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Research review paper

Molecular imprinting of proteins in polymers attached to the surface of nanomaterials for selective recognition of biomacromolecules

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ABSTRACT

This review article summarizes the preparation of polymers imprinted with proteins that exhibit antibody-like specificity due to the presence of well-defined recognition sites. We present the newest developments concerned with use of nanomaterials, such as magnetic and silica nanoparticles, nanowires, carbon nanotubes, and quantum dots as supports enabling the preparation of protein-imprinted polymers via surface imprinting techniques. As an alternative receptor-like synthetic materials, these conjugates are attracting a great deal of interest in various fields including proteomics, genomics, and fabrication of selective sensors. However, imprinting of large biomacromolecules such as proteins still remains a challenge due to the inherent limitations related to protein properties. In the text below, we also describe examples of applications focused on selective recognition of biomacromolecules.

Contents

1. Introduction

The future development of proteomics and genomics requires a deep understanding of the structure and function of living organisms at a molecular level (Alderton, 2009; Cesari, 2009; Whitcombe, 2011). For example, proteomics includes detection and identification of proteins, which concentration can cover a very wide range. It is very difficult to detect low abundance proteins that often have significant biological functions in the presence of high concentrations of other components. Therefore, methods enabling selective detection and quantification of target proteins are useful in a wide variety of fields, including clinical diagnostics, therapeutic monitoring, control of bioreactors, and detection of organisms and toxins (Whitcombe et al., 2011). Immunoassays, which rely on specific interactions between antibodies and antigens, are used routinely in laboratories to detect and quantify proteins in biological samples (Issaq et al., 2007). Although antibodies meet the requirements for specificity, selectivity, and ease of use, these biomolecules still have several fundamental limitations (Thobhani et al., 2010). For example, they are subject to chemical and physical changes or breakdown, and the screening and production of suitable antibodies are costly, tedious, and time-consuming (Yang et al., 2012a; Zhou et al., 2010).

In this respect, alternative receptor-like synthetic materials, such as molecularly imprinted polymers (MIP), offer unique opportunities (Hoshino et al., 2008; Vlatakis et al., 1993; Wulff and Sarhan, 1972).

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MIP have considerable potential as a cost-effective alternative to bioreceptors now used in a variety of sensor applications (Lakshmi et al., 2009; Panasyuk et al., 1999; Riskin et al., 2007). In contrast to biological counterparts (enzymes, antibodies and hormone receptors), molecularly imprinted materials display significant advantages, including high mechanical/chemical stability, ease of preparation, potential re-usability, and low manufacturing cost (Vlatakis et al., 1993; Wulff and Sarhan, 1972).

Molecular imprinting was pioneered by Wulff in the early 1970s (Wulff and Sarhan, 1972; Wulff et al., 1973). Wulff's work enabled preparation of polymer scaffolds with specifically designed cavities decorated with functional groups that acted as synthetic receptors. A detailed description of this field can be found in an excellent review published by Wulff (1995).

Two different molecular imprinting strategies have been developed based on the type of interaction of the imprint with the monomer and include covalent imprinting (Wulff, 1995; Wulff and Schauhoff, 1991) and non-covalent imprinting (Arshady and Mosbach, 1981; Sellergren et al., 1988; Takagish and Klotz, 1972; Takagishi et al., 1982, 1984). A simplified scheme of the process is shown in Fig. 1.

MIP were initially prepared by imprinting one enantiomer and applied for the resolution of racemates (Andersson and Mosbach, 1990; Andersson et al., 1990; Kempe et al., 1993; Lei and Tan, 2002; Sellergren, 1989; Sellergren and Shea, 1993; Wulff and Minarik, 1990; Wulff et al., 1977). Although reasonable selectivity could be achieved, the peak of the stronger retained enantiomer was typically broad due to the slow kinetics of its binding and release (Fig. 2) (Wulff and Minarik, 1990). This problem was fatal for the use of MIP in enantioseparations since MIP could not compete with significantly more efficient chiral stationary phases. In contrast, MIP serving as selective sorbents for solid phase extraction of trace analytes from complex matrices, appear to be a more promising application (Berrueta et al., 1995; Lv et al., 2007a, 2007b, 2008; Matsui et al., 1997; Muldoon and Stanker, 1997; Sellergren, 1994). Based on the specific selectivity of MIP to their templates, selective enrichments and clean-up of desired compounds can be achieved to levels not achievable with other existing methods. This selectivity results in a higher accuracy and lower detection limit (LOD) in the subsequent analyses (Sellergren, 1999). The applications in solid phase extraction have been extended to bioanalysis, biosensors, as well as food and environmental analysis, and several MIP are commercially available.

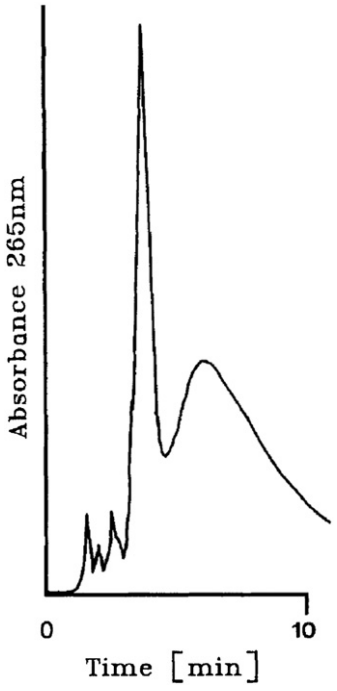

Fig. 2. Chiral liquid chromatography separation of racemic α-phenylmannoside using imprinted polymer. Conditions: flow rate, 1.2 mL/min; temperature, 60 °C; mobile phase, acetonitrile/water/ammonia 82.5/12.5/5 (v/v/v).
Reproduced from Wulff and Minarik (1990) with permission.

While the imprinting of small molecules is straightforward, the preparation of MIP against biomacromolecules, such as proteins, remains a challenge. The bio-imprinting has been independently investigated by the research groups of Keyes (Keyes et al., 1987; Saraswathi and Keyes, 1984), Klibanov (Dabulis and Klibanov, 1992; Braco et al., 1990), and Mosbach (Stahl et al., 1990, 1991). The major difficulties they observed included (i) obtaining pure protein templates, (ii) restricted transfer of proteins within the highly crosslinked polymer networks, (iii) the heterogeneity in binding affinity of the cavities, (iv) insolubility of proteins in typical polymerization mixtures used for imprinting, and (v) the degradation of

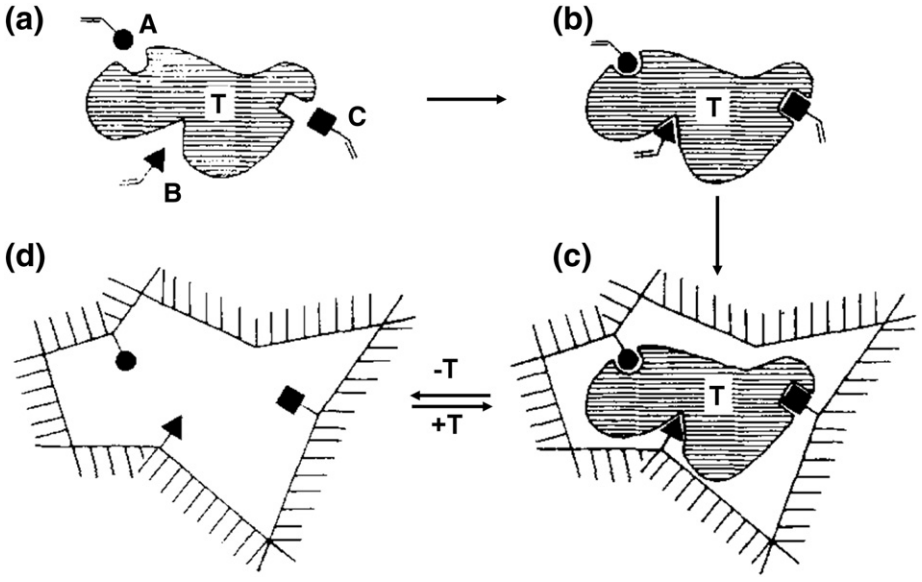

Fig. 1. Schematic representation of the imprinting of specific cavities in a crosslinked polymer by a template (T) with three different binding groups attached to monomers A, B, and C.
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