intercellular adhesion. It is also a cofactor of the Lef1/Tcf family of transcription factors, which are effector molecules in signalling pathways involving Wnt proteins[7]. β-Catenin thereby regulates several fundamental cellular processes. In the authors' screen for regulators of normal epidermal-cell behaviour, β-catenin emerges as a negative regulator of epidermal-cell growth (Fig. 1). Follow-up *in vitro* experiments suggested that this effect is independent of Wnt signalling, and that it stems from a loss of contact-mediated inhibition of proliferation. By contrast, the authors show that β-catenin is required for *Hras1*-induced hyperproliferation, and that this correlates with increased Wnt signalling *in vivo*. Intriguingly, however, a previous study showed[8] that blocking Wnt signalling in the epidermis by expression of an inhibitory form of Lef1 does not impede epidermal tumour formation. Future work is therefore needed to evaluate the involvement of β-catenin and Wnt signalling in tumour development.

Whereas β-catenin has already been implicated in numerous malignancies, Beronja and colleagues' screen identified another gene, *Mllt6*, as also being involved in *Hras1*-induced epidermal-cell hyperproliferation. Chromosomal translocations of this gene have previously been associated with mixed myeloid leukaemia[9]. Although the exact function of the Mllt6 protein is unclear, it is known to influence the subcellular localization of the Dot1a–histone methyltransferase protein complex and to regulate specific gene networks[10]. Like β-catenin, Mllt6 is required for tumour growth induced by *Ras*-gene mutations. The existence of multiple Lef1/Tcf binding sites in the *Mllt6* promoter indicates that it is a potential downstream target of β-catenin-mediated Wnt signalling. However, further investigations are required to determine whether Mllt6 is directly regulated by β-catenin, whether concerted action of the two proteins drives hyperproliferation, or whether Mllt6 is an essential component of another signalling pathway. This will be important to resolve, because it influences the number of potential downstream drug targets.

The bird's-eye perspective taken by Beronja *et al.* to identify regulators of growth has produced a wealth of information. The extensive data sets generated in their study provide the basis for further comprehensive computational analysis. A subset of the genes identified is probably involved in epidermal-appendage formation, rather than strictly in proliferation. Filtering the data on the basis of gene-expression patterns during this phase of embryo development would provide an excellent framework for categorizing genes into those with functions in homeostasis, development and oncogene-induced growth. Moreover, it will be exciting to see whether the genes implicated in Ras-protein-induced growth represent universal mechanisms for abnormal proliferation, or if different tissues have evolved discrete mechanisms for controlling homeostasis. ■

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MATERIALS SCIENCE

Boosting X-ray emission

A spectroscopic technique has been demonstrated that uses stimulated emission to enhance weak X-ray signals for fundamental studies in materials science. SEE LETTER P.191

ERNST FILL

During the past decade or so, a spectroscopic technique called resonant inelastic X-ray scattering (RIXS) has evolved as a powerful tool for probing elementary excitations in materials[1,2]. Excitations accessible to RIXS include charge transfer, crystal-field excitations, magnons, molecular vibrations and even phonons. Recent progress in this field is due to the availability of third-generation synchrotrons as X-ray sources and to advances in X-ray photon detection[2]. However, the method still suffers from a low photon yield because of dominant radiationless processes, requiring high incident photon fluxes that cause damage to the sample under investigation. On page 191 of this issue, Beye *et al.*[3] demonstrate an ingenious way to greatly increase the photon yield for RIXS.

In RIXS, a beam of X-ray photons is directed at a sample, and the photon energy is chosen such that photon absorption elevates an electron from a deep-lying atomic-core energy level to a previously unoccupied state in the material's valence energy band. This process generates a hole — a particle created by the absence of an electron — in the atomic core. This highly unstable state typically decays within a few femtoseconds (1 fs is 10^{-15} s; in the current experiment the core-hole lifetime is 19 fs). Usually, the main decay channel is the Auger process, in which an electron jumps to the core hole and another electron is emitted. RIXS relies on a different decay process in which, again, an electron jumps to the core but, instead of an electron, a photon is emitted

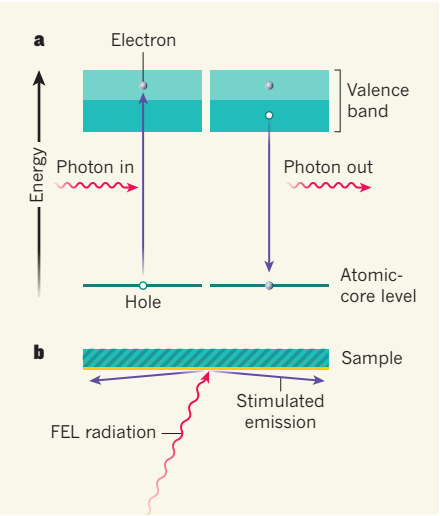

Figure 1 | RIXS spectroscopy using stimulated emission. a, In conventional RIXS, an incident photon generates a hole in a deep-lying atomic-core energy level and an electron in the unoccupied part of the valence energy band (left). An electron from the occupied part of the valence band fills the core hole, leaving a hole in the valence band and emitting a photon (right). The emitted photon provides information about energy states of the underlying material. **b**, In Beye and colleagues' experiment[3], the downward transition is amplified by stimulated emission. A brilliant soft-X-ray free-electron laser (FEL) beam is focused on a crystalline silicon sample and penetrates only about 1 micrometre into the sample (yellow). A high percentage of atoms is excited, allowing stimulated emission to predominate over spontaneous emission and other decay channels. This results in a highly directional emission close to the surface.

(Fig. 1a). The fluorescence yield (the ratio of the rate of radiative decay to total decay rate) is very low, and thus the RIXS signal is weak. Nevertheless, RIXS provides a large amount of information on the chemical and physical features of materials.

In their study, Beye *et al.* irradiated a solid-state sample with a soft-X-ray free-electron laser (FEL), which allows a large fraction of atoms to be excited. In this way, a mechanism known as stimulated emission takes over and the radiative channel is significantly enhanced at the expense of non-radiative processes; in stimulated emission, an incident photon de-excites an excited state by generating a second photon with exactly the same energy and direction. FEL radiation had previously been proposed for excitation[2]. FELs emit brilliant, tunable, monoenergetic photon beams that can be focused to spot sizes smaller than 10 micrometres, inducing a high density of photons (intensity) on the sample. But Beye and colleagues went one step further and applied FEL radiation to generate the sizeable atomic population inversion that is required to induce X-ray amplification (gain) and generate laser light at the energies of the transitions investigated.

The method is related to the concept of an inner-shell X-ray laser. This laser scheme had already been suggested in the 1960s[4], but has only quite recently been realized, also using FEL radiation[5]. In the current experiment, the gain generated is so high that the laser transition becomes saturated — that is, almost all of the excited states are converted into photons and the non-radiative channel is effectively quenched. The emitted radiation is highly directional and radiated close to the sample surface (Fig. 1b). Directionality and amplification may lead to an enhancement of the brilliance of the emitted photon beam by several orders of magnitude, solving the problem of the weak RIXS signal.

In Beye and colleagues' pioneering experiment, the conditions for observing stimulated emission were not optimal. Owing to experimental constraints, the spectroscopic observation had to be limited to a detection angle to the surface of 15°, whereas the emission maximum was found to occur at 9°. Because of this problem, an enhancement of only a bit more than a factor of two was measured. However, the high directionality of the beam was demonstrated clearly, showing the effect of stimulated emission.

The authors' experiment is an important first step towards a new way of using RIXS for fundamental studies. Possible improvements include an elongation of the irradiated spot for increasing the directionality; travelling-wave excitation (in which the excitation sweeps over the sample at the speed of light, with the generated radiation exactly following the excitation) to avoid decay of population inversion before the beam has left the excited material; and a better match of the observation direction to the emission direction.

An open question is how the signal in various spectral regions might be altered by the stimulated-emission process. If all transitions are ensured to be saturated, this may not be a problem. Another challenge pertains to the high directionality of the emission: how can the information on the excitations, which depends on the change in momentum that the photons undergo, be retrieved under this condition? In ordinary RIXS, photons are emitted in different directions and such information is derived from this feature.

Another point concerns the incident-photon energy at which stimulated-emission RIXS can be carried out. With a photon energy of around 100 electronvolts, Beye and colleagues' experiment falls into the very-low-energy regime of RIXS. Higher photon energies are already available with FELs — for example, at the Linac Coherent Light Source at the SLAC National Accelerator Laboratory in Menlo Park, California, which emits photons with energies of up to 10 keV (ref. 6). With more-energetic photons, stimulated-emission RIXS may revolutionize investigations of many chemical elements. However, the shorter lifetime of the excited states that are reached at such photon energies will make inducing stimulated emission more challenging. Application of the technique may be extended to liquids or even gases in order to investigate free atoms or molecules[7]. Owing to the method's increased spectral resolution, the investigation of new low-energy excitations (for example, phonons with energies much below 0.1 eV) may be possible.

This work could open up a new chapter in RIXS studies and lead to the discovery of novel excitations. A further exciting prospect is the potential to make time-resolved measurements using two incident photon beams[8]. ■

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IMMUNOLOGY

Lipopolysaccharide sensing on the inside

Host–cell detection of lipopolysaccharide in the outer membrane of Gram-negative bacteria was thought to be restricted to the cell-surface receptor TLR4. It emerges that lipopolysaccharide can also be sensed in the cytoplasm.

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& KATHERINE A. FITZGERALD

The innate immune system provides an exquisite defence system against micro-organisms, but its excessive engagement can be dangerous. Overproduction of cell-signalling molecules called cytokines and excessive release of other components of dying cells can directly or indirectly injure host tissues and, in extreme cases, may lead to blood poisoning, or sepsis. The primary trigger of such reactions is lipopolysaccharide, the main component of the outer membrane of Gram-negative bacteria. Genetic studies suggested that this component is sensed exclusively through Toll-like receptor 4 (TLR4), a member of an ancient receptor family dedicated to the detection of infectious microorganisms[1,2], but there were some hints of TLR4-independent sensing of lipopolysaccharide[3].

In an exciting paper published in *Science*, Kayagaki *et al.*[4] describe a TLR4-independent sensing mechanism for lipopolysaccharide (LPS) that occurs in the cytoplasm of macrophages — a type of innate immune cell*. Although the identity of the novel LPS receptor remains unknown, the authors show that its engagement results in activation of the inflammatory enzyme caspase-11. The findings greatly enhance our understanding of LPS responses and may have implications for the treatment of sepsis.

The discovery emerged from the authors' examination of inflammasome activation during Gram-negative bacterial infections. Inflammasomes are large, multi-protein complexes found in the cytoplasm that couple pathogen recognition to the maturation of IL-1β and other cytokines. Inflammasomes

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