Обзоры

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Use of Nanoparticles in Theranostics and Breath Analysis of Patients with Cancer

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The review reports on advances in nanotheranostics and breath analysis of patients with cancer over the past few years. It has been shown that carbon nanotube nanoparticles and other therapeutic agents made from new semiconductor materials are very promising for their use in such non-invasive and effective therapeutic technologies as photothermal and photodynamic therapy. Some semiconductor nanoparticles can also be used as biomarkers for certain types of cancer. Results of the breath analysis in oncology were reported.

Introduction

The death rate from cancer in the world is steadily increasing every year. About 10 million deaths were reported in 2020. Armenia is among the top five countries with the highest incidence and mortality from cancer in the Western Asia region. Cancer is currently the second leading cause of death in Armenia, accounting for 21% of all deaths [9]. This review article reports on major advances in nanotheranostics and breath analysis of cancer patients over the past few years. These new methods are impossible without using the achievements of modern physics of semiconductor nanomaterials and nanotechnologies.

1. Modern methods of cancer treatment

The only effective method of cancer treatment today is really a radical resection of the tumor. Of course, today chemotherapy and radiation therapy are the main treatments for almost all types of cancer. But huge advances in both therapies have not resulted in improved survival rates of more than 30% of patients. Conventional imaging modalities for the treatment of clinical cancer (eg, X-ray, CT, positron emission tomography, and MRI) are not always sufficient for early diagnosis and prognosis. This is prevented by serious toxic

side effects in patients, damage to the immune system, etc. In addition, continuous doses of chemotherapy drugs dramatically lower the chemical resistance (resistance) of the tumor and ultimately reduce the effectiveness of chemotherapy. Immunotherapy has made tremendous progress in the treatment of cancer, however, many patients suffer from systemic side effects such as allergic reactions. Despite the enormous progress in modern medicine, the development of new therapeutic approaches is needed.

2. Nanotheranostics

Note that Professor Niels Finsen was awarded the Nobel Prize in Physiology or Medicine for phototherapy based on ultraviolet light treatment. Some non-traditional cancer treatments that have recently been proposed are responsive to external physical stimuli and can be used alongside other current treatments. Such physical stimuli are not only light but also radio frequencies, magnetic fields, ultrasound, or X-rays. Currently, special nanostructures (NS) have been implemented for the diagnosis of cancer therapy (nanotheranostics) [30]. Note that in recent decades, nanobiotechnology has also opened up new possibilities for cancer treatment. Due to its unique potential for increasing surface area, nanomedicine has numerous advantages over traditional therapeutic methods. In this area, many nanocarriers such as metal oxide nanoparticles (NPs), black phosphorus, carbon nanotubes (CNTs), and other inorganic semiconductor nanomaterials can be used in the delivery of anticancer drugs both, and in preoperative conditions. Below, we discuss some of these semiconductor nanocarriers that are of interest due to their multifunctional applications in both the treatment and diagnosis of cancer.

3. Properties of carbon nanotubes (CNTs)

CNTs have attracted much attention from researchers in many fields, including biomedical ones, due to their unique structure and properties. In particular, their numerous applications are discussed in detail in review articles by the author [7] including the applications of CNTs in medicine noted in [4].

CNTs can be realized in the forms of single-walled (SWCNT), consisting of a single sheet of cylindrical graphene, and multi-walled carbon nanotubes (MWCNT), consisting of several concentric layers of rolled graphite. These concentric layers have an inner diameter of 1 to 3 nm and an outer diameter of 2 to 100 nm. The thickness of a single cylindrical carbon layer in SWCNT is 0.2 to 2 nm. SWCNTs have a higher length to diameter ratio. MWCNTs have a wider internal diameter compared to SWCNTs, which can provide more room for high drug loading. Usually, fresh prepared and non-functionalized CNTs have high cytotoxicity and do not dissolve in liquids. Their functionalization makes them soluble and biocompatible. The solubility

of CNTs in aqueous solutions can be sharply increased after their oxidation with strong carboxylic acids.

4. Photothermal therapy (PTT) and photodynamic therapy (PDT)

PTT as a non-invasive, non-traumatic and effective therapy offers local heating of tumor tissues directly using a source of near-infrared radiation (NIR), after which tumor cells become healthy (i.e. destroyed) [1, 21]. Photothermal therapy (PTT) and photodynamic therapy (PDT) are two methods that can be used to treat cancer and demonstrate non-invasiveness and minimal side effects compared to existing radiation therapy and chemotherapy.

As mentioned above, biological systems are known to have high transparency for NIR radiation with a wavelength of 700-1100 nm. It is also known that strong optical absorption of chemically functionalized SWCNTs is found in this special spectral wavelength range. As a result, the NIR light absorbed by the tubes is converted into heat, which is transferred into the tumor. The destruction of cancer cells can be achieved by heating the nanotube to 50–70°C by laser radiation with a high power density (3.5–35 W/cm2) for a sufficiently long time (3–4 min). Ex vitro measurements of heating a DNA-SWCNT solution with a concentration of nanotubes of 25 mg per liter by a laser with a wavelength of 808 nm at radiation of 1.4 W/cm2 even showed that in this way the formation of gas bubbles in the solution and even the possible boiling of the solution can be achieved. Thus, NIR irradiation of SWCNTs injected into a tumor can cause the death of diseased cells without damaging normal cells. As a result of laser heating of the tumor, diseased cells turn into healthy cells over an area at least more than one order of magnitude larger than the sizes of SWCNT.

Note that there is rapid progress in nanotechnology in the field of biomedicine due to the use of CNTs due to their physical and chemical properties and unique architecture, such as extensive surface area modification, high drug loading capacity, and excellent optical performance. CNTs can be used also as excellent transporters for drug but also play an important role in cancer treatment. Due to optimal functionalization, such limitations inherent in CNTs as not always satisfactory water solubility and toxicity to cells have now been overcome. But it is already clear that due to the increased biocompatibility and biodegradability of carbon tubes and their increased ability to penetrate into the tumor, the therapeutic properties in the treatment of cancer are improved thanks to CNTs that are one of the versatile nanomaterials with a wide potential for biomedical applications in the treatment of cancer.

Photodynamic therapy (PDT) is a physicochemical dynamic process that involves three main components: a photosensitizer (PS), light, and oxygen. All of these components interact with each other on the same treatment time scales.

The photodynamic process depends on the PS as well as on the nanomaterial itself. The NS absorbs a photon of light and passes from the ground state S0 to the short-lived exciting singlet state S1. This state and ground state are spectroscopic singlet states.

An excited photon can either return to the ground state, generating fluorescence, or go through a path in which the spin of its exciting electron is reversed, forming a relatively long triplet state [22]. On the other hand, a high probability of a transition from S1 to an excited triplet state S1 is possible. The triplet-excited PS can then directly transfer its energy to the substrate in the form of a proton or an electron. In cancer theranostics, PDT depends on the ability of PS to transfer energy from lasers to oxygen dissolved in the tumor to generate cytotoxic singlet oxygen 1O2. Its effectiveness is reduced due to inadequate oxygen supply to tumors. Thus, the cumulative dose of singlet oxygen is an important factor that is assumed to be a predictor of tissue damage. Singlet oxygen dose prediction based on measurable quantities contributing to photodynamic effects such as light, PS, and oxygen distributions is subject to dosimetry. Strategies, physical principles and methods for measuring direct and implicit dosimetry are summarized in a review article [8? 32]. PDT is effective in the window from 600 to 800 nm. In this wavelength range, the energy of each photon is moderate (~1.5 eV) to excite PS, but low enough to penetrate deep tissues and tumors. Monochromatic light can be easily directed into optical fibers. Together with a fiber optic light source and NP, next-generation cancer nanotheranostics allows PDT to be performed on desired tumor areas without the need for complex NSs that respond to visible or near-IR light to indirectly activate PDT. Finally, the main physical phenomenon that determines PDT in cancer theranostics is the transfer of energy into heat. Irradiation and PDT using SWCNT complexes have significantly increased the therapeutic efficacy of cancer treatment. SWCNT complexes can act as sensitizers for PDT. The photochemical property of CNTs to convert oxygen into singlet oxygen has been used as a method of killing cancer cells with cytotoxic oxygen.

PDT-based cancer therapy is currently at an early stage of development.

So, PTT and PDT techniques allow to kill cancer cells without damaging normal healthy cells, as well as in various cancer imaging modalities, including MRI, radionuclide, and NIR fluorescence imaging. CNTs also exhibit good RF absorption characteristics. CNTs can convert laser energy into acoustic signals and exhibit strong resonant Raman scattering and near-IR photoluminescence, which is advantageous for their use in cancer imaging. In addition, CNTs can be used in nanobiosensors for the early detection of various types of cancer. As noted above, the unique property of CNTs has been used as a method of killing cancer cells at elevated temperatures. The optical coupling of light to CNTs can be enhanced by CNT surface defects to increase the heating of nanotubes. It has been found that doping CNTs with boron and nitrogen impurities (p-type impurities) improves the characteristics of thermal destruction of tumor cells.

The safety of nanomedicine involving CNTs still requires more research in humans to confirm their feasibility in clinical applications.

The combination of PTT and PDT therapies for the treatment of cancer has been implemented in recent years, and several promising results have been presented. Note that CNT-based PTT therapy systems can be combined with chemotherapy and gene therapy methods to increase the effectiveness of cancer treatment. Finally, we also note that SWCNT is not the only nanomaterial that has been used to destroy cells. For example, Au nanoshells with a laser power of 4–35 W/cm2 and irradiation for 4 min were used in [32] for it. Many other NIR absorbing nanomaterials with lower laser power. and shorter exposure times for nanotheranostics will be discussed below.

5. Use of carbon quantum dots

As noted above, CNTs are promising nanotools for the treatment and diagnosis of cancer. Another type of carbon nanomaterials, carbon quantum dots (CQDs), will apparently also be in demand in the near future due to a relatively simple synthesis method, low cost, and environmental friendliness [33]. Well-known quantum dots (QDs) can generally be divided into two categories based on their chemical composition. QDs consist of elements from groups III to V of the periodic table in the first category. QDs consist of elements of II-VI groups of the periodic table in the second category. QDs are semiconductor nanocrystals (2 to 10 nm in diameter). They show superior fluorescent properties compared to conventional chromophores and contrast agents. QDs of the second group are potentially rather toxic.

There are researhes showing that QDs can be conjugated with CNTs, which makes it possible to use their new properties in cancer theranostics. Evidence suggests that CT can be used to image cancer cells, while CNTs destroy cancer cells through thermal ablation. The combination of these two nanomaterials has indeed made it possible to improve the electronic, optical, and biological properties, make biosensors, biological nanoprobes, as well as loading and delivery of nanoparticles into cells [34]. CNTs and QDs are useful research tools in cancer treatment because they have high mechanical stability and nanometric dimensions that allow penetration into normally inaccessible tumor sites [11]. Unlike spherical nanoparticles, the long and cylindrical shape of CNTs is a large internal volume that can be filled with a variety of biomolecules, from small derivatives to proteins [34]. This introduces the possibility of drug loading into an internal cylindrical region, which brings the constructs into a biocompatible form.

Thus, the conjugation of QDs with CNTs will make it possible to use the fluorescent properties of QDs, as well as the CNT photothermal platform, which will make them effective theranostic cancer agents.

6. New photosensitizers

The first report on PDT, based on a study by Yu. Ikada in 1997, found that C60 fullerene can successfully create singlet oxygen under light irradiation [31, 32]. However, fullerene and small organic molecules have a short excitation wavelength, low structural stability, low solubility, and activity, which lead to a delay in the development of PS for PDT.

Other FSs for PDT with light-harvesting ability to absorb visible light and near-infrared (NIR) and efficiently transfer energy are being actively developed. Carbon-based nanomaterials, such as graphite carbon nitride C3N4 (the information about this material was first published in 2014), black phosphorus BP (reported in 2015), and graphene quantum dots GQD (reported in 2012), have advantages - chemical inertness, high photostability, and good biocompatibility. The chemical composition and electronic structure of these materials are easily controlled [25]. Many types of organic PS have appeared, but the use of two-dimensional (2D) PS C3N4, BP and GQD are preferable.

The bandgap of 2D layered C3N4 has biocompatibility and excellent chemical stability [19]. The bandgap is 2.7 eV, and various versions of oxygen can be generated in the visible range. C_3N_4 by developing g- C_3N_4 QDs can absorb red shift light and increase absorption.

Phosphorus atoms in one layer of white phosphor-black are bonded to three other phosphorus atoms by chemical bonds, and different layers are linked by van der Waals interaction [18]. The bandgap BP depends on the number of layers and ranges from 2.0 to 0.3 eV. QDBP is suitable for biomedicine, and has good stability in the physiological environment without obvious cytotoxicity.

Graphene QDs also can be used as PS for PDT. The transverse size is usually less than 10 nm [35] compared to traditional PS, which provides such advantages as good biocompatibility, and high water solubility.

Surface functional groups and structural modifications have a significant effect on GQD. Therefore, surface modification and structural design can improve PDT GQD. Three-dimensional (3D) PSs based on fullerene C60 and its derivatives have a high quantum yield. Due to low solubility in aqueous solution and poor optical absorption in the visible and near infrared ranges, its use for PDT is limited. Note that red light and NIR light have the greatest depth (usually 1–3 mm) of penetration into the tissue at radiation in the range of 600–1350 nm. Optimization of the chemical structure can effectively improve the penetration depth. Microwaves can pass through all types of tissues, induce PDT in advanced cancer, and enhance the lethal effect of microwaves on tumor cells. In conclusion, PDT can provide accurate diagnosis and real-time assessment of therapeutic efficacy through imaging and use in combination with PTT, radiotherapy, chemotherapy, and gene therapy.

7. Analysis of the air exhaled by cancer patients

The analysis of the air exhaled by cancer patients compared with the analysis of the breath of healthy people may be one of the possible ways to establish an early diagnosis in some cancers. It is known that people with a certain type of cancer have a special smell. In addition, this non-invasive method is painless for the patient, which may be useful in the fight against the disease itself and does not give extraneous side effects [3, 5]. Is it possible to use volatile organic compounds (VOCs) as biomarkers of one or another type of tumor? Researchers analyzed the breathing of patients screening for tumors of the colon, stomach, pancreas, and gastric cancer [20, 26]. Recently, laryngeal cancer has been studied to try to identify a set of biomarkers that allow detection of the disease at very early stages of growth. Breath testing has also been able to identify and detect biomarkers in patients with lung, breast, and prostate cancer. VOCs exhaled by people with laryngeal cancer have been compared with those exhaled by healthy people. The results show that the concentrations of some molecules, such as ethanol and 2-butanone, are significantly higher in individuals with squamous cell carcinoma of the larynx.

These facts open up new prospects for researchers of the properties of semiconductor gas sensors, including those working at YSU. Some of the main applications of breath testing methodology are based on the use of "electronic noses", which operate using a series of nanosensors capable of "smelling" the breath of patients in order to apply the "nose" in clinical practice with relative ease. The development of a fast, relatively inexpensive "electronic nose" for early detection of volatile organic compounds will greatly improve prognosis and provide rapid access to effective cancer treatments.

It is known that the prognosis of cancer largely depends on its stage of development at the time of diagnosis. It is known that the chance of surviving cancer detected at an early stage can reach 90%, while the survival rate for advanced cancer approaches 10%. Survival is also highly dependent on the type of cancer. The search for cancer-related VOC signatures has led to studies looking at exhaled VOCs in lung, breast, colorectal, stomach, ovarian, liver, head and neck cancers, and early-stage malignant mesothelioma .Several studies have found evidence that lung cancer can be detected by VOCs in exhaled air. Owlstone Medical's FAIMS (field asymmetric ion mobility spectrometry) technology also has sufficient sensitivity to detect VOCs [15]. FAIMS has been used to detect and stratify ovarian tumors in ovarian cancer using VOCs in a patient's urine.

8. New therapeutic agents

Thanks to the use of nanotechnologies, the possibility of both destroying cancerous tissues with minimal damage to healthy tissues and organs, as well as

detecting cancer and eliminating cancer cells before they form tumors has increased [14]. The use of new therapeutic agents based on nanotechnology leads to a reduction in the risk of disease for the patient and an increase in survival. Some therapeutic nanoparticles for the treatment of solid tumors will be discussed below.

SnO_2

Highly porous SnO_2 fibers functionalized with platinum particles show a five times higher response to acetone than densely packed SnO_2 fibers and show significantly faster response even at low acetone concentrations. Platinum-decorated SnO_2 fibers show a significant improvement in toluene response. Such nanoparticle fibers can be used for accurate diagnosis of diabetes and possible detection of lung cancer (see also our results [6]).

WO_3

Tungsten trioxide WO_3 is a semiconductor material with a bandgap of 2.5–2.8 eV, which provides sensitivity to light in the visible wavelength range [24]. Nanoparticles and nanocrystalline WO_3 thin films have a wide range of applications in microelectronics and optoelectronics, smart windows, gas - sensitive devices, etc. [16]. Recently tungsten oxide has attracted much attention due to its promising biomedical applications. WO_3 nanoparticles significantly improve the visibility of tissue structures in x-ray imaging techniques in computed tomography. Tungsten oxide nanoparticles with photocatalytic properties have found application in PTT and PDT [16, 25, 33] as well as radiation therapy and can be used as a theranostic agent for simultaneous tumor CT and therapy (trimodal action: photothermal, photodynamic and radiation). In cancer theranostics, photoactive semiconductor nanoparticles should have two equally important properties: minimal toxicity in the dark (for normal cells) and maximum activity under irradiation (for tumor cells). Both of these requirements can be partly satisfied by changing the state of the surface and the state of the particles during the synthesis. Various types of nanostructured tungsten oxide have been reported. Methods for the synthesis of WO3 nanostructures have been developed. WO_3 nanoparticles have been shown to be non-toxic to breast cancer cells; they did not cause cell death in the studied concentration range (from 0.2 to 200 μg/ml) and only slightly reduced the metabolic activity of cells.

ZnO

Several in vitro studies have shown that zinc oxide nanoparticles (ZnO NP) can selectively target cancer cells with minimal damage to healthy cells [2, 29]. The antitumor activity of ZnO nanoparticles in solid Ehrlich carcinoma can serve as a basis for the development of new antitumor drugs [29]. The advantage of using ZnO nanoparticles with various particle sizes from 5 to 175 nm in cancer treatment is related to their cytotoxicity against cancer cells with minimal damage to healthy cells. ZnO nanoparticles have low cost of

production. Zinc oxide nanoparticles have proven to be cytotoxic in cancer cells and novel cancer treatment strategies, including ZnO.

Iron oxide and graphene

Various superparamagnetic 2D and 3D lauric acid-coated iron oxide nanoparticles and human serum albumin iron oxide nanoparticles are suitable as a chemotherapeutic agent for the potential treatment of breast cancer [32]. Iron oxide nanoparticles coated with citrate are used for magnetically controlled immune therapy. Rduced graphene oxide (rGO)-Fe_3O_4 nanocomposites are used in PTT [32]. The resulting rGO- Fe_3O_4 nanocomposite exhibited superparamagnetic properties and the ability to raise the ambient temperature by 18–20°C relative to the initial temperature.

Silicon and porous silicon

Silicon has ideal biocompatibility and biodegradability with biological systems. Silicon nanoparticles are excellent for hyperthermia, which involves local heating and killing of cancer cells by irradiation with light, RF radiation or ultrasound. Silicon nanoparticles are poorly visualized optically in size in contrast to porous silicon particles. Systems for controlled delivery of cancer drugs based on mesoporous silica nanoparticles have been proposed [17]. Mesoporous silica particles have attracted much attention due to their special properties [27]. Lu et al. showed that particles with a diameter of 50 nm are optimal for absorption by cells [21].

Hexagonal boron nitride (white graphene).

Hexagonal boron nitride (h-BN) is a promising material for cancer drug delivery. As a nanomaterial of small size, it quickly entered clinical practice. Recent studies have shown that h-BN is a potential candidate in biomedical sciences both as nanocarriers and nanoconverters. The multi-purpose properties of h-BN have attracted huge attention for use in the drug delivery system [35].

It should be noted that the new information, approaches, nanomaterials, and technologies discussed above are very interesting and promising, but their thorough testing in clinics and hospitals is necessary to understand their shortcomings and the possibility of their joint use and the compatibility of the patient's body with uses and the compatibility of the patient's body with other methods prescribed, treatment, drugs and radiation. It is necessary to develop the frequency and duration of medical procedures, etc. but the interest of doctors and physicists in the material presented in this review is obvious.

Conclusion

The article reports major advances in nanotheranostics and breath analysis of patients with cancer over the past few years. Methods of cancer treatment and nanotheranostics are discussed. Carbon nanotubes and many other therapeutic agents made from new semiconductor materials are very promising

for use in such non-invasive and effective therapeutic technologies as PTT and PDT. Laser illumination heats nanoparticles locally introduced into the tumor and made from these semiconductors. As a result, tumor cells turn into healthy ones. The search for volatile organic compounds can be used as biomarkers of particular cancer. The work also analyzes papers about breath analysis of gases exhaled by cancer patients and the use of this method for the diagnosis of various forms of cancer.

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Использование наночастиц в тераностике и дыхательном анализе онкологических больных

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В статье сообщается о крупных достижениях в нанотераностике и анализе дыхания пациентов с раковой опухолью за несколько последних лет. Обсуждаются современные методы лечения рака и нанотераностики. Углеродные нанотрубки и другие терапевтические агенты из новых полупроводниковых материалов весьма перспективны для использования в таких неинвазивных и эффективных терапевтических технологиях, как ФТТ и ФДТ. Лазерное освещение нагревает локально введенные в опухоль наночастицы, изготовленные из указанных полупроводников. В результате опухолевые клетки превращаются в здоровые. Поиск летучих органических соединений можно использовать в качестве биомаркеров той или иной раковой опухоли.

Նանոմասնիկների օգտագործումը քաղցկեղով հիվանդների թերանոստիկայի և շնչառական վերլուծության համար

Վլադիմիր Մ. Հարությունյան

Վերջին մի քանի տարիների ընթացքում նանոթերանոստիկայի և ուռուցքների շնչառական վերլուծության ոլորտում մեծ ձեռքբերումները ներկայացված են այս գրականության ակնարկում: Ցույց է տրված, որ նոր կիսահաղորդչային նյութերից պատրաստված ածխածնային նանոխողովակների նանոմասնիկները և այլ թերապևտիկ նյութեր շատ խոստումնալից են այնպիսի ոչ ինվազիվ և արդյունավետ բուժական տեխնոլոգիաներում օգտագործելու համար, ինչպիսիք են ֆոտոջերմային և ֆոտոդինամիկ թերապիաները: Ցնդող օրգանական

միացությունների որոնումը կարող է օգտագործվել նաև որպես քաղցկեղի որոշակի տեսակի բիոմարկերներ:

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