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Gels as Functional Nanomaterials for Biology and Medicine†

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This perspective focuses on the potential uses of gels as materials in biological and medical applications. It describes how molecular self-assembly can confer well-defined secondary structures (e.g., nanofibers, nanotubes, and nanospheres) in a liquid that initiates functions within biological systems. Some prospects for future development and the challenges for achieving them are discussed.

Gels, composed of a solid network in a liquid medium, present many opportunities for materials scientists. Although the first mechanistic study of gelation began more than a century ago[1] and the remarkably useful application of gels as the media for electrophoresis in DNA sequencing and protein separation started more than a half century ago,[2] the research interest in gels has grown significantly only over the past two decades—more than 95% of the publications on gels over the past 50 years have appeared after 1989. Several seminal works contributed to the exponential growth of those interests. The phenomenon observed by Tanaka, that a gel can collapse upon application of an external stimulus (e.g., changing temperature),[3] has provided an early impetus. Later, Haffman demonstrated that the hydrogels of poly (*N*-isopropylacrylamide) (poly(NiPAAm)), exhibiting a lower critical solution temperature (LCST), shrink and deswell upon raising the temperature. More importantly, the poly(NiPAAm) hydrogels are biocompatible, an essential property that resulted in intensive research on the applications of poly(NiPAAm) in biomedicine.[4]

Research on gels has been largely dominated by the hydrogels of covalently cross-linked poly(NiPAAm) or other polymers until Weiss and Terech systematically investigated organogels formed by low-molecular-weight organic molecules.[5,6] The study of small molecules to form physical gels with an organic solvent not only established the concept of self-assembled molecular fibril (i.e., nanofiber) networks as the matrices of organogels[5−7] but also exemplified the scientific approach for investigating molecular gels,[8,9] which is illustrative for the research on small-molecule hydrogels[10] whose networks are also made of self-assembled molecular nanofibers. Studies on the hydrogels of self-assembled oligopeptides[11,12] not only provided the scaffold or medium for developing various bioengineering applications but also illustrated the potential utility of the hydrogels of small molecules.[10] The most exciting demonstration, however, was not available until Stupp reported that a 3D network of nanofibers formed by the self-assembly of peptide amphiphilic molecules caused a hydrogel to induce the selective differentiation of neural progenitor cells into neurons.[13] This work marked the beginning of synthetic soft materials that have both relatively ordered nanostructures and designated biological functions. This conceptual advance that molecular self-assembly can confer well-defined secondary structures (e.g., nanofibers, nanotubes, and nanospheres) in a liquid and results in a gel offers a new perspective on understanding and designing functional gels for various applications. The following discussion focuses on the potential uses of gels as functional molecular materials in biological or medical applications.

Both biological and synthetic molecules can act as the building blocks for constructing the elastic networks in gels. In nature, complex organisms have long employed gels or jellies as components for various functions, such as the body of a jellyfish, connective tissues in joints,[14] the cornea in the eye,[15] and nuclear pore complexes inside cells.[16,17] Although they share some common features with synthetic gels, biological gels have their own unique characteristics. For example, the networks of biological gels usually possess complex, hierarchical structures that arise from the self-assembly (or alignment) of biomacromolecules. The biomacromolecules sometimes carry out a specific molecular function, such as acting as enzymes. Unlike the simple gels made of cross-linked synthetic polymers, many biological gel materials (e.g., blood clots, blood vessels, lung parenchyma, cornea, and mesentery tissue) exhibit nonlinear elasticity[15] that is essential to their physiological functions in living systems but difficult to duplicate by synthetic gels. Gels in biology, now and for the foreseeable future, will be the inspirational source and ultimate goal for designing, improving, and perfecting synthetic gel materials.

One obvious result from the inspiration of biological gels is to use biological building blocks to create synthetic gels. Three major types of biological building blocks—peptides or amino

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acids, polysaccharides or carbohydrates, and DNA, RNA, or nucleotides—have successfully yielded a variety of gels. Because of their many conformations for forming hydrogen bonds in water or many other solvents, amino acids meet the need of nature for constructing proteins, and derivatives of amino acids are exceptionally useful resources for making synthetic gels. For example, the attachment of a short peptide sequence (several amino acid residues such as RGD[18]) to a synthetic polymer backbone presents a powerful strategy to imbue otherwise passive hydrogels with biological activity. Simple amino acids are, arguably, the most fruitful choice for creating molecular gels[8−10] because the adjustment of the amphiphilicity of an amino acid can easily result in a gelator. For example, Dey and co-workers report in this issue the gelation behavior of a series of low-molecular-weight-hydrogelators based upon *N*-(2-hydroxyalkyl)-L-valine and made from L-valine through the attachment of a simple 2-hydroxyalkyl chain.[19] This work illustrates that the refinement of the amphiphilicity of amino acid derivatives is a facile method for creating efficient gelators. Another interesting example, reported by Suzuki et al.,[20] is a two-component gelation system[21,22] consisting of N^{ϵ}-dodecyl-L-lysine esters (as amine components) and an *N*-dodecyl-L-amino acid (valine, phenylalanine, alanine, glycine, or L-lysine) as an acid component. Either of the two components—the amine or the acid components—hardly forms a gel alone, but a mixture of the two components forms organogels with simple organic solvents. The acid−base interactions, hydrogen bonding, and van der Waals interactions cooperatively create a 3D network of self-assembled nanofibers and result in the gels; they illustrate a simple route to expanding the diversity of molecular gels.

Unlike conformationally flexible amino acids, the bases in DNA and RNA bear rather rigid structures. Whereas the grafting of properly chosen oligomeric deoxynucleotides onto a polymer backbone can certainly induce cross-links and produce gels, a more elegant example relies on the use of DNA ligases to catalyze the cross-link of branched DNA monomers to form gels.[23] The latter approach is particularly attractive because the sequences of DNA allow precise control of the geometries of the branched DNA monomers. Similar to the case of amino acid derivatives,[24,25] the use of an enzyme to catalyze gelation under physiological conditions is an important attribute. A properly modified nucleotide bearing long alkyl chains can behave as molecular gelators to self-assemble into molecular nanofiber networks and yield gels. Generally, the behavior of the DNA gels strongly depends on the temperature or pH of the aqueous solutions used.[26]

Because carbohydrate polymers constitute part of the extracellular matrices, gels that consist of polymers of carbohydrate derivatives have attracted significant research interest and are under active investigation for a variety of applications. In one interesting example reported in this issue, Kaneko reported on gels formed by sacran, the megamolecular polysaccharide extracted from the jellylike extracellular matrix of a cyanobacterium.[27] Because sacran contains carboxylate and sulfate groups and binds with various heavy metal ions, its gels may be used as materials for efficiently removing heavy metal ions. Like amino acids, many derivatives of carbohydrates are molecular gelators. For example, Hamachi et al. recently report one particularly useful supramolecular gelator made from a glycosylated amino acid.[28] Using the hydrogel of the gelator, they construct a novel semiwet peptide/protein microarray that has potential applications in pharmaceutical research and diagnosis.

Recent scientific advances suggest ample opportunities for developing gel materials. The development of the research tools for nanometer-scale science, especially high-resolution microscopic methods (TEM, SEM, or AFM), has greatly improved the efficiency and accuracy of characterizing gel materials. The morphological resemblance of gels and extracellular matrices, the existence of gels throughout living systems, and the recent intensive research activities on gels allow one to speculate that the development of gels for biological applications may become increasingly important and the use of bioactive components or processes for generating gels may offer many opportunities for creating breakthroughs in areas such as medicine, pharmacology, and materials science and engineering. Whereas past successful applications of gels as superabsorbents, in contact lens, or in drug delivery have been based mainly on biocompatible, passive building blocks (e.g., synthetic polymers), the next generation of gel materials will likely have multicomponents and be multifunctional, similar to the complex, functional, and 3D gel materials evolved by nature. On the basis of this simple notion, several promising opportunities stand out.

An obvious opportunity is to develop gels as a general platform for building biomimetic systems to perform biological functions. Examples include the use of gels of recombinant proteins or oligopeptides to mimic extracellular matrices for tissue engineering, patterning gels for controlling spatial arrangements of cells (as shown by an example in this issue[29]), modulating the response of gels to stimuli for developing soft actuators,[30] designing gels or gelation events as low-cost assays for medical diagnoses,[31,32] and increasing the mechanical strength of gels for their applications in joints and other types of load-bearing applications.[33] Besides the use of materials from biology to make gels, it is also important to use bioactive molecules (e.g., drug molecules) to make gels. Via molecular self-assembly in water, it is possible to transform therapeutic agents into analogues that form gels without compromising their pharmacological efficacy.[34] The transformation of the therapeutic agents into "self-delivery" hydrogels could ultimately lead to bioactive molecules that have multiple roles.[35,36] The more promising opportunities could also come

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from the formation of gels inside cells because it is rather easy to create the network of nanofibers for gelation using small molecules, which enter cells more easily than do large molecules.[25] Additionally, the knowledge used in using biological processes to build nanofibers for gelation (e.g., enzymatic hydrogelation[24,25,37]) likely will benefit the construction of artificial cellular architectures in a new area of science—synthetic biology. One of the most remarkable characteristics of gels in living systems is that the nanofibers of biomacromolecules of the gels are being constantly created and degraded. Understanding and mimicking such a process could ultimately lead to gels that carry the function of self-healing, which would provide many new opportunities in biomedicine.

Before realizing the potential applications of the gels described above, many challenges need to be addressed. For example, our understanding of the biocompatibility of gels is still insufficient. It requires both biologists and materials scientists to work together to develop the fundamental science of the biocompatibility of gels. Besides lowering the cost of recombinant proteins and improving the biostability of oligopeptides,[38] it remains difficult to correlate the structures of the molecules and the molecular arrangement in the gels. Despite some theoretical advances, we know little about the relationship between the molecular structures and design principles for the nonlinear elasticity of biological gels. Although it is possible now to use gels to seed cells in two dimensions, it is rather difficult to pattern cells in three dimensions.

Although gel materials reside at the intersection of materials sciences and biology, biologists have shown limited interest in gels, and materials scientists have limited knowledge of the biology of gels. Therefore, the collaboration of scientists from materials science and engineering, chemistry, biology, and medicine will be required in the development of gel materials for biology and medicine. This aspect will become one of the most (if not the most) important and intellectually rewarding elements in gels research. The application of gel materials in medicine and biology is still in its infancy. Regardless of their disciplines, scientists who are interested in gels will likely have endless opportunities to tackle the exciting problems related to gels.[35]

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