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A Mini-Review of Nanotechnology and Prostate Cancer: Approaches in Early Diagnosis

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ABSTRACT

The most important aspect of cancer treatment is early diagnosis. The best serum marker currently available for diagnosis of prostate cancer (CaP) is serum prostate-specific antigen (PSA). However, PSA test does not have high specificity and is not reliable for differentiating benign prostate hyperplasia, non-aggressive CaP and aggressive CaP. In the past decade, great efforts have been made in the development of novel biosensor-based strategies for detection of biomolecules and miniaturization assays for PSA. The emerging nanotechnology in recent years is expected to have a profound effect on healthcare and scientific research in the near future. Specifically, nanotechnology is foreseen to help solve one of the most challenging and longstanding problems of early cancer detection. The current mini-review summarizes the current knowledge and application of nanoarrays, nanosensors, liposomes, improved nanoparticles (dendrimers, diamondoids, gold-based nanoparticles, magnetic nanoparticles and quantum dots) and nanoelectronics in early diagnosis of prostate cancer. This mini-review highlights the most recent advances and innovative solutions in applications of nanotechnology for the detection of CaP biomarkers and early diagnosis of CaP.

Keywords: Prostate cancer, Nanotechnology, Diagnosis

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INTRODUCTION

Prostate cancer is the second most common cancer and the fifth cause of cancer death in men (1). Prostate specific antigen (PSA) is the most widely used tumor marker for diagnosis of prostate cancer (CaP). Elevated amounts of this biomarker in blood serum (more than 4 ng/ml) can be a sign of cancer (2). The importance of early detection in all cancers as well as in CaP is obvious; due to the fact that at early stages of cancer, treatment will be more effective (3). Nanotechnology can present unique approaches in cancer detection techniques and consequently, many efforts have been made to develop novel nanotechnology-based diagnostic tools to detect cancer at early stages (4). With the help of these tools, it would be possible to detect the smallest concentrations of PSA (or any other CaP biomarker). There are different nanoparticle-based molecular methods for early detection of CaP, which can be categorized in two main types of label free and label based (Table 1). Each method has some advantages with varied detection limits; however, all of them can potentially improve the current knowledge of CaP early detection.

The focus of this mini-review is to summarize nano-based CaP detection techniques currently in use or at research stage. First, the known biomarkers related to CaP detection will be discussed and then the latest nanotechnology-based CaP detection techniques will be introduced.

Table 1. Summary of different methods for CaP detection

Categories	Method (examples)
Label-based nano-biosensing	Fluorescent nanoparticles (Quantum Dot, Europium, Terbium Complex)
	Magnetic nanoparticles (Gold nanoparticle)
	Surface enhanced raman scattering (SERS) nanoparticles
Label-free nano-biosensing	Nano wire, Surface plasma resonance (SPR), Carbone nanotube, electrical biosensors, microcantilvers, Scanning tunneling microscopy (STM)

1. Prostate cancer biomarkers

In cell biology, a biomarker is defined as an agent that helps in the detection and isolation of a particular cell type. In medicine, a biomarker can be any substance that could be used for examining an organ function or other aspects of health (5). It can also be a biomolecule whose detection indicates a particular disease state, for example, the presence of PSA in blood serum, higher than a specific level can be sign of prostate hyperplasia or cancer (6-9). Different CaP biomarkers have been developed in recent years (Table 2). These biomarkers can be used in diagnosis tests and monitoring disease progression (9). Despite all the progress made throughout the years in developing new CaP biomarkers, CaP is still one of the most challenging cancers in men. Early, specific diagnosis is an important aspect of cancer treatment. The biomarkers presented bellow pose unique characteristics as well as some disadvantages. Hence, it is believed that no individual biomarker is ideal. The most sensitive, specific diagnostic tests would be those able to detect a combination of all these markers and this is where nanotechnology can be very useful.

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Table 2. Summary of important CaP biomarkers

Biomarker	Type	Localization *	Gene name	GO term** (Biological process)
Prostate specific antigen / Human kallikerin 3	Protein	Secreted	KLK3	Proteolysis (GO:0006508)
Prostate cancer gene 3	ncRNA	Extracellular	PCA3	-
Prostate stem cell antigen	protein	Plasma membrane	PSCA	negative regulation of ERK1 and ERK2 cascade (GO:0070373)
Prostate-specific membrane antigen	Protein	Plasma membrane	FOLH1	C-terminal protein deglutamylation (GO:0035609)

*Adopted from UniPortKB and GeneCard database
**Adopted from QuickGO

Prostate specific antigen, also known as the human kallikerin 3 (hk3) is a 33kD glycoprotein and a member of the family of human kallikerin proteins. It is also recognized as a neutral serine protease (6, 10, 11). It is secreted by pancreatic ducts, the prostatic epithelium and the epithelial lining of the acini (9, 12). When entering the circulatory system, PSA is quickly trapped by protease inhibitors, primarily 1-antichymotrypsin (ACT). However, an amount of it is cleaved by proteases and circulates in the lumen in its inactive form, free PSA (f-PSA). The complex of f-PSA and PSA/ACT is referred to as T-PSA (total PSA), which rises in serum during CaP. Hence, T-PSA monitoring can help in diagnosis of CaP. Prostate specific antigen usually exists in male serum at concentration of around 1 ng/ml, and its accepted normal cut-off value is 4 ng/ml (although there can be some age-specific augmentations). It should be noted that the cut-off limit of T-PSA between prostate hyperplasia and cancer is 4 ng/ml, and concentration of 4-10 ng/ml is considered as "diagnostic gray zone", which predicts the possibility of prostate carcinoma (6, 7, 10).

Different studies have demonstrated that various factors such as tumor mass, presence or degree of prostatic inflammation, circulating levels of growth factors and even presence of chemo-preventers can alter the serum PSA level, indicating the capacity of PSA as an ideal biomarker, not only in prostate disease, but also in tracing the state of progress (7, 13).

The human kallikerin 2 (hk2) is a member of the serine protease family with 80% amino acid sequence homology to that of PSA. The kallikeringene family has 15 members and the most important member of this family after hk3 (PSA) is hk2. Beside these, hk 4, 5, 8, 9, 10, 11, 13, 14 and 15 have been reported as novel biomarkers for detection of prostate, ovarian and breast cancers (12). The presence of kallilkerin in free and bound forms, in blood, has been frequently reported (9). The overexpression of hk2 in CaP was initially detected by immunohistochemical staining, and later confirmed by other investigations, not only in CaP, but also in prostatic intraepithelial neoplasia (7, 9). It is believed that co-usage of PSA and hk2 as biomarkers can improve the accuracy of CaP diagnosis tests (7).

Prostate cancer gene 3 (PCA3), also known as DD3PCA3 or PCA3DD3, is another known marker for CaP detection. It is a non-coding specifically overexpressed in most CaP specimens from the early stages. It was initially found by differential display analysis, a test in which mRNAs expressed in normal and tumor-bearing prostate tissues are compared. According to clinical studies, more accurate results compared to PSA-based tests can be achieved by choosing PCA3 as a biomarker (9, 12). The notable disadvantage of this biomarker is that urine testing requires prostate massage; in order to force the cells, especially tumor cells, to enter the prostatic

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urethra, which can result in some unwanted variation in total biomarker release, because of the differences in duration and intensity of the massage between patients. Therefore, the whole test in general is not efficient enough for clinical use (12).

Prostate stem cell antigen (PSCA) is an integral glycosylphosphatidylinositol-anchored protein that exists on the outer surface of the membrane. It is significantly overexpressed during prostatic intraepithelial neoplasia and CaP, making PSCA a great biomarker for diagnosis of prostatic diseases (14). This marker is another prostate epithelium membrane antigen whose expression rises during CaP stages. It is highly expressed in androgen-independent cancer cells. However, its low expression in normal prostate, kidney, brain and small intestine tissues has been reported. The advantage of this marker is that the level of PSMA could discern between late and early stages of CaP (9, 15).

2. Label-based nanobiosensing

Different and variable labels can be used in combination with nanotechnology for cancer detection. One of the most common methods is to use fluorescent properties for labeling. Quantum dots (QDs) are inorganic flurophores ranging from 2-10 nm in size. The size of the QD can determine its emission wavelength and color. Several features, such as their size variation, high levels of brightness and photo stability make QDs perfect tools in imaging and biological detection (16-19). These structures can be easily excited by a single light source, even white light. Other excitation sources are UV light, blue-violet filtered light and 405 and 488 nm lasers (16). On the other hand, QDs are much more resistant to photobleaching and are around 50 times brighter in comparison with fluorescent proteins and organic dyes (19). In an experience, Dong et al. have used water soluble CdTe QDs for CaP cells' detection. The CdTe QDs were initially coated by L-glutathione and then conjugated with mouse anti-human PSA antibody to directly detect CaP cells. Meanwhile, goat anti-mouse IgG was linked to CdTe QDs for indirect detection. The results showed that both direct and indirect labeling have strong fluorescence intensity (17). In another case study, Härmä et al. used 107 nm streptavidin-coated QDs including β-diketones entrapping N 30,000 europium molecules to detect PSA in mice and reported in vivo detection of CaP xenografts using antibody-coupled QDs (16). |In general, antibody-linked QDs can be used as great probes in cell imaging and cancer cells' detection (17, 18).

More recently, aptamer-conjugated QDs were developed to target membrane PSA, which can be applied in both imaging and smart drug delivery. Using aptamer conjugated CdSe/ZnS QD 490 (emission: 470-530 nm which overlaps excitation of doxorubicin ~480nm), it is possible to use fluorescence resonance energy transfer for imaging and targeted drug delivery sensing. The cited simultaneous imaging, therapy and sensing system has worked successfully in vitro (20). Recently, it has been shown that bioconjugated near infrared (NIR) QD probes can improve imaging and visualization of tumors, especially in deep tissues (21, 22). In order to prevent degradation of the QDs, specific modifications such as addition of amphiphilic triblock co-polymers (containing hydrophilic polymethacrylic segments, two hydrophobic segments of polybutylacrylate and polyethylacrylate) have been suggested. To improve bioavailability, biophile polymers like polyethylene glycol molecules can be added to QDs. In a case study, metastatic CaP cells in mouse bone (tibia) were successfully detected by PSMA antibody-conjugated NIR QDs. The detection limit of this technique was 500,000 prostate cells (0.5 mg of tumor mass) in mouse tibia (21).

Another label used for CaP detection is europium (III), which has been widely used as a nanoparticle, partly because of its long lasting fluorescent property. Streptavidin-coated and antibody conjugated europium (III) nanoparticles are good, modern detectors both in solid and liquid phases. Several studies have used this complex for the

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detection of various cell markers, including PSA (23, 24).

Fluorescent terbium nanoparticles are also handy materials that can be applied in bioassays and cancer diagnosis tests, partly because of their long lasting fluorescence lifetime. With either surface modifications or bioconjugation of antibodies or streptoavidin, terbium nanoparticles can become great, sensitive detectors. In addition, non-toxicity and high stability in basic solutions make these materials more beneficial in various conditions compared to other nanoparticles such as silica-based ones (25).

As a good replacement for fluorescence labeling, surface-enhanced Raman scattering (SERS) is a common technique used in biosensor development. It is used to investigate the vibrational properties of adsorbed molecules by the help of both visible and NIR light. In addition, SERS immunoassays based on antigen-antibody interactions have been widely used in development of biomarkers for early cancer diagnosis. In such assays, Raman dyes are used to label antibodies attached to the nanoparticle probe's surface; the light scattered from the Raman reporter molecule or RRM – which is usually a metal nanoparticle who gets excited in Raman spectroscopy- provides information about the vibrational quantum states of the molecule (2, 26, 27). Compared to fluorescent labels, SERS has some unique advantages: it produces sharper, more specific bands (10-100 times narrower), the excitation wavelength required for SERS is a function of size and composition of the nanoparticle, it could be used in a variety of environments for it is not sensitive to oxygen or humidity, it is less susceptible to photobleaching and has lower limit of detection (28). All these characteristics have made SERS an appropriate, modern diagnostic technique in cancer detection (29-31). Reports have been given on the usage of SERS in a sandwich-immunoassay format using antigen-antibody interactions for the detection of very low concentrations (1 pg/ml) of PSA(2, 27, 29). Another bioanalytical application of SERS is composite organic−inorganic nanoparticles, which are composed by aggregating Ag nanoparticles in the presence of Raman reporter molecules. Husdon and Chumanov used the same technique for in vitro detection of antigen in tissue specimens. They also managed to detect PSA in situ in epithelial prostate tissue (30). In another experiment, Cheng Sun and colleagues used nanoplasmonic resonators (NPRs) for sensitive detection of protease activity, including proteolytically active PSA, in real-time. This, this can be considered as a fast, sensitive and specific technique for one-step detection of proteases activities in very small samples (31).

Magnetic nanoparticles (MNPs) are generally derived from magnetic elements (iron, nickel, cobalt and their oxides), so they can be concurrently functionalized and directed by a magnetic field (32). Super paramagnetic iron oxide (SPIO) is a nano-probe used in cancer detection. Features such as magnetic resonance signal sensitivity, great MRI T2 contrast, low detection limit, low toxicity and excellent biocompatibility has made SPIO an ideal marker in magnetic resonance imaging (MRI). In an in vitro study, the PEG-g-PEI-SPIO complex with a single antibody (scAbPSCA) has helped decrease the MRI T2 signal intensity of CaP cells, resulting in improved imaging effects (14).

Beside early detection, magnetic nanoparticles have attracted a lot of attention as modern cancer therapy equipments. In thermotherapy, the temperature should reach up to 42 □C, while maximum temperature of 55 □C could be achieved in the prostate tissue thermotherapy by the help of MNPs (33).

Gold nanoparticles (AuNP) have great affinity to leaky tumor vasculature (which has been shown in tumor angiogenesis during tumor growth) and unique tumor retention capabilities. In the last decade, usage of gold

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nanoparticles in radio-sensitization of cancer cells, such as CaP cells has been reported (34, 35). Moreover, AuNPs are used as catalysts, for signal amplification in organic and electrochemical reactions. Das and colleagues have used AuNPs as catalysts for signal amplification of p-nitrophenol reduction to p-aminophenol. They reported the detection limit of 1 fg/ml for PSA (36). Moreover, different substances such as GA, a plant extract which is used as a food additive, can be used for increasing gold nanoparticles' stability under both in vivo and in vitro conditions. This biomolecule strongly binds to AuNPs on the protein matrix by the help of its glycoprotein backbone and creates a nontoxic nano-sized complex. The effectiveness of this technique has been shown in radiotherapy and prostate tumor regression without affecting non-target organs (34, 37). Using biobarcodes for nanoparticle fictionalization can help the sensitivity and specificity of CaP detection. Barcode DNA functionalized AuNPs for PSA are 300 times more sensitive than common immunoassays (38).

More recently, Xia et al. developed a colorimetric assay based on AuNPs coated with PSA peptide with a detection limit of 0.02 ng/mL for PSA (39).

3. Label free nanobiosensing

Nanowires are known for their high surface-to-volume ratio and high electronic conductance, which can be simply influenced by any surface perturbations, such as binding of macromolecules (40). By using silicon nanowires, Lieber et al. introduced a label-free, multiplexed method of PSA, PSA-alphal-antichymotrypsin, carcinoembryonicantigen and mucin-L detection (41). The immunological detection of T-PSA using n-type Ln2O3 nanowires and p-type carbon nanotubes on a field-effect transistor-based device has been also reported by Lin and colleagues (29, 30).

Nanotubes, especially CNTs are considered as one of the most promising candidates for nano-sized biosensors because of their electrical and mechanical characteristics. For example, label-free amperometric immunosensors, with CNT electrodes anchored to PSA-mAb, have been used for detection of PSA between the range of 0.25-1 ng/ml. Since prostate hyperplasia and cancer have a PSA concentration difference of 4 ng/ml, the cited electrochemical immunosensor could be beneficial in clinical detections (42). In another case study using the mean of differential pulse voltammetry, T-PSA was successfully detected using a SWNT-modified microelectrode immunoassays with detection limit equal to 0.25 ng/ml, which is more than the cut-off limit of T-PSA between hyperplasia and CaP (43). Yu and colleagues have fabricated SWNT forest platforms filled with multi-label, secondary antibody-SWNT bioconjugates for sensitive electrochemical immune detection of PSA in serum and tissue lysates (10). Gold modified carbon nanotubes can electrochemically measure PSA in only five minutes, with detection limit of 1 ng/ml (44).

The antibody-functionalized Au-gated AlGaN/GaN high electron mobility transistors (AlGaN/GaN HEMTs) are capable of detecting PSA at concentrations ranging between 10 pg/ml to 1 µg/ml. Since its minimum detectable concentration is even less than the cut-off value of PSA for clinical detection, the AlGaN/GaN HEMTs seem to be appropriate electrical biosensors in early cancer diagnosis (45). Jae-HyukAhn et al. have created a field effect transistor device that can detect PSA without much labeling process. In this device, anti-PSA molecules are immobilized on the surface of a molecular-sized nanogap, which is the location of marker (PSA) absorption. This absorption can change the threshold voltage, which can allows electrical detection of the specific binding of PSA (46).

Surface plasmon resonance (SPR) is an affinity-based optical detection technique that involves the interaction of light with electrons of a material, such as a metal (2, 47). This technology has advantages such as low sample requirement and real-time, rapid and

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label-free monitoring of biomolecular reactions (2, 48). However, one of the disadvantages of SPR is its low sensitivity. The specific binding of a biomarker such as PSA to its antibody can be monitored by using local SPR that allows detection of PSA concentrations as low as 0.1 pg/ml (49-51).

The topological and electrical differences caused by attraction of nanoparticle conjugated antibodies on a specific surface containing PSA antigen can be observed by label free scanning tunneling microscopy (41), which is capable of ultrasensitive electrical detection of PSA concentrations as low as 10 fg⁄mL has (52).

Microcantilevers can be used as chemical, physical or biological sensors by detecting changes in cantilever bending or vibrational frequencies (53, 54). Recently, nanocantilever sensors have been developed for detection of CaP tumor-associated antigens (55, 56).

Future perspectives and conclusion

Lifestyle changes, environmental pollutants and an increase in life expectancy are among the major causes of cancer throughout the world. Prevention and early detection of cancer are major health issues in many countries. Although molecular targeted biomarkers have dramatically improved cancer diagnosis in the past two decades, with a significant impact on the diagnosis and staging of CaP, development of new methods and new strategies is still essential.

Application of nanotechnology in molecular diagnostics is still in early stages; however, the application of nanotechnology and development of nanoparticle-based cancer diagnostics in medicine have experienced a rapid growth. It is believed that efficient, specific diagnosis of CaP is possible via tests that are able to detect multiple biomarkers. On the other hand, while PSA is now the most commonly used biomarker in cancer diagnosis and check-up tests, the low cut-off limit between prostate hyperplasia and CaP can cause inaccuracy in results. Nanotecnology gives us the opportunity to develop novel detection techniques with higher sensitivity, lower sample requirement and shorter analysis time on a miniaturized scale. Label based nanobiosensing introduces some unique imaging devices, such as fluorescent nanoparticles (quantum dots, europium, etc.) that have strong, long-lasting fluorescent activity. In addition, SERS nanoparticles can have sharper, more specific bands than fluorophores while being insensitive to humidity or oxygen. In addition, all these nanoparticles have size-dependant variety, allowing them to emit different wavelengths. Magnetic resonance signal sensitivity, low detection limits, low toxicity and excellent biocompatibility makes MNPs unique in cell tracking, MRI, bioseparation and tissue engineering. These nanoparticles can also be used in designing assays with low limit of detection and low antibody requirement. Moreover, label-free nanobiosensing systems like SPR, nanowire-based assays and microcantilevers make it possible to use unmodified samples, with the possibility of highly sensitive real-time measurement. As a good example, SWNT immunosensors are believed to be beneficial in designing novel bio-arrays for multiplexed detection of cancer biomarkers.

In summary, it is expected that nanotechnology will soon make it possible to have cancer test results available within minutes, resulting in reduced hospital or clinic visits, decreased costs and improved clinical outcomes. Finally, important issues such as reproducibility, specificity and cost per test need to be addressed for cancer diagnostic tests before nanotechnology-based platforms are introduced into clinical applications and commercialization.

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