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Historical perspective

Surface modification strategies on mesoporous silica nanoparticles for anti-biofouling zwitterionic film grafting

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ABSTRACT

In the past decade, zwitterionic-based anti-biofouling layers had gained much focus as a serious alternative to traditional polyhydrophilic films such as PEG. In the area of assembling silica nanoparticles with stealth properties, the incorporation of zwitterionic surface film remains fairly new but considering that silica nanoparticles had been widely demonstrated as useful biointerfacing nanodevice, zwitterionic film grafting on silica nanoparticle holds much potential in the future. This review will discuss on the conceivable functional chemistry approaches, some of which are potentially suitable for the assembly of such stealth systems.

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1. Introduction

Ever since Yanagisawa et al. reported on producing three-dimensional network of mesoporous (2–4 nm) silica films in 1990 [1] and the subsequent development of the popular surfactant-templated synthesis by Kresge et al. in 1992 [2], mesoporous silica (MS) nanoparticles have evolved to become an attractive material as nanoparticles for biological applications. The popularity was due to its excellent biocompatibility as well as its high thermal and mechanical stability. Various types of mesostructures can be easily assembled through tailoring of the surfactant template (spheres, fibers, cubic and nanorod etc). Being one of the mostly widely used materials in nanotechnology, its surface chemistry is well understood, highly flexible and its pore dimensions can be easily tuned. MS nanoparticles can reach extremely high surface

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area (900 m^2/g) [1] and demonstrate good thermal and chemical stability, thus rendering it as an excellent medium for drug delivery/transfection agent [3,4]. It had found a healthy repertoire in many bioimaging [4,5], biosensing [6] and gene/drug delivery platform [7,8].

While in-vitro application of MS nanoparticles had been widely reported, one of the major challenges that researchers still face is the maintenance of longevity of the circulating MS nanoparticles when administered in biological environment. This is because that in the serum-rich environment in the body, unmodified nanoparticles would undergo opsonization or coating on the surface by opsonin proteins almost instantly upon administration. This results in the attraction of phagocytic cells towards the nanoparticle target and trigger immunogenic responses that ultimately lead to faster clearance from the body [9]. Furthermore, the phagocytes cannot normally destroy non-biodegradable MS nanoparticles and this may further produce on-site accumulation of these particles in liver and spleen, resulting in many other adverse side effects [10,11]. Hence, biofouling and particulate agglomeration of nanoparticles are by far some of the most pressing issues to address prior to commercialization of nanoparticle-based biosensors.

One of the ways to address the biofouling issue is to render nanoparticles "stealthy" (impervious to protein adsorption) by means of changing the surface chemistry. In fact, surface modifications on MS nanoparticles is fast becoming an essential feature in nanoparticle research and given a wide berth of biological based applications reported, ranging from drug delivery to biosensing/cell imaging, the importance of introducing an anti-biofouling layer cannot be understated. A wide range of methodologies for the nanoparticle design meant for biological applications had already been already discussed in literature but what is more important is the chemistry at this very top layer of the MS nanoparticle's surface that biofouling issues must be addressed. That is where cellular materials and nanoparticles would interact at the very first instances. So far, anti-biofouling properties on the surface of nanoparticles are typically achieved by introducing specific organic layers that will alter some fundamental surface properties such as surface charges and hydration.

Of these, zwitterion-based surface modifications is fast becoming one of the most interesting and efficient ways of introducing highly efficient anti-biofouling films on surfaces. There are numerous ways by which zwitterionic films can be grafted onto the surface of MS nanoparticles. In this review, we sought to discuss many of the common reaction mechanisms used on silica surfaces as well as some of the bioconjugation chemistries that can potentially be feasible on the surface on MS nanoparticles to form covalent linkage to the surface and for the subsequent development of a zwitterion layer on the surface. And prior to discussing the strategies of grafting zwitterion films on MS surface, it is important to examine some of the fundamental aspects of anti-biofouling modifications.

2. Surface hydration and anti-biofouling properties

In the past, many different types of anti-fouling chemical layers had been grafted on the surfaces to produce stealth-like behavior that can efficiently repel protein binding. As early as the 1970s, several groups had reported a reduction in protein adsorption on OH-rich Hydroxylethyl methacrylate (HEMA) modified surfaces [12,13] although it was only in the 1980s when Andrade et al. suggested the notion of surface hydration as a viable reason behind the repellent of proteins on surfaces [14] and this was heavily influenced by earlier studies on 'non-freezing water' layers on phospholipids [15,16]. The solvation interaction energy between proteins and polymer surface was also found to have a significant effect on protein dehydration due to the shedding of the hydrated layer, as proposed by Lu and his coworkers in 1991 [17]. Tsuruta et al. later suggested in 1996 that the entrapment of proteins on surface was a physicochemical phenomenon arising from a readjustment of a perceived "water network" formed on surfaces of hydrophilic polymers and that fouling is also a time dependent process [18]. Over time, it became gradually accepted in mainstream literature that when a layer of water is tightly bound onto a surface, a physical/energetic barrier is formed and this barrier can subsequently discourages the adsorption of incoming proteins. It is also important to note that there are also two types of water–substratum interaction needed to consider, one forming from hydrogen bonding (typical of hydrophilic surface) and the other arising from ionic solvation (on zwitterionic surface). In order for proteins to be absorbed onto the surface, the water layer had to "make room" to facilitate for the protein adsorption. How nanoparticles can gain its anti-biofouling property is through retaining a surface hydrated layer so tightly that the energy required to displace this layer during protein adsorption is highly energetically unfavorable. The strength of water retention on the surface is strongly influenced by the physicochemical property of the material, packing density, as well as thickness of the material. The influence of steric repulsion may also play an important role especially when dealing with long chain polymeric based stealth layers.

In terms of chemically modified surface stealth layer based on the principle of hydration on surface, there are currently two major classes of anti-biofouling layers commonly described in literature for the realization of anti-biofouling surface coating; *polyhydrophilic and polyzwitterionic*.

2.1. Polyhydrophilic

Traditionally, polyhydrophilic materials are the most widely used surface modification for anti-biofouling applications in literature. The most common characteristics of polyhydrophilic materials are their hydrophilicity as well as having region of rich hydrogen bond acceptor/donor sites. Of the many models in literature, the most popular in polyhydrophilic surface modification is poly(ethylene) glycol (PEG) and its structural derivatives.

PEG is typically synthesized via anionic ring opening polymerization of ethylene oxide that is initiated by nucleophilic attack of a hydroxide ion on the epoxide ring. At high molecular weights, PEG is not immunogenic as there are no known anti-PEG antibodies that had been generated in the body against Pegylated nanoparticles. As early as 1994, PEG was used in conjunction with biodegradable polymer (PLA) to form anti-biofouling nanoparticles [20]. However, the examinations were rather rudimentary (involving the co-incubation with albumin) and the design was of a block copolymer type rather than the distinctive layers of core/shell. Nonetheless, the results were sufficiently encouraging to sprout a subsequent following [21,22]. It must be said that while a copolymer based nanoparticle can help resist biofouling, there will definitely some issues pertaining to drug delivery and gene delivery, especially if the nanoparticle is required to 'home' towards a particular cell type. This is due to the overall hydrophilicity of the nanoparticle surface that not only rejects incoming proteins but would also reject its intended cell target as well.

Nonetheless, PEG based materials had ever since been a mainstay candidate in literature for surface modifications due to its excellent protein repellency behavior, especially for those of high molecular weight and had consequently received much research coverage. The protein repellency effect has been broadly described as a formation of initial thin layer of water on surface that effectively inhibited proteins from attaching and this is namely due to the steric entropy arising from the unfavorable change in free energy if the surface film is to undergo dehydration as well as confinement of polymer. Monolayers of PEG derivatized films can conferred a high degree of monodispersity of nanoparticles but in the case of dense layer of PEG polymer, the conformational freedom can be highly restrictive and may limit the possibility for further performing further conjugation chemistry. Nonetheless, they had demonstrated excellent protein repellent properties with a major advantage of size dependent circulation time within the body, i.e. the higher the molecular weight, the longer the undetected circulation