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Review article

Hydrogel microparticles for biosensing

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ABSTRACT

Due to their hydrophilic, biocompatible, and highly tunable nature, hydrogel materials have attracted strong interest in the recent years for numerous biotechnological applications. In particular, their solution-like environment and non-fouling nature in complex biological samples render hydrogels as ideal substrates for biosensing applications. Hydrogel coatings, and later, gel dot surface microarrays, were successfully used in sensitive nucleic acid assays and immunoassays. More recently, new microfabrication techniques for synthesizing encoded particles from hydrogel materials have enabled the development of hydrogel-based suspension arrays. Lithography processes and droplet-based microfluidic techniques enable generation of libraries of particles with unique spectral or graphical codes, for multiplexed sensing in biological samples. In this review, we discuss the key questions arising when designing hydrogel particles dedicated to biosensing. How can the hydrogel material be engineered in order to tune its properties and immobilize bioprobes inside? What are the strategies to fabricate and encode gel particles, and how can particles be processed and decoded after the assay? Finally, we review the bioassays reported so far in the literature that have used hydrogel particle arrays and give an outlook of further developments of the field.

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1. Introduction

In recent years, there has been significant development of hydrogel-based technologies for a range of biotechnology applications including diagnostics [1–3], drug delivery [4,5], and tissue engineering [1,6–8]. Hydrogels are versatile materials due to their hydrophilic, biofriendly, and highly tunable nature, making them applicable in this varied range of contexts. Recent significant advances in types of gel materials [9,10], microfabrication techniques [11–14] and biosensor development [15] have come together to assemble the key components for fabrication of encoded hydrogel particles for biosensing. In this review, we will focus specifically on the development of these unique microparticles for biosensing, methods of synthesis and functionalization, and detection assays that have been reported in literature. We will also comment on the future of the field and the expansion into other areas such as single-cell characterization. This introduction will enumerate the chemical advantages of hydrogels and their initial success in being used in a microarray format, which led to the gel bead-based advances that we will describe later.

Hydrogels, made of cross-linked hydrophilic polymer chains, are readily functionalized with diverse biological entities such as nucleic acids or proteins [5]. Thus, hydrogels can be engineered for capture and detection of clinically relevant analytes including but not limited to proteins, DNA, mRNA, and microRNA (miRNA). Their solution-like environment, chemical tunability and non-fouling nature in biologically complex fluids (e.g. serum), further render hydrogels ideal candidates for diagnostic applications. The three-dimensional scaffold can be porosity-tuned to allow the diffusion and reaction of large biomolecules while remaining structurally stable under harsh mixing or flow conditions.

In a molecular diagnostic context, hydrogels were first utilized for the fabrication of hydrogel sensing planar microarrays (Fig. 1). A wide range of hydrogel chemical compositions have been explored for DNA or protein microarrays, in particular polyacrylamide [2,16,17], polyethylene glycol [18–20], and alginate [21] derivatives. Several methods to functionalize the gels have been explored, ranging from in situ functionalization at the time of synthesis to post-synthesis functionalization utilizing functional groups in the gel [22]. In a series of studies where probe-functionalized polyacrylamide hydrogel pads were immobilized on a surface for DNA detection, hydrogels were found to be superior for biosensing relative to rigid two-dimensional planar surfaces [22–25]. These pioneering studies demonstrated better thermodynamic association constants for nucleic acid hybridization inside the gel environment and proved that biological probes could be functionalized at significantly higher densities than possible on standard microarrays. Further studies extended to antibody-based protein detection revealed similar advantages with regard to probe-functionalization density [2,26]. These favorable characteristics enabled