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REVIEW

Plasmonic nanoparticles in biomedicine

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Summary The use of plasmonic nanoparticles for biomedical applications has been extensively researched, yielding significant advancements in the construction of ultrasensitive bioassays and effective therapy. The unique surface plasmon resonance phenomena of both plasmonic films and nanoparticles with their exceptional absorption and scattering abilities have much potential in revolutionising diagnosis, treatment and evaluation of diseases, in particular cancer. In this review, an overview of recent advancements of plasmonic nanoparticles in the fields of bioassays and therapy is provided, with an emphasis on the mechanisms by which the plasmonic nanoparticles can be employed to enhance or provide signals for the detection of bioanalytes or to treat diseases.

Introduction

Metallic nanostructures have been of particular interest due to their ability to interact with electromagnetic radiation, making them suitable for many biomedical applications, including diagnostics [1,2], therapeutics [3,4] and even the alteration of gene expression [5,6]. The ability of metallic nanostructures to interact with electromagnetic radiation stems from their confinement of electrons to produce quantum effects [7]. One of such effects is the surface plasmon resonance phenomenon, whereby incident light striking thin metal films or nanostructures causes the collective oscillation of electrons at a resonant frequency in these metal films or nanostructures [8]. This results in the intense absorption or scattering of light by the metallic nanostructures, which when coupled to fluorophores or Raman-active molecules, give rise to phenomena like metal-enhanced fluorescence [9] and surface-enhanced Raman scattering [10]. By increasing the intensities of existing signals of fluorescent or Raman labels, assays which employ these labels, for example immunoassays and nucleic acid assays, can have greatly enhanced sensitivities should plasmonic films or nanoparticles be introduced. In addition, plasmonic films or nanostructures can themselves act as sensors by transducing changes in bulk or local refractive index into shifts of their plasmonic bands of absorption in their UV-visible spectra [11]. Such an approach avoids the need for labelling of target analytes with fluorophores or Raman labels, of which blinking and bleaching are problems associated with the former [12,13]. Intense absorption of near-infrared radiation by the metallic nanostructures also causes photothermal heating of their surroundings and the generation of radicals that can be used for therapeutic applications [14,15]. Noble

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metal plasmonic nanostructures like gold and silver nanoparticles are most commonly used due to their relative inertness and visible and near-infrared absorption bands [16], with gold nanoparticles popular for its biocompatibility while silver nanoparticles have larger molar extinction coefficients, giving more sensitive assays [17]. This review focuses on offering a broad perspective for the use of plasmonic platforms in biomedicine like bioassays and therapy. In the following sections, the plasmonic platforms are reviewed with typical mechanisms for the plasmonic approach to biomedical applications. We hope that this article will provide a comprehensive coverage of current standings of this field and offer new perspectives into the development of plasmonic materials for more effective bioassays and therapy in biomedicine.

Bioassays

Metal-enhanced fluorescence

Plasmonic enhancement of fluorescence occurs due to the coupling of fluorophores to the strongly confined electromagnetic fields of plasmonic nanoparticles or plasmonic metal films [18]. These strongly confined electromagnetic fields are generated as a result of interaction between light and localised surface plasmons of plasmonic nanoparticles or surface plasmon polaritons for films. The plasmonic materials then relay the radiation outward, increasing the radiative scattering efficiency of the fluorophores [19]. More recently, interactions between plasmonic nanoparticles and fluorophores were explained by the radiating plasmon model, whereby the enhanced emissions and decreased lifetimes of the fluorophores are due to the coupling of the fluorophores at their excited states with surface plasmons of the nanoparticles [18]. For the construction of metal-enhanced fluorescence assays, the distance-dependence of metal-enhanced fluorescence has been extensively employed. To further improve the sensitivity of metal-enhanced fluorescence, different strategies targeting the individual components of fluorescence assays have been developed. Also, studies have also been done to improve the practicality of such fluorescence assays.

Bioassays based on distance-dependence of metal-enhanced fluorescence

The fluorescence enhancement by plasmonic nanoparticles or plasmonic films has been shown to be dependent on the distance between the fluorophore and the plasmonic nanostructure [20]. Quenching occurs when the fluorophore is close to the plasmonic surface, while fluorescence is greatly enhanced when the distance between the fluorophore and the plasmonic surface increases beyond the quenching distance [21]. To study such distance-dependence, numerous approaches have been proposed to control the distance between the fluorophore and the plasmonic surface [21—28]. These include the use of DNA spacers [22,23], the layer-by-layer technique [27,28] and the deposition of and SiO_2 [28]. These approaches, however, are limited in the control of the thickness of the spacers. Chi et al. used the polymerisation of oligo(ethylene glycol)methacrylate to deposit thin polymer films on gold, a highly controllable process, to study the distance-dependence of metal-enhanced fluorescence of gold [29]. Fluorescence was found to be quenched when the fluorophore and the gold surface were 15 nm apart, while fluorescence enhancement was observed with an increase in the polymer thickness beyond the quenching range for films that are tens of nanometres thick, with a maximum enhancement with a 39-nm thick film.

Two different approaches exist for the use of the distance-dependent property of metal-enhanced fluorescence for bioassays, namely the quenching-to-coupling approach [22,30,31] and the signal enhancement approach [32,33]. The quenching-to-coupling approach refers to a 'molecular beacon-like' approach whereby a single molecule, usually DNA, conjugated to a fluorophore acts like a molecular beacon, with initial quenching of the fluorophore due to close proximity of the DNA—fluorophore conjugate to the plasmonic nanostructure. Subsequently, the molecule of interest binds, resulting in a change in the configuration of the DNA holding the fluorophore and the increase in distance between the fluorophore and the plasmonic nanostructure, resulting in coupling and hence de-quenching [22]. Some examples include that reported by Peng et al. who demonstrated the use of a DNA hairpin probe conjugated to a fluorophore and bound to silver nanoparticles immobilised on a glass slide [34]. The fluorophore was thus quenched in the absence of the target DNA due to its close proximity to the silver nanoparticles while fluorescence was restored with the hybridisation of the target DNA as the hairpin DNA changed its configuration, moving the fluorophore away from the surface of the silver nanoparticles. Li et al. reported the potential-dependence of the reorientation of DNA being investigated by metal-enhanced fluorescence [35]. Applying a positive potential caused the double-stranded DNA conjugated to the fluorophore lying on the electrode surface, thus resulting in fluorescence quenching, whereas, a negative potential resulted in the perpendicular arrangement of the DNA—fluorophore conjugate and the restoration of fluorescence. However, in addition to the large increase or decrease in fluorescence intensity, a slow relaxation process occurred whereby fluorescence intensities were restored to intermediate values (Fig. 1). Such findings may be able to facilitate advanced electrochemical detection of DNA in future. Moreover, Degliangeli reported the direct detection and quantification of microRNA with a very low limit of detection of 0.2 fmol without any target amplification [36]. This was performed using DNA probes conjugated to a fluorophore which were immobilised onto gold nanoparticles. In the absence of a target microRNA, the fluorophore remained close to the gold nanoparticles and its fluorescence was quenched. In the presence of the target microRNA, the DNA-microRNA hetero-duplex was formed and cleaved off the gold nanoparticles by the endonuclease duplex specific nuclease. Such cleavage resulted in the diffusion of the fluorophore away from the gold nanoparticles, allowing the fluorescence signal to be observed. Signal enhancement can also occur as microRNA remains intact after cleavage as shown by the attainment of the maximum fluorescence intensity whether microRNA was added in excess or in defect. Given that the fluorescence maximum was reached