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Guest Editorial

A Prelude to Engineering of Cell Microenvironment Using Novel Hydrogels

This prelude to Engineering of Cell Microenvironment Using Novel focuses on reporting recent advances and trends in the development of functional hydrogel systems to engineer cell microenvironment for various emerging applications, such as biomanipulation, tissue engineering, and regenerative medicine. Typically, hydrogel systems are network of macromolecular polymers crosslinked through physical or covalent bonds. The unique three-dimensional (3D) net structure endows hydrogels with highly absorbent ability and flexible mechanical properties. These characteristic properties of hydrogels offer them with biomimicking properties to natural extracellular matrix (ECM) in vitro, especially useful for biomedical and pharmaceutical applications. In recent years, novel hydrogel systems with extra structural features, functionalities, or properties have gained increasing attentions and exhibited significant impact for biological, biomedical, and pharmaceutical applications. Such state-of-the-art hydrogel systems can be hybrid, nano/microstructure patterned, multifunctional, and responsive. These add-on features of the functional hydrogels enable the precise manipulation of cell biological, physical, mechanical, and electrical microenvironment in vitro, demonstrating to be ideal model systems to direct dynamic tissue regeneration and to study basic cell biological behaviors.

The collection of papers covers a diversity of research areas involving the fabrication and application of different hydrogel systems, reflecting the latest progress and future perspectives in the development of functional hydrogels for engineering cell microenvironment. We believe that the research work presented would be interesting and informative to the readers.

One important research direction using hydrogels is to create 3D cell microenvironment in vitro to recapitulate the native cellular behaviors and functions, such as cell adhesion, proliferation, differentiation, and tissue maturation. Precise manipulation of cell environment through mimicking the native ECM would also benefit the translation of research into therapies and commercial applications and advancing fundamental understanding of cell–matrix interaction. Du et al. provided a concise review of the recent advances in the application of engineering embryonic stem cell (ESC) microenvironment for directed cell differentiation. Although this paper covers a broad topic on physical and biochemical strategies for ESC differentiation, it also highlights the creation of 3D hydrogel-based microenvironment as the stem cell niche to direct ESC differentiation and self-renewal under feeder-free condition. Another study contributed by Wang et al. provides an example of recent advances in creating patterned hydrogels using micro/nanotechnology to precisely control the growth direction of nerve cells and axons. They explored the guiding ability of chitosan micro/nano hybrid structures for nerve cell growth and found that the nerve cells can grow along the ridges of the microstructure and some even grow across the groove. More interestingly, the hydrogels with microscale ridges and nano-patterns in between can guide cell growth along the ridge more effectively with enhanced cell proliferation.

Another emerging research area of hydrogels is to develop hydrophobic or hydrophobic/hydrophilic hybrid interface for engineering control of cell–material interactions, thus manipulating cell/tissue morphology. One typical example is fabricating cellular spheroids in vitro, as they present the critical morphology of a variety of cell types that exist in vivo, such as ESCs, cancer cells, and pancreatic cells. Two different approaches have been introduced for the fabrication of cellular spheroids in vitro for biomedical and pharmaceutical application. Xu et al. introduced a simple and novel method to generate high-throughput breast cancer cell (MCF-7) spheroids using polyacrylamide/gelatin methacrylate (GelMA) hydrogels as templates. The well-distributed arginine–glycine–aspartic acid cell-adhesive binding sites contributed by GelMA provide anchors for initial cell attachment. This study also demonstrated good controllability over the shape and size of cell spheroids by regulating cell seeding density and culture time. Akay et al. presented an alternative method to develop 3D brain cancer spheroids using poly(ethylene glycol) hydrogel microwells. Three-dimensional tumor models well mimic the physiological conditions in vivo and provide valuable insight for effective anticancer drug sensitivity. In another study, Lee et al. developed a polydimethylsiloxane-based microfluidic cell chip for cytotoxicity test. To demonstrate their proof-of-concept validation, they performed on-chip cytotoxicity tests for Nepali Chiya extract using HeLa cell line.

Another exciting advance in hydrogel systems is in situ gelation of responsive hydrogels. Such "smart hydrogels" usually undergo liquid to solid phase transition upon external stimuli, such as temperature, ultraviolet (UV) light, *p*H, etc. These hydrogels also allow minimal invasive methods for delivery due to their unique characteristic properties. Li et al. developed an injectable and UV crosslinkable N-methacryloyl chitosan (N-MAC) hydrogel, which was hybridized with hydroxyapatite (HA) to accelerate regeneration of rabbit calvarial bone defect in vivo. The N-MAC/HA was delivered through injection and solidified upon UV irradiation in situ and demonstrated potent osteoinductivity with 50% closure of defect site 6 weeks postimplantation.

One of the most exciting advances in the area of hydrogels is increasing recognition of genetic information container (i.e., DNA) as natural polymer for material science and engineering. The rising interest in genetically engineered hydrogels lies in the unique properties of DNA, including biomimeticity, precise molecular weight, and the strict sequence-dependent recognition of double-stranded DNA. Additionally, DNA molecule has been systematically studied for the structure or biological mechanism and has demonstrated the ability to build arbitrarily designed features from rationally designed DNA molecules. Currently, the biggest challenge in fabricating DNA-based bulk hydrogel materials for biomedical and pharmaceutical applications is to produce DNA molecules in mesoscale or even macroscale scales. In this issue, Qi et al. contributed a review on the state-of-the-art technologies for fabricating DNA-based bulk materials, including

nonspecifically crosslinking (e.g., EGDE-TEMED paired chemical reaction and DNA metabolic enzyme-mediated ligation), rationally DNA chain folding with arbitrarily designed geometry (e.g., DNA tile based self-assembly and DNA origami directed self-assembly), and utilizing DNA as smart molecular "glue" to assemble bulk materials. DNA-based bulk hydrogel systems may open a new path for the application in tissue engineering and regenerative medicine.

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