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# Hydrogel as a bioactive material to regulate stem cell fate

Yung-Hao Tsou, Joe Khoneisser, Ping-Chun Huang, Xiaoyang Xu*

*Department of Chemical, Biological, and Pharmaceutical Engineering, New Jersey Institute of Technology, Newark, NJ 07102, USA*

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The encapsulation of stem cells in a hydrogel substrate provides a promising future in biomedical applications. However, communications between hydrogels and stem cells is complicated; various factors such as porosity, different polymer types, stiffness, compatibility and degradation will lead to stem cell survival or death. Hydrogels mimic the three-dimensional extracellular matrix to provide a friendly environment for stem cells. On the other hand, stem cells can sense the surroundings to make the next progression, stretching out, proliferating or just to remain. As such, understanding the correlation between stem cells and hydrogels is crucial. In this Review, we first discuss the varying types of the hydrogels and stem cells, which are most commonly used in the biomedical fields and further investigate how hydrogels interact with stem cells from the perspective of their biomedical application, while providing insights into the design and development of hydrogels for drug delivery, tissue engineering and regenerative medicine purpose. In addition, we compare the results such as stiffness, degradation time and pore size as well as peptide types of hydrogels from respected journals. We also discussed most recently magnificent materials and their effects to regulate stem cell fate.


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* Corresponding author.
*E-mail address:* xiaoyang@njit.edu (X. Xu).

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## 1. Introduction

In the past our understanding of biomaterials was quite a different view from the current understanding. Our views of biomaterials where dominated by the idea of an inert, inactive and non-viable substance for the use on living organisms. We now hold a greater prospective on the technical aspects and characterization of biomaterials and the need for them to interface with native tissue [1]. Hydrogels are three-dimensional systems with hydrophilic polymer chains [2] that link and have high water content [3,4]. Because of hydrogels special traits, such as modifiable chemical properties, biocompatibility, elasticity, the capability to act as a growth medium and the ability to mimic the extracellular matrix (ECM), they have broad uses in biomedical research [5] that spans from drug delivery [6,7] to regenerative medicine [3] to tissue engineering [8] and are gaining attention due to their ability to encapsulate cells. They are the subjects of numerous academic and industry projects/research [9–11], they have useful characteristics and their substrates allow for the influence of numerous variables [12,13]. Hydrogels are often thought of in two categories, natural and synthetic. Natural hydrogels or naturally derived hydrogels consist of collagen, alginate, hyaluronic acid and chitosan to name a few [14]. These are increasing used in research as they exhibit desirable properties such as, biodegradability and therapeutic cell interactions [6]. On the other side of the spectrum, synthetic hydrogels may offer mechanical advantages such as strength and better elastic properties. Some examples of synthetic hydrogels are poly (ethylene glycol) commonly referred to as PEG, poly vinyl alcohol (PVA) and polyacrylamide (PAM). Each type of hydrogel, synthetic and natural, contain desirable traits and arrangements, that make them an encapsulating biomaterial [15] and are highly suitable, as such these combined traits are expressed in the form of hybrid hydrogels [16]. One such example is an alginate hydrogel, which can achieve high stiffness, one factor in the regulation of stem cell fate [17]. These hydrogels are commonly used in tissue regeneration and are often implemented in the form of injectable hydrogels [18]. The uses of these biomaterials are in an attempt to mimic native tissue [19], hence the term biomimetic hydrogel and often follow tissue characteristics, such as elasticity [10]. A spark in uses of hydrogels is in modifiable/tunable hydrogels [20] and this is where new kinds of hydrogels comes in, one of whom is elastomeric hydrogels that allow favorable stress related properties [21]. Another notable type of hydrogels is the environmental responsive hydrogel, which change to gel from external cues. One subset of this category is thermoresponsive hydrogels, which uses temperature as an activation of its abilities [22]. An important and main application in hydrogels as a bioactive material is the uses and effects of hydrogels in stem cell therapy [23]. In the field, this is often referred to as regulation of stem cell fate [17]. These hydrogels act as media to allow better viability of the stem cell and help in the proliferation [19] and retention [24] of the cells. In the span of decades of research and achievements, the scientific community has developed numerous advanced biomaterial systems composing of different properties and uses in clinical applications [25] for a wide range of medical complications all throughout the health related fields. Accomplishments can be attributed to a wide range of interdisciplinary work, which have set the foundation for therapeutic strategies. The scope of this review covers the uses of hydrogels for the regulations and use of stem cell therapies in regenerative medicine, tissue engineering and other therapeutic applications.

## 2. Hydrogels as a bioactive material

### 2.1. Natural

Many polymers used for hydrogel fabrication comes from nature, including alginate, collagen, fibrin, chitosan, gelatin, hyaluronic acid among many others. These polymers have advantages of inherent biocompatibility, environmental sensitivity and are abundant in source [36]. Some of the natural polymer based constructs contains degradation moieties such as hydrolysable ester groups and enzyme-mediated hydrolytic amide groups. In addition, gels made from natural polymers present natural binding sites, which provide the interaction between cells and hydrogels. However, low stability, poor mechanical properties and rapid degradation rate are major disadvantages of the natural-based hydrogels [44]. In this section, we discussed some of the most commonly used natural polymers.

#### 2.1.1. Alginate

Alginate is a polysaccharide extracted from brown algae, which is a natural anionic polymer electrolyte. It is a strictly linear copolymer that composed of two monosaccharides of α-L-guluronic acid (G) and β-D-mannuronic acid (M) respectively [26]. Because of its abundance, inexpensiveness and biocompatibility respectively, it is featured in a number of published articles, and its uses have been increasing in recent years [27–29]. Alginate has a characteristic that when it interacts with divalent ions, such as $Ca^{2+}$, $Sr^{2+}$ and $Ba^{2+}$ it will become a dense three-dimensional structure called an "egg box" to improve the mechanical properties. However, it may be hard to control the degradation rate, as it is a considerable challenge for cationic polymers. The major disadvantages of natural materials are poor mechanical properties as well as cell adhesion [27]. One group developed a hybrid hydrogel comprised with alginate and poly ethylene glycol diacrylate (PEGDA) to achieve toughness greater than natural cartilage due to a PEG network with a high elasticity and reversible crosslinking qualities under deformation of alginate [30]. On the other hand, because of the poor adhesion property of alginate-based hydrogel, RGD sequences peptides are used to improve cell adhesion. Mooney group successfully developed a model where GRGDY-modified alginate hydrogel showed the cellular interaction between the hydrogel and mouse skeletal myoblasts [26]. In addition, other variables such as stiffness and porosity shows an effect in the cell's fate, his group studies stress relaxation of the alginate-based hydrogels to regulate stem cell fate and activity. Interesting results present, that the hydrogel with faster relaxation property accommodates better cell spreading, differentiation and proliferation than slower relaxation. As such, the stress relaxation may be the key parameter to regulate stem cell fate for cell culture [31]. Surprisingly, the geometry of hydrogel is another significant factor effecting cells viability. One study founds out when using sphere alginate based hydrogel (Diameter = 1.5 mm) Fig. 1 can not only contain great biocompatibility but also restore blood-glucose control for above 180 days [32].