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News & views

Biomedical materials

Composite gels designed to stick to biological tissue

Sophia J. Bailey & Eric A. Appel

Materials that adhere tightly to human tissues can promote healing and boost the sensitivity of biomedical diagnostic devices. An 'evolving' gel has been made that synergizes two strategies for forming interfaces with tissue.

The interfaces that form between living tissues and biomedical materials, often referred to as biointerfaces, greatly influence the ability to detect and treat disease. Unfortunately, the development of biomedical devices has historically involved a trade-off between using materials that can be fabricated easily into the devices and using those that adhere to tissues at the cellular level. Reporting in *Nature Chemical Engineering*, Shi *et al*. present a clever, yet simple, strategy to make materials that combine easy handling with robust interface formation[1]. The authors show that hydrogels — water-rich networks of polymers — embedded with tiny starch granules form dynamic biointerfaces that 'evolve' over time, and have many potential uses across biomedicine, from tissue regeneration to sensing.

Materials that are intended to help repair damaged tissues must provide a tight biointerface to promote cell–material interactions, and have a porous or degradable matrix to allow for cellular growth[2]. Typically, macroscopic patches are used to promote such healing, but patch materials are limited in their ability to conform tightly to damaged tissue that is irregularly shaped, and often do not adhere well to cells. Alternatively, therapeutic materials consisting of cell-sized microparticles can promote adhesion and provide ample space for cellular infiltration. However, the structural forms that can be fabricated from microparticles are severely limited (macroscopic patches, for example, are difficult to make). Special methods are needed to deliver such materials to the body — and the microparticles are then often not well retained.

Biointerfaces are also crucial for the sensitivity of diagnostic bioelectronic devices, because inadequate contact with tissues leads to poor sensing and transmission of electrical signals. Typically, attachment to tissues is promoted by using extremely thin and flexible devices combined with adhesives[3,4]. Hydrogels can improve contact at these interfaces because they are soft and flexible, allowing for conformal contact with irregular tissues, and because their high water content promotes ion transport and improves electrical conductivity[5]. Improving the adhesive properties of bioelectronics that incorporate hydrogels could further enhance device signals, and could extend a device's lifetime in challenging environments, such as on a beating heart.

Shi *et al*. now report a biointerface made from a hydrogel composite that addresses the need for materials that can be shaped easily into various forms, but that also provides tight, durable tissue adhesion. The hydrogel matrix is made up of gelatin — a protein derived from collagen, an important component of human tissues — to ensure biocompatibility and biodegradability.

A previous study by some of the authors of the current work reported that granule-embedded hydrogels possess tissue-like properties such as viscoelasticity[6]: a combination of solid and liquid-like behaviours that enable tissues to maintain their shape and undergo dynamic reorganization. Shi *et al*. now exploit these properties to promote the initial adherence of their hydrogels to uneven tissue surfaces and to enable the subsequent release of starch granules, the surfaces of which had been modified with drugs such as aspirin to encourage cell-level interactions. The biointerfaces formed by the gels evolve over time. Initially, the interfaces consist of a macroscopic material that sticks to the tissue. But the gel matrix then releases granules and degrades, producing an interface consisting of granules interacting with cells (Fig. 1). The adhesion and release behaviours were observed in tissue both *ex vivo* and *in vivo*.

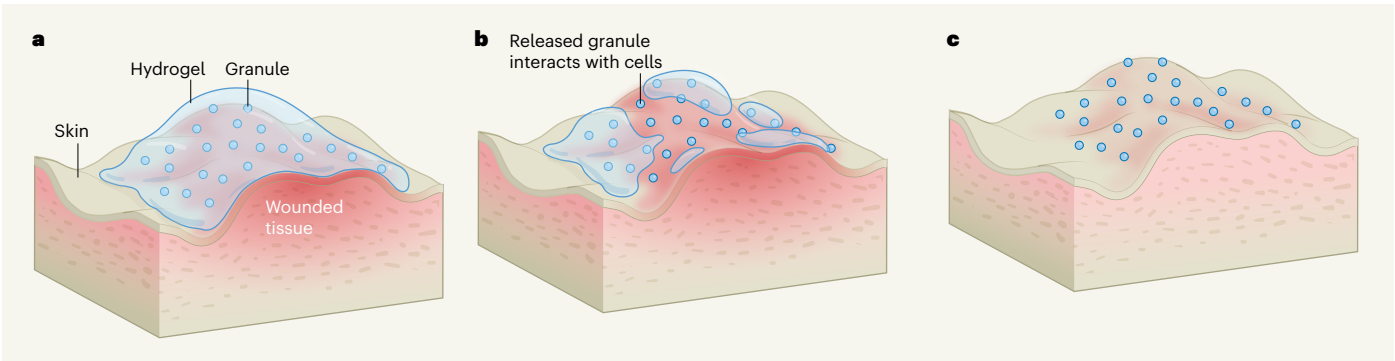

Figure 1 | Evolving hydrogels for biomedical applications. **a**, Shi *et al*.[1] present materials consisting of a biodegradable hydrogel (a water-rich network of gelatin proteins) embedded with micrometre-scale starch granules. The granules' surfaces were modified by the attachment of drugs such as aspirin, to encourage interactions with cells. The authors report that these composite hydrogels adhere tightly to tissue surfaces. **b**, **c**. Over time, the hydrogel matrix degrades, releasing the granules, which then interact with tissue cells. Applying these composites to damaged tissue speeds healing. When incorporated into diagnostic bioelectronic devices that are placed directly on tissue, the materials can boost the electrical signals produced by the devices (not shown).

These observations were corroborated through molecular-dynamics simulations, which showed that these behaviours underpinned the formation of tight biointerfaces.

Shi and colleagues demonstrated the versatility of their granule-embedded hydrogels for regenerative medicine using animal models of skin-wound healing, inflammatory colon disease and tissue recovery after heart attack. Tissue regeneration was observed to be better than after treatments that used the hydrogel or granule components alone. The therapeutic synergism of the hydrogel–granule combination arises because the gelatin matrix prolongs exposure to the granules over the course of treatment, and this is one of the hallmark benefits of hydrogels for drug delivery[7]. This slow release maintains the biointerface and is followed by slow degradation of the entire material.

The authors' hydrogel is also easy to manipulate and can be moulded into numerous forms — ranging from oral medications to bandages. In a particularly convincing demonstration of this ease of handling, the authors integrated the hydrogel into an intricate bioelectronic mesh device that records electrical signals directly from heart tissue. Impressively, the device recorded the beating of a rat's heart for 270 minutes, with granule release enabling stable adherence and promoting bioelectrical signal transmission. This long-term, surgically relevant recording shows that these evolving hydrogels provide beneficial interfaces for bioelectronics, and not just for tissue repair.

Although the findings are certainly compelling, the superiority of these granule-releasing hydrogels has been demonstrated only over historically lacklustre materials: granule-free gelatin hydrogels, which are minimally dynamic and unsophisticated. Numerous biomimetic hydrogels have been reported[8] to have viscoelastic properties that could also promote initial adherence to irregular tissue surfaces. And engineering of the surface chemistry of such materials (rather than of embedded granules) can also promote cellular interactions[9]. Future studies should investigate whether Shi and colleagues' composite materials provide benefits over state-of-the-art biomimetic hydrogels.

Moreover, the adhesion of the granules to tissues arises from nonspecific interactions that lack the complexity of natural biological interactions, such as those between receptors and proteins. It might be possible to engineer granules that recapitulate such complex interactions more directly. If so, exploring biologically relevant granule–cell interactions might open up other exciting therapeutic benefits.

Further studies are therefore needed to fully assess the advantages of Shi and colleagues' biointerface design strategy. But if this approach can indeed provide superior biointerfaces with a broad range of tissues, it could greatly improve treatment and diagnosis throughout the field of medicine. Time will tell whether this design strategy truly sticks.

Sophia J. Bailey and **Eric A. Appel** are in the Department of Materials Science & Engineering, Stanford University, Stanford, California 94305, USA. **E.A.A.** is also in the Department of Bioengineering, and at the Chem-H Institute and the Woods Institute for the Environment, Stanford University; and in the Department of Pediatrics – Endocrinology, Stanford University School of Medicine.
e-mail: eappel@stanford.edu

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