Figure 2 | Mechanistic picture of the reverse saturable absorption system realized through triplet–triplet energy transfer. The system comprises 1 wt% of an organoiridium donor (D), 5 wt% of a perdeuterated pyrene acceptor (A) and 94 wt% of a β-estradiol matrix. Exposure of the transparent composite film to a weak visible light from a xenon lamp excites D to the S_1 state. The T_1 state of D is formed with high efficiency, thanks to the small energy difference between the S_1 and T_1 states. Efficient energy transfer from D to A leads to the population of the T_1 state of A. Because of the long lifetime and large absorptivity of the triplet excitons of A at room temperature in air, the excitons populate the T_1 state of A with increasing irradiation power. The accumulation of the long-lived triplet excitons enables the reverse saturable absorption (RSA) process to occur even under illumination of continuous incoherent light in the low fluence region. The chemical structures of D, A and β-estradiol are also shown.

triplet excitons of the guests by restricting their molecular motion at room temperature and preventing them from exposure to detrimental species such as oxygen and moisture[7–10].

The formation of the long-lived triplet excitons of A through efficient energy transfer from the T_1 state of D allows for effective accumulation of excitons in the T_1 state of A on irradiation of the composite films with weak light (Fig. 2). The $T_1 \rightarrow T_2$ transition of the heavily populated T_1 state of A leads to a large increase in light absorption and hence a dramatic decrease

in light transmittance as the irradiation power increases. Thanks to efficient RSA, the transmittance of a composite film with an optimal D–A combination gradually decreases from 60% to <10% on irradiation with continuous light with an intensity change from 0.001 to 1 W cm^{-2}; a remarkable OPL effect with low-power irradiation under ambient conditions is thus demonstrated[3].

The RSA system presented here opens up avenues for the development of heretofore inaccessible OPL materials with great potential for practical applications. Thin

films with well-defined power-transmission thresholds, for example, could be used to develop photonic computing systems. Pre-setting of transmittance changes as 0 and 1 states might lead to the construction of photonic calculators with speeds much faster than electronic computers, given the fact that photons travel much faster than electrons. Also, the judicious use of OPL materials can prevent undesired effects of exposure to intense radiation. For example, it is known that jobs requiring the use of tools such as ultraviolet sterilizers, welders and lasers subject the operator to prolonged exposure to intense, harmful light[11]. The exploration of OPL materials that are able to filter such radiation will undoubtedly contribute to high-tech solutions beneficial for the operator's well-being. ❒

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CELLULAR MECHANOTRANSDUCTION

Stiffness does matter

Extracellular-matrix stiffness regulates cell behaviour even when decoupled from ligand density and tethering.

Sanjay Kumar

Cells are exquisitely sensitive to biophysical signals encoded within components of the tissue microenvironment, in particular the extracellular matrix (ECM). A core technological implication of this concept

is that cell behaviour can be controlled by designing material scaffolds that incorporate specific structural and mechanical cues. Perhaps the most accessible (and widely studied) of these biophysical cues is ECM stiffness, which has been shown to control

cell motility[1], stem cell differentiation[2,3] and tumour progression[4,5] among other cellular phenomena. Yet which micro- and nanoscale material properties a cell 'senses' when presented with a scaffold of a given macroscale stiffness has been

a matter of debate. In part, the ambiguity stems from the fact that strategies used to vary bulk material stiffness may produce secondary effects (such as altering the density of cell-adhesive ligands or the porosity of the underlying scaffold) that by themselves can also control cell function[6]. For instance, it has recently been shown that gel porosity (softer hydrogels have much larger pores than stiffer ones) can affect how tightly adhesive ligands are tethered to the gel scaffold and thus the degree to which these ligands can be deformed by the cell[7]. Now, two studies published in *Nature Materials* explore these potential confounding effects. On the one hand, David Mooney and colleagues decoupled ECM stiffness from ligand density by creating an interpenetrating polymer network (IPN) system, and used it to dissect how stiffness controls mammary epithelial morphogenesis in three-dimensional culture[8]. On the other hand, Adam Engler and colleagues systematically modulated the stiffness, porosity and ligand–substrate coupling (the latter two affect ligand tethering) of polyacrylamide (PAAm) gel culture substrates[9], and studied how all these properties affect the differentiation of tissue stem cells. These studies show that, in practice, stiffness rather than ligand tethering governs mechanosensitive cell adhesion and differentiation, and that similar matrix-stiffness values can yield dramatically different phenotypes depending on the density of specific adhesive ligands.

Mooney and colleagues sought to understand how ECM stiffness influences the assembly of mammary epithelial cells into acini — three-dimensional hollow spheroids that are widely used as an organotypic model to study breast-tissue development, homeostasis and neoplasia. Previous work had shown that increases in ECM stiffness can disrupt acinar structure[4] and mammary tubulogenesis[10] by activating integrin-dependent signalling and by stimulating contractility. Yet such studies often used tissue-derived ECM systems — such as collagen I or reconstituted basement membrane (rBM) — that do not allow for unambiguous manipulation of matrix stiffness in a fully three-dimensional environment without concurrently changing the density of adhesive ligands. Although synthetic or semi-synthetic matrix systems (such as poly(ethylene glycol)) have allowed for improved control of stiffness, these materials lack the native adhesive signals needed for proper acinar assembly and stability. Mooney and co-authors reaped the benefits of natural and synthetic matrices by assembling
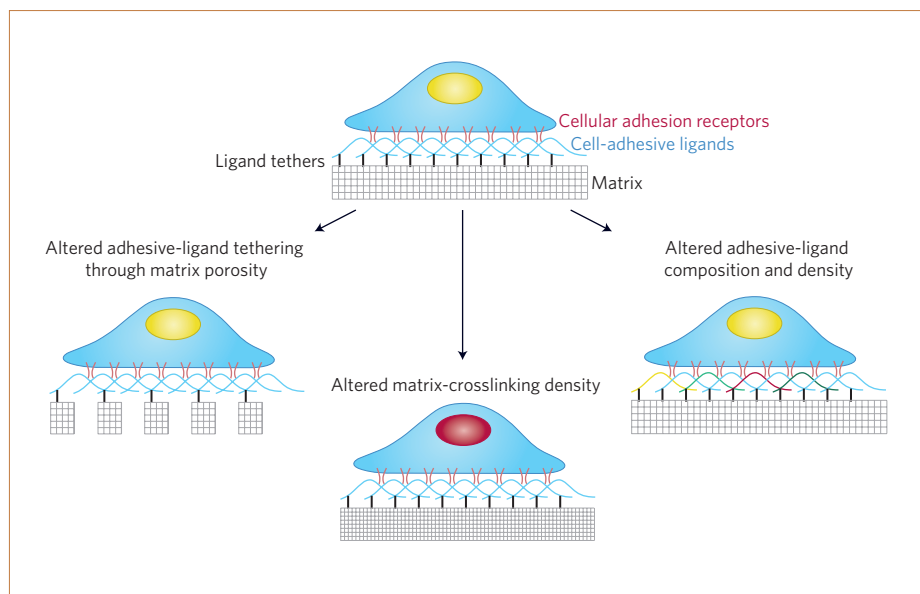

Figure 1 | Matrix stiffness and ligand density, rather than adhesive-ligand tethering, regulate cell behaviour. When changes in the stiffness of the gel matrix (usually achieved by modifying its crosslinking density; grey) are decoupled from changes in the density of adhesive ligands[8] (blue) or of ligand tethers[9] (black; matrix porosity usually affects tethering), the behaviour of cultured cells, which sense the mechanical properties of the matrix through receptors (red) for adhesive ligands, is seen to depend solely on matrix stiffness (this is indicated by the cell with a red nucleus). Changes in the density of specific adhesive ligands can in certain cases abrogate the effect of changes in stiffness, as with the induction of malignant phenotypes in mammary epithelium[8].

hybrid polymer networks from two components: the polysaccharide alginate, the stiffness of which may be controlled by crosslinking with varying amounts of calcium, and rBM, which provides laminin and other functionally important adhesive ligands. The authors show that these two components seamlessly interleave to form an IPN, and that increasing stiffness in this system independently of ligand density produces the expected malignant phenotype. Notably, this transformation is accompanied by the disruption of hemidesmosomes — adhesive plaques that anchor cytoskeletal intermediate filaments to the ECM in normal acini. They also show with genetic and pharmacological studies that the stiffness-dependent malignant phenotype is driven by a molecular pathway featuring the signal-transducing proteins laminin, laminin-receptor integrin β4, Rac GTPase and PI3 kinase. Interestingly, laminin enrichment within rBM suppresses this phenotype, such that normal acinar formation is observed in either pure, concentrated rBM matrices, or in stiff rBM/alginate matrices doped with excess amounts of rBM. On the basis of these results, Mooney and colleagues propose a model in which stiffness and ligand composition — in particular the density of specific basement membrane ligands

(in this case, laminin) — antagonistically drive integrin-β4 signalling. If stiffness is low or laminin concentration is high (or both), integrin β4 engages intermediate filaments and assembles into hemidesmosomes, resulting in normal acinar assembly. If stiffness is high and laminin concentration is low, integrin-β4 signalling is funnelled towards Rac-GTPase/ PI3-kinase-based signalling, subverting hemidesmosome assembly and inducing the malignant phenotype.

Alternatively, Engler and collaborators sought to dissect the contributions of ECM stiffness and adhesive-ligand tethering on cell behaviour, and did so by focusing on the differentiation of mesenchymal stem cells (MSCs) and adipose-derived stem cells (ASCs). A central impetus for their efforts was the recent suggestion that, in crosslink-induced stiffening of PAAm and other hydrogels, the tightness with which ECM-anchored cell-adhesive ligands are tethered to the hydrogel (brought about by differences in surface porosity) drives apparent stiffness-dependent cell behaviours, including MSC differentiation[7]. Engler and co-authors revisited this question by using a number of complementary approaches. First, by purposefully choosing the concentrations of PAAm monomer and

crosslinker, they were able to fabricate a family of synthetic ECM substrates with equivalent stiffness but varying pore size. On culturing MSCs and ASCs on these gels in the presence of differentiation factors, they found that stiffness rather than pore size is most predictive of spreading and lineage commitment (with soft gels promoting adipogenesis and stiff gels promoting osteogenesis, as expected). When they chemically varied the degree of ECM–protein anchoring (as verified by atomic force microscopy), they again found that MSC differentiation remained firmly dependent on ECM stiffness. The authors also showed that this result may be recapitulated by incorporating short adhesive peptides to the backbone of the PAAm gel rather than by conjugating full-length ECM proteins to its surface. From their set of results, Engler and collaborators conclude that hydrogel ECM stiffness drives stem cell adhesion and differentiation in the absence of ligand-tethering effects (Fig. 1).

Because stiffness is a bulk material property and cells are microscale entities with nanoscale force sensors, studies that attempt to bridge these dramatically different length scales are critical to understanding how cells sense and process stiffness cues from the ECM. In this respect, on top of the substantial effort that has been devoted to identifying molecular mechanosensors that channel stiffness cues, Mooney and co-authors' study reveals an unexpected layer of nuance by showing that a given mechanosensor (integrin β4) can induce either normal or malignant behaviour depending on the abundance of an accessory factor (laminin). Moreover, the authors make rBM — which

is ubiquitous as a model matrix despite its lack of chemical definition and its limited capacity for tailoring — more amenable to mechanobiological studies by interweaving it with a semi-synthetic matrix system. And Engler and colleagues inject a fresh measure of confidence in studies that have used PAAm and other hydrogel substrates to probe stiffness-dependent effects. Given that for nearly two decades PAAm has been a mainstay tunable substrate system for mimicking the stiffness range of natural ECM[11], this is no small contribution. Engler and colleagues' findings also synergize with recent reports showing that effective ECM stiffness may be varied using silicone microposts of defined lengths, and that results in these systems are consistent with those obtained using two-dimensional hydrogels[12].

Furthermore, the studies of Engler, Mooney and collaborators expose major open questions and unmet needs. For instance, rBM is typically harvested from mouse tumour tissue and is acknowledged to suffer from batch-to-batch variability. Even if the alginate/rBM IPN system of Mooney and co-workers is significantly more controllable than rBM alone, it still requires rBM for the provision of bioactive matrix cues; hence, a fully defined epithelial-morphogenesis matrix system that may be reliably scaled up and could be applied clinically is clearly needed. And even if the stiffness of a hydrogel substrate influences cell behaviour independently of ligand tethering, this does not rule out the possibility that cell-adhesive tethers may play important roles in three-dimensional or other tissue-like matrix environments. ECM protein ligands

represent an important mechanical link between cell and scaffold, and it is at least conceivable that these linkages may vary over time and space in complex, dynamic microenvironments. For the same reason, the stiffening of actual tissue may be driven or accompanied by changes in ligand composition and density, making the end phenotype the net result of many interdependent inputs. Addressing these questions will again likely require tissue-mimetic materials that preserve the design modularity of synthetic matrices while retaining the biological instructiveness associated with native matrices. Ample opportunity thus remains for materials scientists to make important contributions to cell biology, and the studies of Mooney, Engler and their colleagues provide valuable roadmaps for doing so. ❐

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THERMAL EMISSION

Ultrafast dynamic control

Control of thermal emission with microsecond switching times has been achieved by using sub-band transitions in composite quantum-well and photonic-crystal structures.

Ognjen Ilic and Marin Soljačić

The most familiar example of a thermal emitter is the Sun. Because of the thermal motion of charged particles, its 5,800-K hot surface most strongly emits radiation in the green (at a wavelength around 500 nm). More generally, the relationship between temperature of a black body and wavelength of emission is captured by Wien's displacement law: the peak wavelength

of emitted light is inversely proportional to a black body's absolute temperature. Hence, peaks of emission of hotter stars are shifted towards the blue, and those of colder stars towards the red. Thermal emission can also be controlled in the absence of a temperature change by incorporating periodic features with length scales comparable to the wavelength of thermally emitted light[1–3]. Writing in

Nature Materials, Susumu Noda and colleagues have now pushed this concept a step further. They developed a composite structure that combines photonic crystals and quantum wells, allowing for dynamic control of thermal emission at speeds that are more than four orders of magnitude faster than conventional means of temperature modulation[4].

Photonic crystals exhibit a photonic