thickness of the global spherule deposit is largely a function of projectile size. The authors apply this model to published data (see Table 1 of the paper[2]) on the size distributions and thicknesses of 14 well-studied spherule beds to estimate probable ranges for projectile sizes and velocities. They find that many of these spherule beds formed from very large projectiles, in the range of 17 to 70 km in diameter (the K–Pg asteroid that formed the Chicxulub crater was 9–14 km). Many of the velocity ranges are rather high for typical asteroid impacts (20 km per second), as much as 21–25 km s^{-1}. Perhaps this is consistent with the higher velocities of Bottke and colleagues' E-belt impactors, which are now depleted and no longer significant for the modern Solar System.

For researchers familiar with the spherule beds, these two papers[1,2] help to confirm what has long been suspected — that some of these deposits record impacts far greater than the K–Pg Chicxulub event. At least three of the Archaean spherule beds (3.2-Gyr-old beds S3 and S4 and the 2.6-Gyr-old Reivilo bed) have higher concentrations of iridium, and thus meteoritic material, than the global K–Pg layer. If many spherule beds are global deposits, then they have 10–100 times more ejecta than the K–Pg boundary layer. Although the new studies provide theoretical support for impact models of the early Earth and Moon, there is still much to be learned, especially for the lunar impact history.

Not all researchers have accepted the LHB hypothesis, and the number and age of the lunar basins is a matter of dispute that can be resolved only with new lunar sample-return missions. There are also unresolved complexities in the spherule-bed record. Three beds from about 3.2 Gyr ago (S2, S3 and S4) all occurred in a brief (about 20-million-year)[6] interval that would be improbable under the Nice model. And the beds' chromium isotopic compositions[6], although meteoritic, are distinct from those in three younger (about 2.5-Gyr-old) spherule beds[7], suggesting that they are derived from separate populations of impactors. These problems do not refute the models in the papers[1,2], but they do require more data and even better models to be solved. ■

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DRUG DISCOVERY

Time in a bottle

A biological clock synchronizes animal behaviour and physiology with Earth's 24-hour rotation. Drugs targeting the clock's 'gears' show promise for treating obesity and other metabolic disorders. SEE ARTICLE P.62 & LETTER P.123

JOSEPH BASS

When spring approaches, many countries set their clocks forward by one hour. The following morning, we are reminded of the strong pull exerted by our own internal clock as we are forced to wake up one hour earlier than usual. Such minor disruption of sleep patterns can lead to fatigue and is associated with a rise in the incidence of certain heart disorders[1]. These undesirable effects occur because our internal clock — which tracks the circadian (day–night) cycle — controls not only our sleep patterns but also many physiological processes that anticipate the rhythmic environmental changes tied to the Sun's rising and setting. In this issue, Solt *et al.*[2] (page 62) and Cho *et al.*[3] (page 123) illuminate the molecular mechanisms by which the circadian clock regulates metabolism in mice, and provide evidence to suggest that drugs targeting clock components may offer treatment for disorders such as obesity and diabetes.

In the late 1990s, the finding[4] of biological rhythms in cultured fibroblast cells indicated a broad role for the circadian clock in cell physiology. Subsequently, circadian oscillations were observed[5] in the expression of at least 10% of the genome in mouse tissues. At the molecular level, the circadian clock consists of a feedback loop that involves activator and repressor proteins, and repeats itself every 24 hours. Activators induce the expression of repressors, whereas repressors inhibit activators' expression.

One of these repressors is REV-ERB-α, a member of the nuclear-receptor family of proteins[6]. In addition to controlling the expression of activators' genes[7], REV-ERB-α modulates the production of lipids and bile acids in the liver[8,9], and the formation of fat cells[10]. Whereas the activity of most nuclear receptors is induced on binding to specific steroid hormones, REV-ERB-α has been shown[11,12] to bind instead to haem (an oxygen-binding molecule) and, in turn, to regulate haem synthesis[13]. These findings have increased interest in the development of synthetic compounds that, by binding to REV-ERB-α, could modulate the protein's function.

Notwithstanding these advances, the part played by REV-ERB-α in the circadian clock has remained enigmatic because mice lacking this protein show relatively minor defects in their behavioural rhythms[7]. A possible explanation for this is that a closely related protein, REV-ERB-β, can compensate for REV-ERB-α deficiency, as suggested by studies[14] of cultured cells.

To understand the circadian functions of the two REV-ERB proteins, Cho *et al.*[3] identified the genomic regions that these repressors occupy in the mouse liver. This analysis revealed that both proteins bind to regulatory regions of genes encoding not only numerous core components of the clock but also proteins involved in various metabolic pathways. Therefore, REV-ERBs probably control circadian oscillations through effects beyond modulation of the clock activators. Whether the action of REV-ERBs on clock genes is crucial for the oscillations in cellular activity in other organs — such as the brain — requires additional study.

Mice deficient in REV-ERB-α have been shown[7] to have an increased mortality. So, to carry out experiments with mice lacking both REV-ERB proteins, Cho *et al.* used a genetic-engineering technique known as Cre/*lox* recombination to generate a mouse strain in which the simultaneous deletion of both genes could be experimentally induced in adulthood. The authors monitored these double-mutant mice running in wheels as a test for circadian dysfunction, and found that the animals' running rhythms had a markedly shortened period length when compared with those of control animals. Moreover, the double mutants displayed an altered response to light.

The researchers compared several metabolic parameters of the double-mutant mice with those of control littermates. The mutant mice had elevated blood levels of triglyceride lipids and of glucose, decreased levels of free fatty acids and a lower respiratory exchange ratio (the relative amount of exhaled carbon dioxide and inhaled oxygen). These metabolic alterations are consistent with an increased generation of energy from fat in the mutant mice.

Cho and colleagues' work[3] provides additional evidence for REV-ERBs as central elements of the circadian clock, and demonstrates that these proteins participate in the control of liver metabolism. To gain further insight

into the functions of REV-ERBs, additional analyses of oxidative metabolism — the process by which cells obtain energy from the oxidation of organic compounds — and exercise tolerance in the mutant mice would be needed. For example, metabolic indicators could be monitored across time and under dynamic conditions, such as during a high-fat diet.

Enter Solt and colleagues[2]. Using a high-throughput screen against the entire family of nuclear hormone receptors in cultured human cells, the authors identified a group of related molecules that selectively activated REV-ERB-α and REV-ERB-β. Two of these compounds were suitable for studies in mice, and were investigated further.

The researchers found that the compounds reduced the amplitude of the oscillations in clock-gene expression in cultured cells. And, when injected into mice, the drugs repressed the expression of clock genes. Indeed, the treated mice displayed altered wheel-running rhythms in constant darkness, but not under standard light–dark conditions (12 hours light, 12 hours dark). The cause of reduced drug activity under light–dark conditions on the animals' behaviour requires further investigation but may reflect a direct response to light that bypasses the clock mechanisms — an effect known as 'masking'. The authors carried out further studies in cultured cells that support the idea that the drugs' effects in mice are due to activation of REV-ERBs and not to modulation of other proteins.

Solt *et al.* report that, in addition to the actions on the circadian clock, the compounds protected the animals from certain metabolic disorders associated with obesity and high-fat feeding. The treated mice showed resistance to diet-induced obesity and an increased consumption of oxygen, as well as a reduced food intake during the light period when they are usually sleeping. Moreover, the animals had an altered profile of gene expression in the liver, fat and muscle. In particular, changes in the expression of enzymes involved in the metabolism and transport of fatty acids point towards enhanced oxidative metabolism and reduced lipid storage. The drug treatment also ameliorated metabolic alterations in genetically obese mice that lacked the hormone leptin.

Overall, the results reported by Cho *et al.*[3] and Solt *et al.*[2] re-emphasize the tight coupling of the circadian clock with metabolism, and the special role of REV-ERBs as a nodal point in this relationship. They also suggest that these nuclear receptors may repress the expression of more clock components than previously thought.

Furthermore, the studies raise the possibility of 'putting time in a bottle' — the development of drugs to manipulate biological clocks — for the treatment of metabolic disorders. Admittedly, such an effort entails a chicken-and-egg riddle: any compounds targeting REV-ERBs' activities may affect metabolic parameters either directly, by modulating the expression of metabolic targets, or indirectly, through effects on the clock. Moreover, as REV-ERB proteins are produced in an oscillatory manner, the actions of any drug would be limited to the window of REV-ERB expression. ■

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SOLID-STATE PHYSICS

Electrons do the split

Interacting electrons that are confined to move in a one-dimensional structure do not simply jam together like cars in rush hour. Inelastic X-ray scattering shows that the electrons act as if they split into separate fractional entities. SEE LETTER P.82

RALPH CLAESSEN

In physics, a phenomenon is often best explained by reducing it to its simplest version. For example, to understand the quantum-mechanical motion of non-interacting electrons in a crystalline solid, the case of a one-dimensional crystal lattice suffices to introduce the concept of electronic band structure, which describes the range of energies that the electrons may have in the solid. But when it comes to interacting electrons, this approach fails. Coulomb repulsion between any two electrons is much stronger in one-dimensional solids than in their higher-dimensional counterparts, and many-body effects emerge that lead to an apparent fractionalization of the electron[1–5]. With this fractionalization, the electron's spin and charge seem to form separate quasiparticles — spinons and holons, respectively — that move independently of each other and have different velocities. On page 82 of this

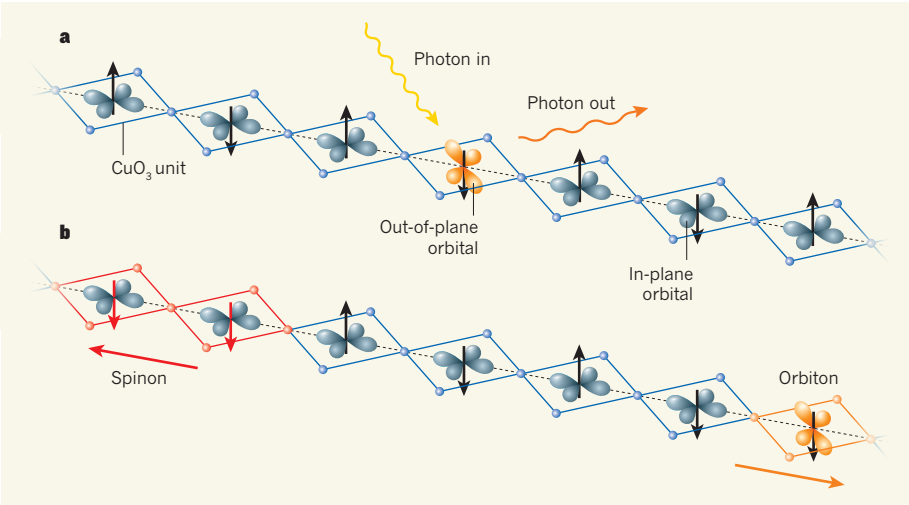

Figure 1 | Electron fractionalization in a one-dimensional structure. **a**, Schlappa and colleagues' system[6] consists of a chain of copper oxide units (CuO_3). In the ground state, all units contain 3*d* electrons in the same in-plane orbital, and the direction of the local 3*d* spins (arrows) alternates between neighbouring units. Shining X-ray photons on the chain excites the electrons in one of the units into an out-of-plane orbital of higher energy. **b**, The authors show that the X-ray irradiation leads to an immediate splitting of the excitation into two separate quasiparticles of different velocities: a spinon, which is associated with a local perturbation in the spin arrangement, and an orbiton, which carries the orbital excitation.