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# Engineering cell microenvironment using novel functional hydrogels

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ABSTRACT

Cell microenvironment plays critical roles in regulating cellular activities both spatially and temporally. Engineering cell microenvironment using hydrogels has attracted increasing attention given their native-mimicking properties. In particular, developing hydrogels with specific functions has recently emerged as novel biocomposites to enable the regulation of cell microenvironment from a variety of aspects such as the biological, mechanical and electrical microenvironment. In this review, the state-of-the-art methods for the preparation and application of several novel functional hydrogels are presented, including magnetic hydrogels, photoresponsive hydrogels, conductive hydrogels, thermoresponsive hydrogels, molecule-response hydrogels, as well as tough and stretchable hydrogels. In particular, the applications of these functional hydrogels for engineering cell microenvironment are also reviewed. Concluding remarks and perspectives for the future development of functional hydrogels are addressed.



## 1. Introduction

Cells *in vivo* are situated in a three-dimensional (3D) complicated microenvironment composed of various biological, physical and chemical cues [1,2]. These biological, physical and chemical microenvironments play critical roles in regulating cellular activities (e.g., proliferation, migration, differentiation) both spatially and temporally [3–5]. Therefore, it is of great importance to engineer cell microenvironment *in vitro* to reconstruct the native cellular behaviors and functions for various applications, such as tissue engineering and regenerative medicine. For this, hydrogels have attracted increasing attention given their native-mimicking properties including biological adhesion, biodegradation, biocompatibility and high permeability that allow molecules of different sizes to transport out of and into [6–9]. However, the limitations of the conventional hydrogel systems in controllability, actuation, response and mechanical properties [10–12] make it challenging to engineer complex cell microenvironment *in vitro* to mimic the native microenvironment [13].

With advances in polymer science, various novel functional hydrogels have recently been developed through functionalizing the conventional hydrogels with certain special properties (e.g., magnetic response, photo response, electrical conductivity). These special properties endow hydrogels with additional potentials and widen the scope of their applications in engineering cell microenvironment (Fig. 1). For instance, the mechanical environment of hydrogels with embedded magnetic nanoparticles can be

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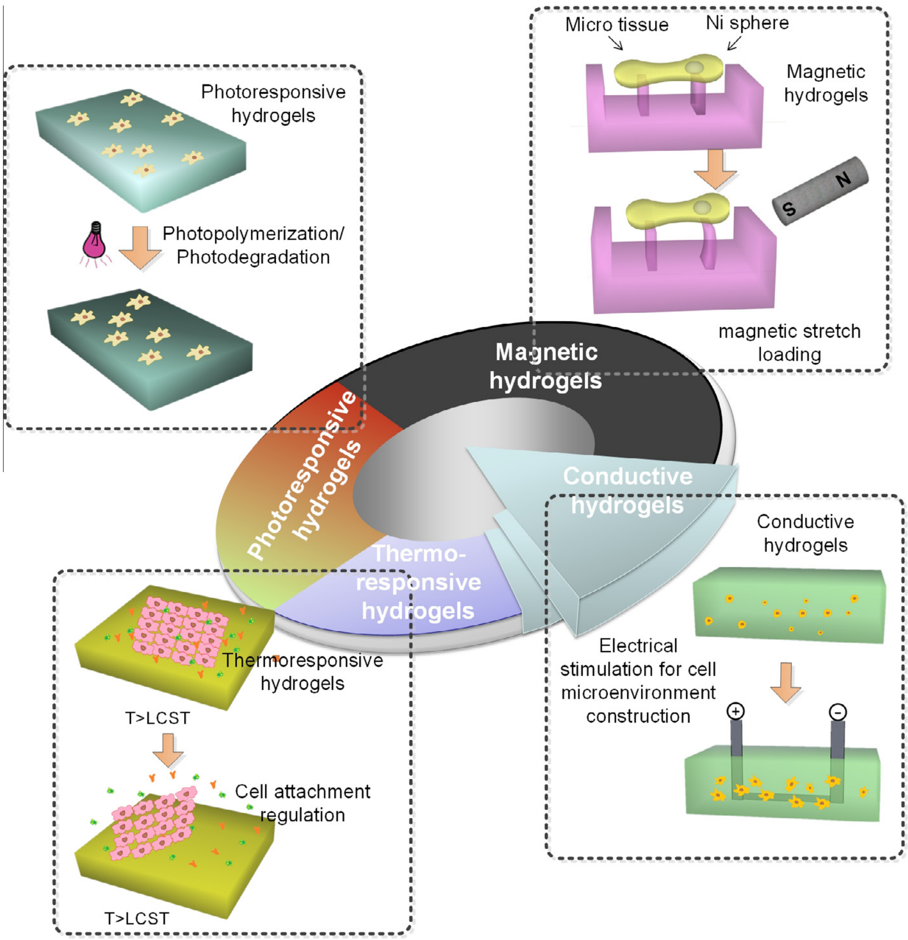


**Fig. 1.** Schematic illustration of engineering cell microenvironment using novel functional hydrogels, including magnetic hydrogels to manipulate mechanical microenvironment through magnetic stretch loading, conductive hydrogels to change the electrical microenvironment via electrical stimulation, photoresponsive hydrogels to manipulate the mechanical microenvironment through photo-degradation, and thermoresponsive hydrogels to manipulate the biological microenvironment by changing the temperature.

easily manipulated through the hydrogel deformation by using an external magnetic field (MF) [14]. Conductive nanomaterials have been incorporated into cell-encapsulating hydrogels, especially for cardiac tissue and neuronal regeneration, to facilitate the electrical signal transport and thus enhance the cellular function via electrical stimulation [15]. Thus, the developments of functional hydrogels enable the construction and manipulation of complex cell microenvironment *in vitro* with more controllability.

Although there exist several reviews on different types of functional hydrogels, they mostly emphasize the hydrogel materials and the synthesis methods [16–20]. In this review, we aim to present an overview of recent studies on the novel functional hydrogels with a focus on their applications in engineering cell biological, physical and chemical microenvironments. Several types of functional hydrogels, including magnetic hydrogels, photoresponsive hydrogels, conductive hydrogels, and other functional hydrogels will be addressed. In each section, we will start with a brief introduction of the hydrogels followed by some examples of their applications in engineering the cell microenvironment.

## 2. Functional hydrogels for engineering cell microenvironment

### 2.1. Magnetic hydrogels for engineering cell microenvironment

Magnetic hydrogels have recently emerged as a novel kind of hydrogels for their active and controllable responsive properties to an external MF with widespread applications, such as tissue remodeling, drug delivery systems, enzyme immobilization, local hyperthermia therapy and soft actuators [14]. Magnetic hydrogels are commonly composed of magnetic micro/nano particles (MPs) (e.g., $Fe_3O_4$, $\gamma$-$Fe_3O_4$ and $CoFe_2O_4$), enabling their quick response to an external MF. The responsive properties are influenced by several factors, including the type, concentration, size and even the spatial distribution of MPs [21,22]. Several