

mice neurogenesis was reduced. Also, learning and memory were impaired in young mice after they received injections of plasma from old, but not young, mice.

What are the factors in the blood that differ between young and old mice and so affect neurogenesis? Villeda and co-workers ruled out direct effects of cells migrating from old to young mice in the parabiotic pairs, because cells from the older mice cannot enter the brain of young mice. They therefore compared a subset of plasma proteins — 66 to be exact — between young and old mice, evaluating young–old parabiotic pairs to see which proteins were more abundant in the older animals but reduced in the younger mice. They fixed on an unlikely culprit for altering neurogenesis, the chemokine protein CCL11.

Chemokines constitute a genetically and structurally coherent group of immune mediator molecules called cytokines. But although they were originally discovered through their ability to direct the migration of inflammatory white blood cells, chemokines are now recognized as being regulatory factors in the development of tissues as diverse as the central nervous system and the urogenital system<sup>6</sup>. One chemokine, CXCL12, and its receptors CXCR4 and CXCR7, have been accorded pride of place in neurogenic-niche physiology because of their well-known roles in the development and function of the central nervous system<sup>7–9</sup>. CCL11, by contrast, has been mainly linked to allergic conditions such as asthma. So, do the levels of this chemokine simply correlate with an anti-neurogenic environment, or could it be that CCL11 actively affects neurogenesis?

Villeda *et al.*<sup>3</sup> provide several lines of evidence suggesting the latter possibility. When the authors injected this chemokine systemically into young animals, neurogenesis was reduced. Moreover, antibodies that neutralize CCL11, when co-injected with the chemokine systemically or into the neurogenic niche itself, reversed this decline in neurogenesis. Furthermore, brain slices from mice given CCL11 injections showed reduced long-term potentiation (LTP), a neurophysiological correlate of learning.

Exactly how CCL11 affects neurogenesis and cognitive function remains unclear. *In vivo*, CCR3, the receptor through which CCL11 signals, has not been reproducibly identified on NSCs or on the neural progenitor cells that arise from them; so it is likely that an indirect mechanism is at play. Previous work suggested that CCL11 could affect neurogenesis through several pathways. For instance, its receptor could be present on microglia,<sup>10</sup> the brain cells that can produce cytokines and that, under some conditions, impair neurogenesis<sup>11</sup>. Also, exposure of NSC-containing mixed-cell cultures to CCL11 leads to decreased proliferation of NSCs<sup>12</sup>. However, the CCL11/CCR3 signals may not always be deleterious: mice

lacking CCR3 show greater neuronal loss than those with the receptor when the peripheral segment of their facial nerve is severed<sup>13</sup>.

It is possible that CCL11 modifies the action of another cytokine. Myeloid cells in the meninges membranes lining the brain are maintained in a state of restrained inflammation through the action of the regulatory cytokine interleukin-4 (ref. 14); this state of muted inflammation promotes learning and memory. CCL11 suppresses the ability of interleukin-4 to restrain the inflammatory functions of myeloid cells<sup>15</sup> and might thus reduce neurogenesis, causing memory and learning deficits.

But regardless of the mechanisms involved, the good news from this report<sup>3</sup> is that NSCs in the ageing brain do not undergo irreversible decline and can respond to a favourable environment, which includes the circulation. The precise link between NSCs, neurogenesis and blood cells is probably complex, involving more than just CCL11. For example, an earlier study<sup>16</sup> found that individual mice from a genetically heterogeneous stock show widely variable levels of neurogenesis, and that the degree of neurogenesis is strongly correlated with the ratios of two subsets of T cells in the blood — those expressing the CD4 or CD8 marker proteins — but is weakly correlated with a variety of behavioural tasks. What's more, altering the ratios of CD4- and CD8-bearing T cells modulates neurogenesis, rather than vice versa.

So it seems that there is a much more robust

connection than previously suspected between the sites of neurogenesis in the adult brain and the systemic circulating pool of cells and proteins. Given the difficulty of manipulating neurogenic niches directly, this information is encouraging and should inspire increased activity in both joggers and neuroscientists. ■

**Richard M. Ransohoff** is in the *Neuroinflammation Research Center, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA.*  
e-mail: ransohr@ccf.org

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#### MATERIALS SCIENCE

## Dry solution to a sticky problem

**Sticking plasters revolutionized the protection of minor wounds, but they're not ideal for fragile skin. A material that mimics the adhesive properties of certain beetles' feet might provide a solution.**

JEFFREY M. KARP & ROBERT LANGER

Adhesives that stick to skin for long periods of time, or over multiple cycles of use, are vital for medical applications. Such materials have to conform to stringent standards — for example, they must maintain robust adhesion during repeated application and removal without irritating the skin, and be non-toxic. Writing in *Advanced Materials*, Kwak *et al.*<sup>1</sup> report an exciting advance towards achieving these standards: an adhesive tape that uses micrometre-scale pillars on its surface to stick to skin. This innovation bypasses the need for a glue-coated surface, as is commonly used in conventional skin adhesives.

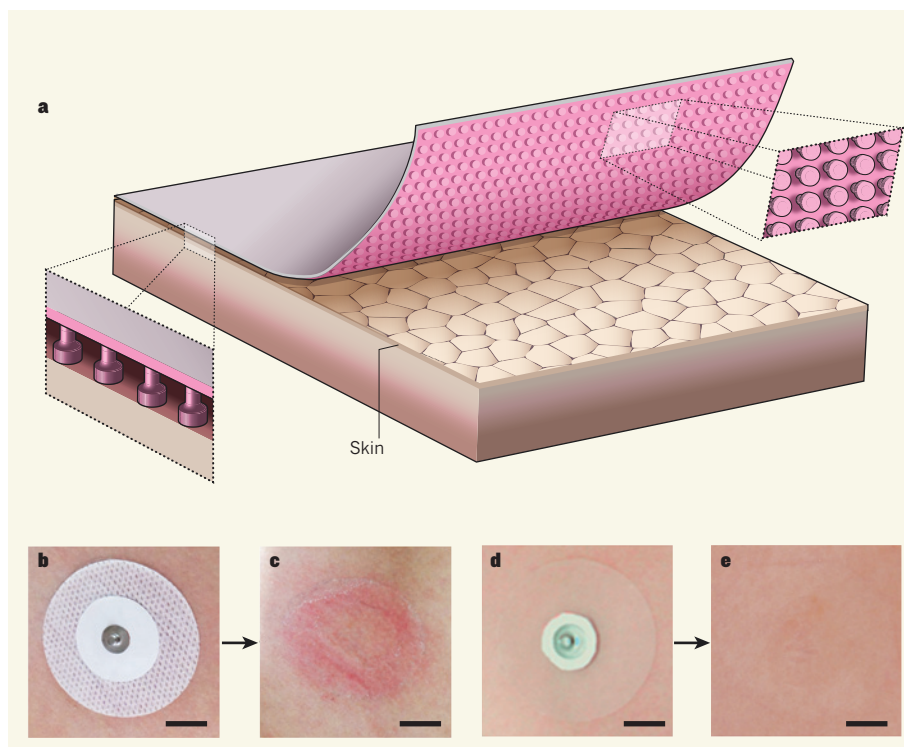
Skin adhesives are currently used billions of times a year — for example, in over-the-counter sticking plasters for the treatment of minor skin wounds, in transdermal patches for controlled drug delivery<sup>2,3</sup>, and in tapes for affixing tubes or sensors to the skin in hospitals. Despite the remarkable success of these materials, a remaining challenge is to find adhesives suitable for use on the delicate skin of newborn infants and the elderly. Aged skin is particularly fragile, making it more susceptible to inflammation and damage<sup>4</sup>. Given that the number of people aged over 60 will double during the next two to three decades<sup>5</sup>, the need for skin adhesives for the elderly is becoming increasingly pressing.

Pressure-sensitive surgical tapes first appeared in 1845, when the surgeon Horace Day applied rubber adhesive to strips of fabric<sup>6</sup>. For several years thereafter, minor cuts were treated with separate gauze and adhesive tape, but custom tailoring of the materials was required for domestic use. The first integrated skin-adhesive device — the Band-Aid — was invented in 1920 by Earle Dickson<sup>7</sup>, an employee at the company Johnson & Johnson. Dickson noticed that gauze and adhesive tape did not remain attached to his wife's fingers, which she frequently injured in the kitchen. He therefore placed gauze in the centre of a strip of tape and covered the adhesive and gauze with a layer of crinoline to maintain its tack and sterility. Johnson & Johnson began mass-producing these sticking plasters shortly thereafter, and today it is estimated that more than 100 billion of Dickson's Band-Aids have been made<sup>7</sup>.

The adhesives currently used for sticking plasters are polymeric, pressure-sensitive adhesives based on acrylic compounds<sup>8</sup>. Although effective, acrylic adhesives can leave behind sticky residues, and they lose their grip after repeated use. To bypass the need for these glues, researchers have focused on adhesion mechanisms used by animals such as beetles and geckos, whose feet stick to walls without any glue. The mechanism of gecko-foot adhesion was elucidated<sup>9</sup> in 2000, nearly two millennia after Aristotle first reported the phenomenon: each gecko foot contains up to 500,000 hairs, each tipped with hundreds of projections known as spatulae. Similarly, the feet of beetles in the Chrysomelidae family are covered with tiny mushroom-shaped structures that help them cling to surfaces.

Gecko spatulae are roughly hundreds of nanometres in length, whereas the mushroom-shaped structures of Chrysomelidae beetles' feet are on the micrometre scale. It is possible to mimic these adhesive structures using nanometre- or micrometre-scale engineering to modify the surfaces of materials. Synthetic gecko-inspired adhesives have been made, but it has been difficult to optimize their properties for successful adhesion to wet tissues (such as those found inside the body). To solve this problem, we have previously used a hybrid approach, whereby a rubbery polymeric substrate with the surface nanotopography of gecko feet was coated with a thin layer of tissue-reactive glue<sup>10</sup>. The resulting material maximized adhesion to wet tissue while minimizing tissue inflammation.

Kwak *et al.*<sup>1</sup> have focused on achieving adhesion to dry skin in the absence of glue. They patterned the surface of a rubbery, non-toxic substrate with micrometre-scale, mushroom-shaped projections (Fig. 1) — a topology reported to be ideal for maximizing adhesion<sup>11</sup> — varying the dimensions of the projections until they achieved optimal adhesion to human skin in a direction perpendicular to its surface. Remarkably, the substrate



**Figure 1 | Glueless.** **a**, Kwak *et al.*<sup>1</sup> have made a polymer material that has a surface covered in micrometre-scale, mushroom-shaped projections (upper inset). The projections mimic those found on certain beetles' feet, and allow the substrate to adhere to human skin without the use of glue (lower inset). **b, c**, Commonly used sticking plasters (**b**) use an acrylic adhesive to stick to skin, but can leave behind a sticky residue and cause redness (**c**). **d, e**, A patch made from Kwak and colleagues' material (**d**) reduces these effects (**e**). Scale bars, 1 cm. (Graphic adapted from ref. 1. Photos reproduced from ref. 1.)

maintained good adhesion through up to 30 cycles of attachment and removal, without causing significant damage to skin.

To demonstrate the functional utility of their adhesive, the authors integrated it into a wearable diagnostic device that monitors the heart using electrocardiography. When attached to a patient's chest, the device recorded several vital signals from the heart in real time over a period of two days. For commercial applications, however, Kwak and colleagues' material will probably require higher levels of adhesion — the reported system<sup>1</sup> achieved about 43% of the adhesion of a moderately sticky acrylic.

The authors' work is part of a growing body of research aimed at finding new materials that form interfaces with tissue. For example, another recent paper<sup>12</sup> describes single-use ultrathin membranes that adhere to skin using only van der Waals interactions, and which incorporate electronic components that can be used to perform electrophysiological recordings. For long-term applications, these technologies should be tested both in the presence of humidity or perspiration and to see how they cope with the shedding of dead cells. New approaches may be required to address such issues, perhaps involving surface-responsive materials<sup>13</sup>. Nevertheless, there is every hope that innovations such as that of Kwak *et al.*<sup>1</sup> will one day bring new technologies to the bedside. ■

**Jeffrey M. Karp** is at the Center for Regenerative Therapeutics, and the Department of Medicine, Brigham and Women's Hospital, Cambridge, Massachusetts 02139, USA. **Robert Langer** is at the David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA.

e-mails: [jkarpp@rics.bwh.harvard.edu](mailto:jkarpp@rics.bwh.harvard.edu); [rlanger@mit.edu](mailto:rlanger@mit.edu)

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