Self-Assembled Materials Form Mini Stem Cell Lab

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A sac formed by the self-assembly of small and large molecules can be used to instantly encapsulate stem cells. (The culture medium gives the sac its pink color.) © 2008 Science

Imagine having one polymer and one small molecule that instantly assemble into a flexible but strong sac in which you can grow human stem cells, creating a sort of miniature laboratory. And that sac, if used for cell therapy, could cloak the stem cells from the human body's immune system and biodegrade upon arriving at its destination, releasing the stem cells to do their work.

Futuristic? Only in part. A research team from Northwestern University's Institute for BioNanotechnology in Medicine has created such sacs and demonstrated that human stem cells will grow in them. The researchers also report that the sacs can survive for weeks in culture and that their membranes are permeable to proteins. Proteins, even large ones, can travel freely across the membrane.

This new and unexpected mode of self-assembly, to be published March 28 in the journal *Science*, also can produce thin films whose size and shape can be tailored. The method holds promise for use in cell therapy and other biological applications as well as in the design of electronic devices by self-assembly, such as solar cells, and the design of new materials.

"We started with two molecules of interest, dissolved in water, and brought the two solutions together," said Samuel I. Stupp, Board of Trustees Professor of Materials Science and Engineering, Chemistry and Medicine, who led the research.

"We expected them to mix, but, much to our surprise, they formed a solid membrane instantly on contact. This was an exciting discovery, and we then proceeded to investigate why it happened. Understanding the surprising molecular mechanism was even more exciting."

One of the molecules is a peptide amphiphile (PA), small synthetic molecules that Stupp first developed seven years ago, which have been essential in his work on regenerative medicine. The other molecule is the biopolymer hyaluronic acid (HA), which is readily found in the human body, in places like joints and cartilage. Stupp recently had started a new research project on the regenerative medicine of cartilage, which drew him to hyaluronic acid.

"This is a clear example of informed discovery," said Stupp, director of the Institute for BioNanotechnology in Medicine. "We knew there was something interesting about the interaction between peptide amphiphiles and biopolymers from our previous work on nanostructures that can cause blood vessels to grow. And we were particularly interested in hyaluronic acid because of its role in cartilage, a tissue that adults cannot regenerate and, when damaged in joints, causes grief to humans."

Using just these two molecules, Stupp and his team can make many different structures, the two most important being sacs, which have a solid membrane on the outside and liquid inside, and flat membranes of any shape. The researchers can make the structures large or small, pick up the material with tweezers, stretch it and even easily repair the sacs through self-assembly should the material tear or have some other defect. The sacs also are robust enough to be sutured by surgeons to biological tissues.

The large (hyaluronic acid) and small (peptide amphiphile) molecules come together through supramolecular interactions, not by chemical reaction, in which covalent bonds are formed.

In the case of the flat membrane, the researchers put the peptide amphiphile solution at the bottom of a shallow mold and added on top the hyaluronic acid solution. The two interacted on contact, creating a solid. By varying the mold, the researchers produced a variety of shapes, including stars, triangles and hexagons, each having two chemically different surfaces. When dry, the materials are stiff and strong, like plastic.

In creating a sac, the researchers took advantage of the fact that hyaluronic acid (HA) molecules are larger and heavier than the smaller peptide amphiphile (PA) molecules. In a deep vial, they poured the PA solution and into that poured the HA solution. As the heavier molecules sank, the lighter molecules engulfed them, creating a closed sac with the HA solution trapped inside the membrane.

Having formed the sacs, Stupp and his team next studied human stem cells engulfed by the self-assembly process inside sacs that they placed in culture. The researchers found that the cells remained viable for up to four weeks, that a large protein -- a growth factor important in the signaling of stem cells -- could cross the membrane, and that the stem cells were able to differentiate.

“We expect that genes, siRNAs and antibodies will cross the membranes as well, making this mini cell biology lab a powerful device for research or therapies,” said Stupp. “For the development of cancer therapies, we will be able to confine cells within the sacs and study their reaction to different types of therapies as well as to signaling by different cells in neighboring sacs.”

In a clever demonstration of self-repair, if the sac’s membrane had a hole (from a needle injection, for example), the researchers simply placed a drop of the PA solution on the tear, which interacted with the HA inside, resulting in self-assembly and a sealed hole.

“The membrane is a fascinating and unusual structure with a high degree of hierarchical order,” said Stupp. “The membrane grows through a dynamic self-assembly process which generates hybrid nanofibers made up of both molecules and oriented perpendicular to the plane of the membrane. This architecture is very difficult to get spontaneously in materials. Using the right chemistry, the thick membrane structure could be designed to get conduits of charge in solar cells or nanoscale columns of catalytic nanostructures that would extend over arbitrary macroscopic dimensions.”

While the underlying, highly ordered structure of the sacs and membranes has dimensions on the nanoscale, the sacs and membranes themselves can be of any dimension and are visible to the naked eye.

Video: Self-assembling sacs form instantly when two aqueous solutions, one containing small molecules (first drop) and another containing high molecular weight polymers (green drop), are brought together.

Source: Northwestern University