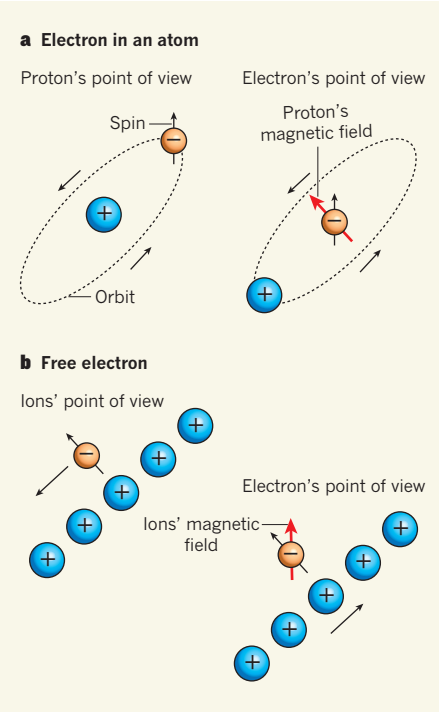

Figure 1 | Spin–orbit coupling. **a**, In an atom, an electron (orange) orbits the nucleus (blue; here composed of a single proton). From the electron's point of view, the proton orbits the electron and produces a magnetic field that couples with the electron's spin and alters its orbit. **b**, If the electron is roaming freely through a group of ions, from the electron's point of view it is the ions that move. The ions' motion generates a magnetic field that couples to the electron's spin. In real solids, this coupling between the electron's spin and its motion (spin–orbit coupling) is more complex, but the essence of the interaction is the same as that depicted here. Lin and colleagues[2] engineer spin–orbit coupling in a neutral atomic system.

used a pair of lasers to transfer linear momentum to the atoms' centre-of-mass and create mixed atomic spin states, which are composed of two different spin orientations. The mixed-spin states couple directly with the momentum transferred to the atoms' centre-of-mass (orbital) motion, creating a 'dressed state', thus leading to an artificial spin–orbit coupling. (For a review of related ideas, see ref. 6.)

A great advantage of the authors' experiment[2] lies in the possibility of controlling spin–orbit coupling — from no coupling at all to strong coupling — through optical means. If the lasers are turned off, spin–orbit coupling disappears: the spin and the centre-of-mass motion are independent. If the lasers are turned on, spin–orbit coupling occurs and scales with the lasers' intensity. This type of control is not typically available in condensed-matter systems such as in semiconductors or superconductors.

What's more, Lin and colleagues[2] have shown that the artificial spin–orbit coupling can be used to change the interaction between atoms that are in different spin states. The ability to change the interactions between a pair of atoms allows the researchers to study transitions between a phase in which atoms with different spin states repel weakly, and are mixed in the same spatial region (lasers off), to a phase in which atoms with different spin states repel strongly and are spatially separated (above a threshold of laser intensity).

The authors' creation and control of artificial spin–orbit coupling in atoms has implications beyond atomic-gas physics, in particular because there is no fundamental reason why their experiments should not be performed with fermions. In condensed-matter systems, the spin–orbit coupling of the constituent electrons (fermions of spin ½) can have important consequences for semiconductors, superconductors and magnetic materials. In mercury telluride (HgTe) semiconductors, for example, strong spin–orbit coupling can produce topological insulators[7]. These unconventional semiconductors insulate electric current in their bulk but conduct electricity on their surface, a rather unusual and peculiar effect that may be useful for electronic applications. The creation of adjustable artificial spin–orbit coupling in atoms opens up exciting possibilities for realizing quantum simulators of topological insulators and exotic forms of superfluidity and superconductivity. ■

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PROTEIN FOLDING

Protection from the outside

Protein folding is a high-stakes process, with cell dysfunction and death being the unforgiving penalties for failure. Work in bacteria hints that organisms manage this process beyond the boundaries of the cytoplasm — and even the cell.

EVAN T. POWERS & WILLIAM E. BALCH

Protein misfolding can instigate disease one way or another[1]: it can cause both loss of function by leading to an insufficient amount of functional proteins, and gain of toxic function through the aggregation of misfolded proteins. Suppressing misfolding and aggregation is the job of the proteostasis network[2,3], particularly the various classes of chaperones — evolutionarily conserved proteins that help other proteins to fold productively. Folding protection must operate in many environments, both inside and outside the cell. Writing in *Nature Structural and Molecular Biology*, Quan *et al.*[4] identify in bacteria a new structural class of chaperone called Spy that, unusually, functions outside the typical cellular remit for chaperone activity.

For their analysis, Quan and colleagues created two 'sandwich fusion proteins' by inserting L53A I54A Im7 — an unstable version of the protein Im7, which is often used in protein-folding studies[5] — into two other proteins: β-lactamase and DsbA. When folded, β-lactamase and DsbA confer resistance to the antibiotic penicillin and to cadmium ions (Cd^{2+}), respectively. However, the insertion of a foreign protein into their sequences makes their folding dependent on the folding of the inserted protein. Thus, in the sandwich fusion proteins, L53A I54A Im7 folding leads to two independent selectable markers: penicillin resistance and Cd^{2+} resistance.

The authors[4] induced expression of their fusion proteins in the periplasm of the bacterium *Escherichia coli*; the periplasm is the space between the inner and outer membranes in Gram-negative bacteria. In most cases, they observed no resistance to either penicillin or Cd^{2+}, presumably because the inability of L53A I54A Im7 to fold prevented β-lactamase and DsbA from folding. A number of strains, however, did gain both penicillin and Cd^{2+} resistance.

The resistant strains also produced a massive amount of Spy, suggesting that this little-known periplasmic protein had a hitherto unrecognized chaperone activity. The researchers corroborate this result *in vitro*, showing that Spy can inhibit both aggregation and promote folding, even at

sub-stoichiometric concentrations.

Quan *et al.* also show that Spy activity is independent of the cellular energy molecule ATP. This is not surprising, given that the protein functions outside the cytoplasm. However, operation of Spy at sub-stoichiometric concentrations is surprising, because chaperones that work in this way generally use ATP[6]. According to conventional wisdom, it is difficult — if not impossible — to imagine a mechanism for how a chaperone actively remodels the protein-folding energy landscape without an energy input. It is equally difficult to reconcile Spy's effects on protein folding and aggregation with a simple holdase mechanism, in which a chaperone passively binds to unfolded proteins.

There could be several explanations. To protect nascent peptides emerging through the inner membrane, Spy could work during protein translation, binding transiently to nascent proteins to stabilize them. Spy could be an efficient protective osmolyte, and thus thermodynamically stabilize proteins' native states by promoting the formation of hydrogen-bonded secondary structures[7], which would be consistent with its high levels in the periplasm. Or Spy could be a steric foldase — a type of chaperone that stabilizes the folded state of proteins by binding to them[8]. Clearly, Spy's mechanism of action merits further investigation.

The discovery of Spy adds to the current repertoire of chaperones functioning in the periplasmic space of Gram-negative bacteria[9] and raises questions about the existence of extra-cytoplasmic, or outer, proteostasis networks (the outPN) in complex eukaryotes (plants and animals). Whereas the bacterial inner membrane rigorously protects the cytoplasm and the intracellular proteostasis networks (inPN), the outer membrane is permeable to small molecules (those with a molecular mass of less than roughly 600). It functions as a filter to retain periplasmic proteins close to the surface of *E. coli*, thus preventing their dilution in the environment. It is perhaps only a modest stretch to compare the bacterial periplasmic space to the interstitial spaces in vertebrates (Box 1).

Unfortunately, our knowledge of the composition and function of the outPN in complex eukaryotes is limited. Although small amounts of the classic chaperones Hsp70 and Hsp90 can be found outside the cell under stress conditions[10], their roles remain controversial, and the lack of extracellular ATP makes them ill-suited to a chaperoning role outside the cell. In addition, abundant plasma proteins such as albumin and globulins can bind to other proteins, but their potential role as outPN components remains to be carefully explored. Nonetheless, there is evidence for potential outPN players that chaperone defective proteins — including α1-acid glycoprotein[11], α-1-antitrypsin[12,13], asialoglycoproteins[14], plasma gelsolin[15], clusterins[16], α2-macroglobulins[17] and transthyretin, which is thought to be protective against Alzheimer's disease[18].

Is there an equivalent of stress-related Spy induction in humans? At least one possibility is the proteins whose levels increase during the acute-phase response to inflammation[17] (such as α1-acid glycoprotein and haptoglobulin) and that have protein-folding protective functions. Even the innate and adaptive immune responses could be seen as highly evolved outPN systems (Box 1).

Undoubtedly, the intracellular proteostasis network is conserved and universal[2,3]. But the observations[4,9] that the seemingly lowly *E. coli* can protect itself from a periplasmic folding problem by the production of Spy and other non-ATP-dependent chaperones could shift our view of the role of the interstitial space towards it being a home for a comparable extracellular proteostasis network in vertebrates[2,3]. Indeed, the outPN in vertebrates could report on and manage extracellular protein-folding stress, working in parallel with inflammatory and immune responses (Box 1). After all, like *E. coli*, vertebrates experience stressful situations every day. ■

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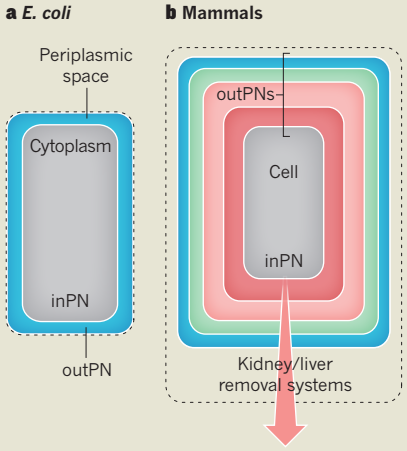
BOX 1
Chaperone networks

In addition to the intracellular proteostasis network (inPN) in its cytoplasm, *Escherichia coli* produces many chaperones[8] — including Spy, identified by Quan *et al.*[4] — that protect protein folding in the periplasm in an ATP-independent manner (**a**).

Mammals have a number of distinct interstitial spaces filled with bodily fluids that could also operate independently of ATP to protect the major organ systems (**b**). However, unlike the periplasmic space of *E. coli*, which is open to the environment, the interstitial systems are closed. Interstitial fluids ultimately communicate with the environment through the kidney filtration system, or through uptake and metabolism by the liver.

Plasma (red) provides components of the extracellular chaperone network (outPN) to the peritoneal (abdomen), pericardial (heart), pleural (lungs), synovial (joints) and amniotic fluids (for simplicity, all grouped in pink). Each might form an interstitial system protecting a separate organ system, and all have a rich protein content, reflecting their passive coupling to plasma. Both the lymphatic system (green), which houses a key arm of the immune system, and the central nervous system's cerebrospinal fluid (CFS; blue) seem to be separate from the plasma outPN-related fluids. CFS is largely devoid of protein, but is possibly protected by the blood–brain barrier through the plasma outPN. E.T.P. & W.E.B.



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