CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Swell Findings in Hydrogels

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Targeted surgery requires spatial and temporal selectivity, which is an elusive goal; the realization of this goal may be aided by materials that undergo conformational changes in response to remote stimuli. A recent study by Cangialosi et al.[1] is notable in this regard; it shows that a hydrogel made up of water, polyacrylamide, and specific short DNA sequences that cross-link the strands of polyacrylamide (Fig. 1A) can be induced to expand dramatically — by up to 100 times in volume — through the addition of sequence-specific DNA hairpins that interrupt, bind, and then push apart the short DNA cross-links. This extraordinary degree of swelling was accomplished by the formation of concatemers, which are long, continuous DNA molecules that contain multiple copies of the same DNA sequence linked in series — a process that the authors call a hybridization cascade. The longer the concatemers, the more voluminous the gel (imagine each strut of a scaffold elongating by approximately the same amount at the same time). The authors further showed that they could control the extent of swelling by adding fixed proportions of "blocking" hairpins designed to interfere with the hybridization cascade.

Shape-changing hydrogels that actuate in response to cues such as temperature, light, and pH have already been described.[2] An unusual property of the hydrogel described by Cangialosi et al. is its local selectivity: multidomain, two-dimensional structures can be engineered such that each domain is responsive to a hairpin with a specific DNA sequence (Fig. 1B). The hydrogel (or a specific domain of the hydrogel) swells only when DNA hairpins that are of a specific sequence are added to induce bending and twisting of the structure and actuation.

Cangialosi et al. patterned a hydrogel into a defined but irregular shape that had a main body and small appendixes (subdomains) that contained different DNA–cross-linked domains. By changing the thickness and geometry of the hydrogel in a specific subdomain (or subdomains), the shape of the gel and its movement could be controlled. An attractive property of the DNA hydrogels described by Cangialosi et al. is their durability; after actuation they remained in an active position for approximately 2 months, and before actuation they were stable in buffer at 4°C for at least 4 months. Another attractive property with respect to interfacing with human tissues in situ is the high water content of the gel.

Selective actuation of small parts of the hydrogel (i.e., domains defined by their shape and by the specific DNA sequence of the cross-links in the domain) creates opportunities for targeted interventions in which the shape of an anatomical structure is modified. One hypothetical example of such an intervention involves the use of hydrogels for the management of saccular cerebral aneurysms. In current practice, such aneurysms are often managed by inserting a coil of flexible wire into the aneurysm through an endovascular approach. A hydrogel-based expander could be helpful in this context. For example, the hydrogel could be placed in the aneurysm and expanded (by adding DNA hairpins) to fill the aneurysm (Fig. 1C).

The remote actuation of a miniature device inside the body remains an unsolved issue, as noted by Cangialosi et al. A wireless means to actuate magnetic materials involves propelling or anchoring small devices inside the body through the application of external magnetic fields. However, issues such as biocompatibility, possible incompatibility with magnetic resonance imaging, and the rapid diminishment of

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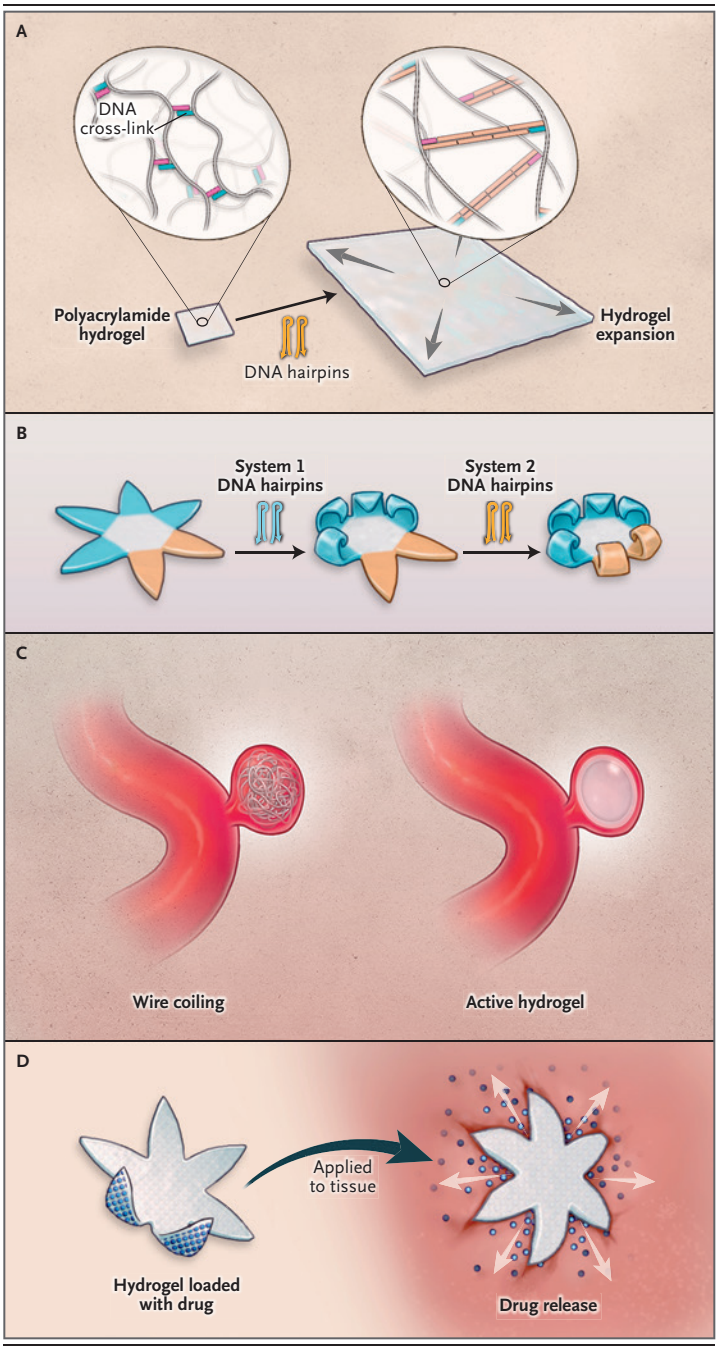
Figure 1. The Hybrid Hydrogel: DNA and Polyacrylamide.
Panel A shows the DNA–cross-linked polyacrylamide hydrogel. DNA hairpins can be inserted into the cross-link to induce expansion and swelling of the hydrogel. Panel B shows an example of a DNA-programmed change in shape, in which petallike grippers are controlled through sequential application of different DNA hairpins. Panel C shows how hydrogel could be used instead of wire coiling to fill a saccular cerebral aneurysm. Panel D shows that a structure loaded with a drug can grip tissue and release its cargo. (Panels A and B were adapted from Cangialosi et al.[1] with permission from the American Association for the Advancement of Science.)



force over increasing distance limit this approach. Light sources and ultrasound transducers also have been used for remote and selective actuation of endoluminal tools, but because of the limited extent to which light penetrates the body and the near omnipresence of acoustic barriers (e.g., air vesicles and bones), researchers have had to use catheters and endoscopic tools to deliver light and ultrasound to target tissues.

The approach used by Cangialosi et al. to control changes in shape enables the selective actuation of the hydrogel by injection of DNA. The DNA–cross-linked hydrogel could be shaped as a petallike gripper (Fig. 1D), a drug capsule, or a small ring and positioned in the body for later actuation (e.g., to close a surgical wound, release a drug, fill in a vascular aneurysm, or form an anastomosis).

Further studies, however, are warranted before hydrogels such as the one proposed by Cangialosi et al. can be tested in humans. Controlling the change in the shape of the gel is feasible under laboratory conditions: how easy it will be to control the rate and extent of gel expansion in vivo is currently not known. Another concern relates to the reversibility of the hydrogel swelling (hydrogel shrinking), which has not been addressed experimentally. Finally, the extent to which force is generated during swelling is poorly understood. All that being said, at a time when there is an increased emphasis on personalized medicine, shape-changing hydrogels with DNA activation represent an interesting development.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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2. Koetting MC, Peters JT, Steichen SD, Peppas NA. Stimulus-responsive hydrogels: theory, modern advances, and applications. Mater Sci Eng R Rep 2015;93:1-49.

DOI: 10.1056/NEJMcibr1712116
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