Editorial

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Nanomedicine

How are we applying nanogel composites in biomedicine?

"…nanogels have gained attention for biomedical applications due to their high water content, 3D structure and high biocompatibility as well as their relatively large size that enables them to encapsulate biomacromolecules like proteins or genes. [They] have been shown to be excellent scaffolds for preparing composites as a novel class of advanced materials."

Mrityunjoy Kar
Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany

Maria Molina
Departamento de Química, Universidad Nacional de Rio Cuarto, Ruta Nac. 36 km 601, 5800 Rio Cuarto, Argentina

Marcelo Calderón
Author for correspondence:
Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany
Fax: +49 30 838 459368
marcelo.calderon@fu-berlin.de

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"Any problem can be solved using the materials in the room."
In Peter C Wensberg, Land's Polaroid: A Company and the Man Who Invented It (1987) – Edwin Herbert Land

"There's plenty of room at the bottom."
Lecture given at an American Physical Society meeting at Caltech on 29 December 1959 – Physicist Richard Feynman

The past decade has witnessed an exponential growth in nanomaterial science and research for a variety of biomedical applications, such as drug and gene delivery, anticancer therapeutics, diagnostics and imaging, tissue engineering and stem cell based therapies. Nanosystems based on natural, semi-synthetic and synthetic polymers are widely used in biomedical research [1,2]. In particular, nanosized hydrogels, so-called nanogels, have gained attention for biomedical applications due to their high water content, 3D structure and high biocompatibility as well as their relatively large size that enables them to encapsulate biomacromolecules like proteins or genes [3,4]. Moreover, nanogels have been shown to be excellent scaffolds for preparing composites as a novel class of advanced materials, which comprise both nanogels and other constituents such as polymers or inorganic nanoparticles.

According to IUPAC, a composite is defined as a "multicomponent material comprising multiple, different (non-gaseous) phase domains in which at least one type of phase domain is a continuous phase" [5]. The advantage of composite materials is that the properties of all the components are added up and ideally not influenced by each other. In nanogel composites, the individual properties of different materials can therefore be added to the nanogel properties. Composites are generally prepared at the macro level by mixing techniques, for example, ball milling, shear mixing, precipitation, etc. as well as by polymerization of certain monomers in the presence of nanogel scaffolds, yielding semi-interpenetrating networks (SIPN). The easy synthesis and synergetic combination of properties render nanogel composites very interesting and suitable for biomedicine research. Composite materials, however, are different from hybrid materials, where the constituents are combined at a molecular level by orbital interaction and exhibit new properties not necessarily found in the individual components.

Drug delivery in cancer therapy

The advantageous properties of nanogels, such as 3D structural stability, high surface

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area and functionality, biocompatibility and increased retention time make nanogel composites very useful for drug delivery applications [6,7], especially against cancer [8,9]. For treatment of non-small-cell lung cancer, for example, pH-responsive chitin-poly(caprolactam) nanogel composites are being studied to deliver doxorubicin (Dox) [8]. The Dox-encapsulated composite nanogels show better swelling in acidic pH compared with neutral pH and significant cytotoxicity toward cancer cells in *in vitro* studies. The beneficial property of chitin (a positively charged natural polymer) in the nanogel composite is that it swells at lower pH, which facilitates the release of the encapsulated Dox. This swelling and enhanced drug release cannot be achieved by only using the poly(caprolactam) nanogels. In another study, bioresponsive nanogel composites based on chitin and poly(lactic acid) are used in therapy for liver cancer [9]. Dox is loaded successfully into the nanocomposites and shows a better release profile in acidic pH than in neutral pH. Apart from the advantageous properties of chitin, the negatively charged lactic acid can enhance the encapsulation of positively charged Dox due to ionic interactions.

Stimuli-responsive nanogels offer the unique possibility to have spatio–temporal control over the properties of the composite systems. For example, thermoresponsive nanogels can change their physical properties (such as swelling and shrinking) upon a thermal trigger. Our group is exploring thermoresponsive nanogels that have been semi-interpenetrated with charged polymer composites for the delivery of Dox to multidrug-resistant cancer cells. We have successfully overcome the drug resistance in *in vitro* as well as *in vivo* studies by using a negatively charged polymer. The proposed mechanism involved a slow rate release of the drug after uptake that avoided the efflux transporter of the resistant cells and thus allowed the drug to reach the nucleus [10]. This last case is a clear example of the advantages of using composites, in particular SIPN, where semi-interpenetration with a charged polymer is the key to decrease the unspecific release of Dox.

Cancer therapy & diagnostics

Cancer therapy is a broad research area that is constantly trying to develop an effective and noninvasive treatment by using hyperthermia [11], radiation [12] and electromagnetic frequencies [13]. One important aspect of successful cancer treatment is to have diagnostic tools for an efficient early detection of cancer as well as to obtain information about the progression stages of cancer [14]. In recent literature, stimuli-responsive nanogel composites and their applications in biomedicine were summarized and reviewed [15]. Nanogel composites are being developed for cancer therapy and diagnostics by utilizing gold nanoparticles [16], magnetic nanoparticles [17] and quantum dots [18]. Gold nanoparticles combined with chitin–manganese dioxide (MnO_2) nanogels have been developed for magnetic hyperthermia cancer treatment [19]. These nanogel composites show conductivity and heating under a radio frequency source at 100 W compared with chitin–MnO_2 only nanogels. The nanogel composites were used for cancer cell ablation with radio frequency, and promising results have been achieved with several cancer cell lines. These inorganic components, such as gold and magnetic nanoparticles, can be additionally used for magnetic resonance imaging (MRI), as well as quantum dots can be used for fluorescence imaging in cancer diagnosis. Although inorganic nanoparticles are having various useful properties, such as hyperthermia, enhancing MRI signal, fluorescence, etc., their use in biomedicine is limited due to the disadvantageous properties, such as toxicity as well as short circulation and retention times. All these above-reported examples show the beneficial effect of nanogels when they are utilized to overcome those disadvantages of inorganic nanoparticles to deploy their useful properties in biomedicine.

Apart from the inorganic nanoparticle-based nanogel composites, SIPN nanogels are also effectively utilized in photothermal cancer therapy [15]. SIPN nanogels that use conductive polymers are very interesting due to their ability to transform light to heat energy. With this, the heat energy transformed from light sources can be utilized to kill cancer cells, which is known as photothermal therapy [20]. One major drawback of working with conductive polymers is their poor solubility in water. Semi-interpenetration into nanogels has shown to be a suitable strategy to overcome this disadvantage. Recently, we reported the synthesis of an SIPN based on polyaniline and a thermosensitive nanogel [21]. For the SIPN, highly water dispersible nanogels comprised of dendritic polyglycerol and N-isopropylacrylamide were used. This system was shown to be effective for the photothermal treatment of cancer *in vivo*.

Tissue regeneration

Polymer composite materials are widely used in biomedical applications [22], especially in stem-cell-based tissue regeneration [23]. Nanogel composites are of great interest to fulfill the tissue regeneration niche due to their advantage to offer multiple biochemical properties, which cannot be fulfilled by using only nanogels or individual polymers. For example, self-assembled heparin nanogels combined with gelatin are being explored as injectable composites for the treatment of urinary incontinence. The nanogel composites are injected into the urethral wall and narrow the urethral lumen to prevent urine leakage upon sneezing or coughing [24]. The same nanogel composites loaded with growth factors show continuous release for up to 28 days, which stimulate the regeneration of the urethral muscle tissue surrounding the urethral wall and promote the recovery of its biological function [24]. Moreover, nanogels of lithium-neutralized polyacrylic acid are being combined with a biodegradable polyhydroxybutyrate matrix for bone regeneration and drug delivery [6]. The nanogel composites are used to prepare films and to study their chemical, structural and mechanical properties toward bone regeneration and drug delivery.

Nanogel composites & its future

The above-mentioned reports clearly show the potential of nanogel composites toward biomedicine. By modifying the composition of the nanogels, these composites can be further tuned to obtain desired physicochemical properties toward drug and biomacromolecule delivery, cancer therapy and tissue engineering. The advantages from using the 3D nanogel component in the composite system are the enhancement of the structural integrity and improvement of the system's functional properties. For example, if the individual components were just mixed physically and applied without nanogels, the stability of the systems would be low because all the independent components would diffuse and quickly disintegrate.

Nanogel composites hold a tremendous amount of potential for a number of therapeutics due to their enormous possibility to obtain multifunctional nanoscale materials. Every biological process requires different functionalities to work efficiently. Nature has utilized around 20 amino acids as building blocks of proteins with a large number of functionalities to control individual biological processes. The extracellular matrix, for example, is composed not only of proteins but also of several other polymers such as proteoglycans and polysaccharides, where all the components are essential to maintain a healthy tissue environment and ensure regulatory functions. In polymer science and engineering, it is still quite challenging to develop materials with such complexities. Most synthetic polymers or naturally obtained commercially available polymers, such as hyaluronic acid, heparin, gelatin, etc., are only mono-, di- or trifunctional, which decreases their possibility to be used in a broad range of biological applications from drug delivery to tissue engineering. In nanogel composite materials, it is possible to intelligently mix various materials with different properties to develop a product with better susceptibility to interact with biological functions, which is the main interest toward many developments in biomedicine. However, there is still a long way that needs to be paved when it comes to the clinical application of nanogel composites, particularly about their structure–activity relationship, pharmacodynamics, pharmacokinetics, capability to cross biological barriers and scale-up of the synthesis.

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