equal. At this point, groups of molecules adopt the same low-energy structure as the crystal; once these 'nuclei' exceed a critical size, they can grow spontaneously. The time taken to form such nuclei depends on the rate at which the molecules can reorganize themselves. This rate itself decreases as the temperature of the liquid is lowered — if this is done sufficiently rapidly, the system may reach such low temperatures that reorganization stops before the critical nuclei have a chance to form. The system is left in a rigid, amorphous state — it forms a glass.

This scenario could theoretically occur in any liquid. For a glass to form at practical rates of cooling (those that can be achieved in a laboratory), it is necessary for the formation of the critical nucleus to be 'frustrated', so that the process takes longer than usual. This can be brought about because the preferred local arrangement of the molecules does not readily propagate periodically out to the length scale required to form a crystal nucleus of the critical size. Therefore, experimental attention focuses on the intermediate-range structure of the glass-forming materials, where the frustration of nucleus formation should be apparent.

Salmon and colleagues' experiments are based on neutron diffraction, in which oscillations in the number of neutrons scattering at different angles reflect the relative positions of pairs of atoms. In binary systems such as $ZnCl_2$ and $GeSe_2$, the intensity pattern includes information on the distribution of all atom pairs (in the case of zinc chloride, for example, Zn–Zn, Zn–Cl and Cl–Cl). But Salmon *et al.* exploit the fact that neutrons scatter from different isotopes of the same element with different amplitudes: by performing experiments on three samples with the same chemical but different isotopic compositions, they were able to separate the diffraction pattern connected to each atomic pair and therefore examine the structure of the glass in exquisite detail.

Two characteristic length scales can be distinguished in the observed structures: first, a strong preference for the Zn or Ge atoms to have four Cl or Se nearest neighbours arranged at the local level as a tetrahedron, generating a chemical ordering that extends to large distances; second, an intermediate-range order, associated with the way these tetrahedra are linked together. Despite the differences in the chemistry of $ZnCl_2$ and $GeSe_2$, their structures are remarkably similar on both the short and intermediate length scales. Thus, different types of chemical interaction seem to have given rise to similar structures that, from the observation that both materials are good glass-formers, allow for the frustration of crystallization. On the other hand, even at this resolution there is no readily discernible structural feature that can account for the difference in the 'strength' of the two liquids, as seen in the temperature dependence of their viscosity. ■

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Cell biology

Sterol sensor comes up for air

Renee M. Garza and Randolph Y. Hampton

In one example of a feedback mechanism in mammals, cells switch cholesterol synthesis on or off depending on the availability of sterol. A rewired version of this pathway in yeast acts instead as an oxygen sensor.

Writing in *Cell*, Espenshade and colleagues[1] describe a previously unknown strategy by which cells sense oxygen levels. The mechanism uses an evolutionarily conserved and medically relevant pathway for sterol regulation in an unexpected way.

Over the past few years, a molecular drama has been unfolding in our understanding of how cholesterol synthesis is regulated in mammals. The overarching idea is simple: when cells need more cholesterol, they increase the levels of enzymes that make it, by increasing the expression of the enzyme-encoding genes. But the underlying mechanism for this is quite unexpected. Thanks to heroic work led by Brown and Goldstein[2], we now have a clear idea of how cholesterol-regulated gene transcription occurs. Perhaps the only unsurprising feature of this transcriptional regulation is that it centres on a transcription-factor protein: SREBP (for 'sterol-regulatory-element-binding protein').

The SREBP molecule contains a portion that carries out transcription ('TF' in Fig. 1a, overleaf), connected to a transmembrane domain. Freshly made, full-length SREPB is anchored in the membrane of a cellular compartment called the endoplasmic reticulum (ER) — tethered like a pit bull on a chain, and unable to reach its targets in the nucleus. Active SREPB is liberated from its membrane anchor by cleavage, and it is this cleavage that is controlled by sterol levels. Although SREBP resides in the

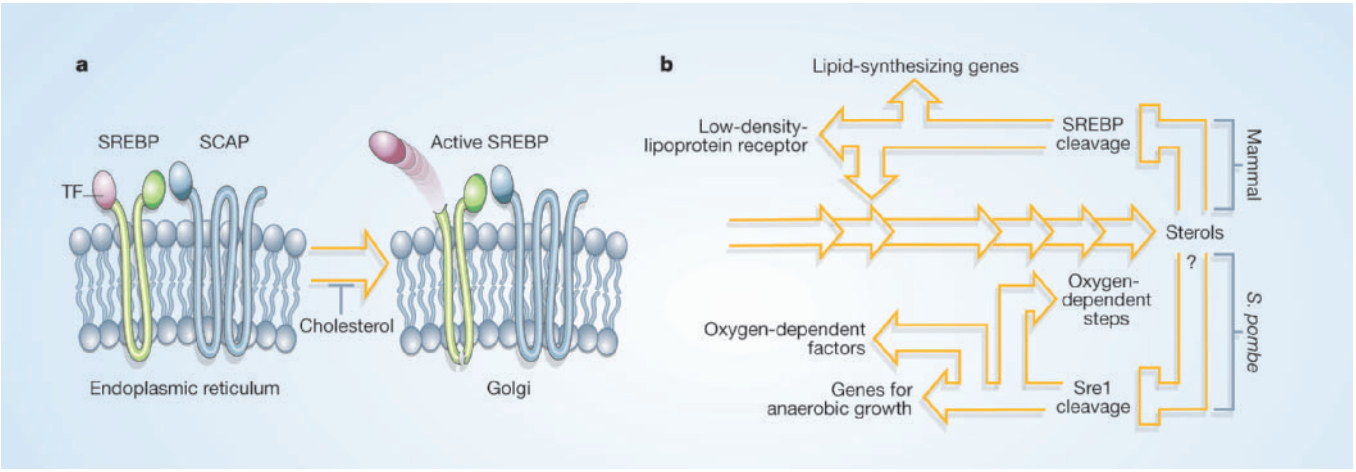

Figure 1 **New tricks for a familiar pathway.** a, **The SREBP-processing pathway. The gene-transcription factor SREBP, which regulates sterol biosynthesis, resides in the endoplasmic reticulum in mammalian cells. It is transported to the Golgi by SCAP, where it is cleaved twice to release an active transcription factor (TF). Binding of cholesterol to SCAP inhibits such transport[2].** b, **Top, mammals use SCAP-dependent cleavage of SREBP to provide feedback control of cholesterol synthesis, and to regulate other genes involved in lipid metabolism. Thus, if sterol levels are high, SREBP cleavage is inhibited, and these genes are no longer activated. Bottom, the newly discovered 'rewired' pathway from fission yeast[1]. The membrane-bound SREBP counterpart Sre1 is regulated by sterols (or possibly other signals) through Scp1, to control genes involved in oxygen-dependent functions and those required for anaerobic growth. This pathway seems to function to sense and respond to oxygen.**

ER membrane, the two protein-cleaving enzymes that liberate the active fragment occur in another compartment, the Golgi. When sterol levels are sufficiently low, SREPB is carried from the ER to the Golgi, where cleavage — and thus activation — occurs. When sterol levels are high, the movement of SREBP to the Golgi (and hence cleavage) is blocked.

This 'traffic control' is effected by the protein SCAP (for 'SREBP-cleavage-activating protein'). SCAP binds to SREBP and carries it out of the ER by entering the vesicular pathway that shuttles between the ER and the Golgi. SCAP also has a membrane-embedded motif that directly binds cholesterol. Cholesterol-bound SCAP no longer exits the ER, and so cholesterol inhibits production of active SREBP (Fig. 1a), thereby governing its own synthesis.

Genome sequencing studies show that *Schizosaccharomyces pombe* (fission yeast) also has versions of SREBP and SCAP, called Sre1 and Scp1, respectively. Given that this fungal species synthesizes cholesterol's cousin ergosterol, this is perhaps to be expected. But the surprises came when Espenshade and colleagues[1] explored the molecular details of the *S. pombe* feedback pathway.

The authors found that Sre1 is cleaved to a soluble form and that this cleavage is regulated by sterol in an Scp1-dependent manner, just as in mammals. However, the transcriptional targets of Sre1 are quite distinct. Testing of candidate genes, combined with microarray techniques to analyse gene expression more broadly, showed that the early, rate-limiting reactions of sterol synthesis — those regulated by mammalian SREBP — were completely unaffected by changing levels of active Sre1. Consistent with this, loss of either Scp1 or Sre1 through mutation had no effect on the growth of *S. pombe*, whereas in mammals loss of the SREPB pathway renders cells totally dependent on added sterols.

Instead, Espenshade and colleagues' analysis indicated that the relevant regulatory function pertains to oxygen. Genes regulated by Sre1 include those encoding: enzymes in the late, oxygen-dependent parts of the sterol-synthesis pathway; enzymes required for the biosynthesis of haem (an oxygen-binding molecule); and several other oxygen-related factors, including some that are needed for yeast cells to survive low oxygen levels. Thus, it seems that sterol-regulated cleavage of Sre1 is used to signal oxygen availability (Fig. 1b).

The authors go on to show that several predictions of their oxygen-sensing model are borne out. First, *S. pombe* cells that lack Sre1 or Scp1 cannot survive in anaerobic conditions. These mutant cells do survive, however, if allowed to express the cleaved form of Sre1 (the 'TF') by molecular-biological trickery. Furthermore, the presence of Sre1 and Scp1 enables the cells to adapt to low-oxygen conditions in ways that would be predicted if these proteins were involved in oxygen sensing — for instance by increasing the cells' capacity for the oxygen-dependent reactions of ergosterol synthesis. Finally, the cleavage of Sre1 is massively stimulated by lowering the oxygen concentration, indicating that the relevant perturbation indeed causes the proposed physiological response.

Although we don't know what signal regulates Scp1-mediated cleavage of Sre1, it is reasonable to suppose that it is a sterol — perhaps ergosterol (the end result of the sterol pathway in *S. pombe*), but possibly some other sterol generated in the pathway, or a derivative of one of the pathway molecules. And perhaps a second oxygen-dependent signal works together with sterols to regulate Sre1 cleavage. There seems to be great flexibility in the kinds of molecules that can be sensed by the sterol-sensing motif found in SCAP and related proteins[3–5], so it may be best to await the next chapter in this new use of the SREPB pathway.

Whatever the specific signals, this 'rewiring' of the SREBP pathway makes a lovely kind of sense. Synthesis of sterols is absolutely dependent on oxygen. Thus, the choice of sterol synthesis as a fiduciary indicator of oxygen levels is a good one, and one that probably exists in more than one yeast species.

This ground-breaking study raises some fascinating questions. Is this a broadly used mode of oxygen sensing in nature? Does it occur in many fungi, and thus provide an Achilles' heel that can be exploited to develop new antifungal drugs? What is the range of molecules sensed by the many SCAP counterparts found in nature? The emerging picture is that these membrane proteins may be widely used sensors of intramembrane signals that affect any aspect of biology in which lipid molecules are involved. ■

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