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Nanoparticles as Biomarkers and Biosensors

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Abstract

Biomarker, a measurable indicator of some biological state or condition, has journeyed for better from organic fluorescencent substances to chalcogenide quantum dots to biocompatible metal oxide semiconductor nano particles. Single-band up-conversion nanoparticles have been realized doing away with any kind of spectral interference with the living cell autoflourescence. Zinc oxide based thin films and nanostructures have shown striking performance due to its high isoelectric point and other multifunctional characteristics besides non toxic nature to in vivo applications. Rare earth doped ZnO and $ZnAl_2O_4$ nanoparticles can be used as biomarkers. Also, nanomaterials such as nanoparticles, nanorods, nanowires, etc. offer large surface to volume ratio and therefore they can offer high sensitivity. Added with the advanced nanofabrication techniques ZnO based portable biosensors will not remain a dream but still a lot of diligence is required to achieve the target.

Introduction

A biomarker generally refers to a measurable indicator of some biological state or condition, for example presence of life in an organism or disease in the organism. A biomarker is a detectable or traceable substance which can be already present or can be introduced into an organism to examine certain organ function. Biomarkers indicate a change in the state of a protein that correlates with the risk or progression of a disease, or with the effect of given medicinal treatment. Detection of biomarkers requires biosensors bioanalytical devices which take shape on integration of disciplines like engineering, medical, physical and biological sciences. Thus the efficacy of biosensor lies in the capability to deliver an unambiguous measurable output signal response for either diagnostic or therapeutic purpose when a biomarker interacts with the transducing surface of the sensor. Nanomaterials such as nanoparticles, nanorods, nanowires, etc. effectively improve the performance characteristics of a biosensor [1-3]. Nanotextured surfaces intensively impact the sensor performance offering unique features besides increased surface area for bimolecular binding [4,5].

Metal oxide based nanoparticles as biomarkers

Though organic fluorescence biomarkers are widely used in biology and medicine [6,7], they fall short of good resolution of marker's emission from cell's auto fluorescence during in vivo studies due to their quite wide emission and excitation bands. Moreover, marker excitability reduces upon excitation resulting in fall of the signal. To this handicap, a solution can be found in semiconductor based nanoparticles. Initially chalcogenides viz. CdTe, CdS and CdSe nanoparticles (NPs)/quantum dots (QDs) were taken with their surface capped using relevant material to obtain selectivity [8,9].

The signal intensity thus obtained is much higher than the auto flourescence of the living tissues and also than that obtained from in use flourescent dyes but the debilitating parts are

i. fluctuations of emission energies as a function of size of QDs [10],

ii. fluorescence intermittency [11-14] and

iii. the toxicity of Cd which has a lot of chances to be freed from its compound due to photolysis and/or due to slow dissolution effected by the living cells and bodily fluids.

In order to overcome these shortcomings, biocompatible metal oxide semiconductor nano particles ZnO, $ZnAl_2O_4$ and ZrO_2 came in as biomarkers. Their luminescence is activated using rare earth ion dopants [15] so that the emission spectra be a function of RE properties and not that of the size of nanoparticles. For this reason size of the NPs is kept much larger than the QDs. A control on their shape, size, morphology and crystallographic phase can be had by choosing appropriate method of synthesis and/or optimization of various process parameters/chemicals [16,17]. Wet chemical methods hydrothermal, microwave assisted hydrothermal method [18], sol gel method [19,20], and pulsed laser ablation in liquid medium [21] may be used for synthesis of

NPs. Photo excitation of RE doped oxide nano biomarkers using visible light avoiding ultraviolet radiation which is highly toxic for living cells is explored [18]. Along with biocompatibility, biodistribution and elimination of the marker from the human body is also important. Emission from such biomarkers and that from cells have unambiguously different decay times and therefore a time resolved PL can separately detect them. The 4f-4f excitation of RE intra shell transitions leads to weak emission whereas 4f 5d or charge transfer excitations [22] limit the choice of hosts. However, use of Y_2O_3 in RE doped oxide nanoparticles is a way out. ZrO_2 nanoparticles doped with Pr, Tb or Eu and stabilized by Y_2O_3 make the system very attractive for biological and medical applications [17,22].

RE doped ZnO NPs exhibit strong defect related wide PL bands [23] but Al codoping of ZnO: Eu nanoparticles improves the situation [18]. Intense RE emission was obtained for Pr doped ZrO2 NPs [24] involving two photon infrared (IR) excitation process thereby completely getting rid of cell's auto fluorescence. These NPs were tested on adult mice and results were encouraging regarding quick uptake, biodistribution and elimination from the body [25,26].

Detection of biomarkers - Biosensors

Preparation of ssingle-band up-conversion nanoparticles with different colors have been reported [27] which could achieve the multiplexed simultaneous in situ biodetection of biomarkers in breast cancer cells and tissue specimens. Better simultaneous quantification of proteins as compared to classical immunohistochemical (IHC) technology was obtained. Sensitive, selective and multiplexed molecular detection is needed for gene and protein profiling, drug screening and clinical diagnostics [28-30]. For cancer diagnosis, the identification of potential diagnostic biomarkers and target molecules among the plethora of tumor onco-proteins is required.

An unfailing but simple technology is required for quantitative analysis of biomarkers existing simultaneously/dynamically in tumour cells and tissues [31-35]. Diagnosis as well as prognosis of tumours is based on classical immunoenzyme based IHC methods with single wavelength detection. Reproducibility of results using IHC is not up to the mark as it is a semi quantitative method to which heterogeneity of most of the tumours adds up as a difficulty.

For such situations fluorescence imaging with optical microscopy is a better alternative offering higher detection sensitivity and direct relationships for biomarker quantification and prediction of therapeutic response. Though the results obtained using fluorescence dyes regarding protein biomarkers are closely related with the clinical finding but the photo bleaching occurring in organic dyes during multicolor fluorescence measurement poses severe limitations [36-38]. Moreover, separate excitation wavelengths or sources are required. These limitations can be overcome by quantum dots (QD). QDs are few nanometers sized semiconductor particles with their optical and electronic properties remarkably different from those of larger particles. Many QDs show electro or photo luminescence and the emission frequencies can be precisely tuned by changing the dots' size, shape and material, giving rise to potential applications viz. medical imaging besides transistors, solar cells, LEDs, diode lasers, second harmonic generation and quantum computing. Being more photo stable and excitable in the same spectral range, QDs are advantageous as compared to fluorescent dyes provided any spectral interference with the intrinsic fluorescence of biological tissues is minimized, which can be effected by prolonging the illumination duration of QD stained specimens [39,40]. Spectral deconvolution of the data is also required and such techniques slow down the screening rate and sensitivity.

Another alternative is the use of rare earth up conversion nanoparticles (UCNPs), which can be excited by the wavelengths in the infrared region which are not absorbed by the tissue. Due to up conversion, photoluminescence emissions will be in the visible range. Rare earth ions with +3 oxidation states have much narrow emission line widths as compared to those from QDs thus reducing any inter emission overlap and thereby facilitating multiplexed detections of biomarkers [37,38,41]. Red and near infrared [42,43] single band up conversion emissions have been realized. A simple and brilliant method of achieving single band up conversion emission with different colors in the blue, green and red regions is reported [39] by coating the up conversion nanocrystals with a screen layer containing an organic dye with a high molar absorption coefficient as nanofilters to remove the unwanted emission bands.

The biomarker expression levels in breast cancer cell specimens determined using these single band UCNPs, standard western blotting (WB) and immunohistochemical technologies (IHC) exhibit excellent correlation among these three methods; however, the WB and IHC methods can probe only one biomarker at a time. Significantly, the application of antibody conjugated single band UCNP molecular profiling technology can achieve the multiplexed simultaneous in situ biodetection of biomarkers in breast cancer cells and tissue specimens and produces more accurate results for the simultaneous quantification of proteins present at low levels compared with IHC [39].

The single band UCNPs were prepared by b $NaGdF_4$:20% Yb, 2% Er@NaGdF4 (core nanocrystal), pure silica layer (spacer) and amino reactive organic dyes doped silica layer (selective nanofilter capping of the nanocrystals). The choice of the dyes is such that they absorb all the emissions except one and thus the layer acts as a filter.

ZnO as biosensor

Zinc oxide based thin films and nanostructures have shown unparalleled and promising performance due to high isoelectric point and other multifunctional characteristics. Further being

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biocompatible, ZnO has extensively been studied as a material for biosensor development. The fascinating properties of ZnO help retain biological activity of the immobilized biomolecule and help in achieving enhanced sensing performance. And the technological advancements have transformed the diagnostic biosensors to a hand held portable one. ZnO can form anisotropic nanostructures such as nanoparticles, nanorods, nanowires etc. and therefore has capability to recognize biomolecules, deliver drug particularly in the treatment of malignancy and to be used for novel bioelectronics devices [44,45].

Due to its wide band gap of 3.37eV and fast electron transfer kinetics, ZnO is an appropriate material for designing electrical or electrochemical sensors. ZnO due to inherent inhomogeneities zinc interstitials and oxygen vacancies in its structure exhibits different binding affinities for various functional groups such as thiol, carboxyl and phosphonic acid groups [46-48]. Biomarkers indicative of pathophysiological conditions, which include proteins, enzymes or metabolites, are released into bloodstream when cardiac muscles experience stress due to ischemia [49]. Measurement of these biomarkers helps in diagnosis and prognosis of diseases. For the purpose, ZnO biosensors are promising as they meet the clinical requirements but still a long journey is required for making them a regular diagnostic tool.

Conclusion

Biomarkers and biosensors take shape with the integration of engineering, medical, physical and biological sciences. Organic fluorescence biomarkers which are widely used in biology and medicine do not offer good resolution between marker's emission and cell's auto fluorescence during in vivo studies due to their quite wide emission and excitation bands. Capped CdTe, CdS and CdSe quantum dots give good signal intensity but pose a severe problem of toxicity. Rare earth doped metal oxide semiconductor nano particles ZnO, $ZnAl_2O_4$ and ZrO_2 are promising biomarkers. Nanomaterials such as ZnO nanoparticles, nanorods, nanowires, etc. offer large surface to volume ratio besides being biocompatible and therefore they are used for biosensing with high sensitivity. Added with the advanced nanofabrication techniques ZnO based portable biosensors will not remain a dream but still a lot of diligence is required to achieve the target.

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