

THE ROLE OF NANOTECHNOLOGY IN CANCER TREATMENT AND DIAGNOSIS

Vanessa Micaela dos Santos Teixeira

Student of the Integrated Master in Pharmaceutical Sciences

Faculty of Health Sciences

University Fernando Pessoa, Porto, Portugal

12082@ufp.edu.pt

Ana Catarina Silva

Assistant Lecturer

Faculty of Health Sciences

University Fernando Pessoa, Porto, Portugal

Assistant Lecturer

Faculty of Pharmacy

University of Porto, Porto, Portugal

acsilva@ufp.edu.pt

Carla Martins Lopes

Assistant Professor

Faculty of Health Sciences

University Fernando Pessoa, Porto, Portugal

Researcher

Institute for Biotechnology and Bioengineering

University of Trás-os-Montes e Alto Douro, Vila Real, Portugal

cmlopes@ufp.edu.pt

ABSTRACT

Cancer treatment is one of the major challenges of modern medicine. Several attempts have been made, in order to find more successful treatments. Nanotechnology can be applied to target drugs to the surface or to the interior of specific cells. In addition, it can also be used in diagnosis and prognosis of diseases. Therefore, nanotechnology opened a new vast exploiting area for cancer treatment. The studies must go on to obtain tailor-made therapies, with low adverse side effects and improved efficacy.

KEYWORDS

Cancer; Nanotechnology; Therapeutic; Diagnosis.

RESUMO

O tratamento do cancro é um dos grandes desafios da medicina moderna. Várias tentativas têm sido feitas nesta área, com o objectivo de obter tratamentos mais eficientes. A nanotecnologia pode ser usada para direccionar fármacos para a superfície ou para o interior de células específicas. Estes sistemas podem ser usados no diagnóstico e prognóstico de doenças. A nanotecnologia surge assim como uma nova área de conhecimento do tratamento e diagnóstico do cancro. Os estudos devem prosseguir tendo em vista a obtenção de terapias individuais, com poucos efeitos adversos.

PALAVRAS-CHAVE

Cancro; Nanotecnologia; Terapêutica; Diagnóstico.

1. INTRODUCTION

Cancer is a widespread disease which has been extensively studied. Traditional treatments with chemotherapeutic agents impart lots of toxicity problems to patients, because they are not selective to tumour cells. The goal is to find a way of circumvent the problem, i.e., develop a system that could target therapeutics to cancer cells, avoiding the healthy ones.

Nanotechnology has been claimed as a new smart technology that produces systems with the ability of targeting drugs to specific sites in the body. Such systems include submicron nanoparticles (NPs) composed of several materials (e.g., polymers, lipids, virus, metals), or devices (e.g., carbon nanotubes and nanowires) (Cho et al.).

Although there is no thorough cure for cancer at later stages, cancer has a good chance to be treatable and the prognostic could be favourable if it would be detected prematurely. Therefore, the development of innovative technologies, specific and reliable for detecting cancer at early stages, with easy access to patients is a demand (Kateb et al.).

This review refers the different applications of nanotechnology in cancer treatment, diagnosis and prognosis. Future direction of research is also suggested.

2. NANOTECHNOLOGY AND CANCER DIAGNOSIS

Concerning cancer diagnosis, the main areas in which nanotechnology is being developed include: early stages cancer detection proteomics; improvement of sensitive and specific nanopatforms for simultaneous malignant mass analysis; identification of associated biomarkers; imaging diagnostics.

The traditional screening methods for cancer diagnosis are usually at the tissue level, which has low efficiency and specifically fails to detect cancer cells, namely at very early stages of the disease (Choi et al.).

Molecular imaging has become a high accurate area in cancer diagnosis. Advances in nanotechnology have demonstrated the promise of NPs for non-invasive tumour imaging (Lee et al.; Medarova et al.). Starting with single biomarkers, initial successes of nanotechnology in molecular imaging have been included in all imaging modalities such as optical, nuclear, ultrasound, computed tomography, and magnetic resonance imaging (MRI).

Extensive research has shown that NPs are taken up and accumulate preferentially in various cell lines, including cancer cells through an enhanced permeation and retention effect (Wang et al.). The specific size-dependent properties of the NPs (e.g., optical, electronic, magnetic, chemical and physical) allow to develop nanodevices, including target-specific and sensitive contrast agents, multimodality imaging probes, or even multifunctional reagents for *in vivo* imaging. Nanodevices have the potential to detect the presence of molecular changes associated with cancer, even when they occur only in a small percentage of cells, providing a rapid and sensitive detection of cancer-related molecules (Vishwakarma et al.). Different nanodevices have been applied in cancer diagnosis such as gold NPs, quantum dots, magnetic NPs, magnetic iron oxide NPs, carbon nanotubes and nanowires. Conjugated with drugs and targeting molecules, nanostructures have the potential for selective imaging of different human cancers (Pathak and Katiyar).

Gold NPs have been used as stable and versatile agents for molecules due to their special size-dependent optical properties (Yong et al.). According to their size and shape, gold NPs can absorb and scatter light from the visible to near-infrared region providing deep tissue penetration which is very important in *in vivo* imaging (Copland et al.). Modified gold NPs have been developed to improve their contrast properties and higher affinity to cancer cells than to healthy cells (Aaron et al.; Liu et al., "A One-Step"; Mani et al.).

Quantum dots (QDs), nanoscale crystals of a semiconductor material, are very stable light-emitters that are emerging as a powerful biomolecular and cellular imaging tool for better cancer diagnosis since their discovery. QDs have unique optical and electronic properties compared with traditional organic fluorescent dyes such as size-tunable light emission, improved signal brightness, enhanced stability of the fluorescence signal, and the ability of being excited with one source light and to emit simultaneously different fluorescence colors (Chan and Nie). They can be bioconjugated with targeting antibodies to detect molecular signatures (Gao et al.). QDs are excellent optical imaging nanoprobe for evaluating the specificity of tumour-targeting ligands *in vitro* in cancer cells and *in vivo* in animal cancer models (Wang et al.). QDs have also been integrated into nano-biochips to detect multiple cancer biomarkers, which can reduce the detection time compared to traditional enzyme-linked immunosorbent assay (ELISA) (Jokerst).

Other types of NPs (e.g., magnetic NPs, silica NPs and metal NPs) have also been investigated for cancer biomarker detection. Silica NPs doped with fluorescence resonance energy transfer dyes have been used for the optical differentiation of leukaemia cells (Chen et al.). Super paramagnetic iron oxide-based NPs have been used as precursors for the development of a target-specific MRI contrast agent. These nanostructures present great advantages for *in vivo* tumour imaging when compared to other types of NPs such as a long blood retention time, biodegradable materials, and a low toxicity (Lee et al.).

Carbon nanotubes represent another potential type of nanodevices for cancer biomarker detection which is currently being used to develop DNA biosensors. Carbon nanotubes-based biosensor with a field-effect transistor has been used for detection of lung cancer biomarkers from exhaled breath samples (Peng et al.). A multifunctional dendrimer-modified multi-walled carbon nanotube has been recently developed (Shi et al.). Dendrimers have a treelike, branched shape. The branching creates a large surface area into which several ligands can be attached. These structures have been used in MRI as contrast agents and they have aided visualization of various pathological processes.

Different types of nanowires (e.g., silicon, gold, conducting polymer) have also been applied to biomarker detection (Lee et al., "Nanogram"; Fan et al.; Fang et al.). Functionalized nanowires are coated with capture ligands (e.g., antibodies or oligonucleotides) giving them excellent properties of selectivity and specificity (Nie et al.). In the presence of target molecules, the specific molecular binding will change immediately the electrical conductance within the nanowire that can be measured.

Other nanotechnology with an interest in cancer diagnosis includes cantilevers (Liu et al., "Nanogram") and nanopores. Nanoscale cantilevers can be used as components of biosensors. These can be coated with molecules (e.g., antibodies) capable of binding to specific biomolecules that only cancer cells secrete. When the target molecule binds to the antibody on the cantilever, produce a physical change of the nanostructured, which can be

monitors in real time. Nanoscale cantilevers can provide rapid and sensitive detection of cancer-related molecules. Nanopores based on antigen-antibody interaction have been investigated for detecting specific biomolecules related to cancer (Mirsaidov et al.).

3. NANOTECHNOLOGY AND CANCER THERAPY

Unfortunately, early cancer diagnosis is useless if not coupled with effective therapy. Conventional chemotherapeutic treatments are not selective, affecting both cancer and healthy cells, which induce severe systemic toxicity and produce drug resistance. A potential use of nanotechnology in cancer therapy is the specific targeting of malignant cells while sparing the healthy ones. This approach involves the attachment of monoclonal antibodies or cell surface receptor ligands to NPs, which can then bind specifically to cancer cells and allow delivery of smaller doses of toxic substances. Success of targeted therapies depends on the expression of the targeted molecules by cancer cells, which can also serve as cancer-specific biomarkers.

Different types of NPs and nanodevices are under different stages of clinical development. Due to its biological compatibility, lipids are one of the most promising strategies that can be used to prepare delivery systems, like liposomes and solid lipid nanoparticles (SLN). Currently, liposomal formulations of several chemotherapeutic agents (e.g., doxorubicin and daunorubicin) have been approved for treatment of metastatic breast cancer and Kaposi's sarcoma (Fanciullino and Ciccolini) or are currently in clinical trials. These drugs have also been successfully encapsulated into SLN (Kang et al.). **Coating the surface of NPs with polyethylene glycol (PEG)** is a common technique used to alter chemical formulations (liposome or otherwise) into "stealthy" NPs with increased circulating half-lives (Ferrandina et al.).

Biodegradable polymers have increased the application of different polymer-based drug delivery systems (e.g. NPs, micelles and dendrimers) in oncology. **Several kinds of polymeric based-NPs** (e.g. albumin, poly(alkylcyanoacrylate), poly(lactic acid), poly(glycolic acid), poly(lactide-co-glycolide)) are tested for the treatment of various cancers (Miele et al.). **Multi-functional polymeric micelles** for targeting ligands and/or imaging and/or therapeutic agents are being actively developed (Nasongkla et al.). Dendrimers are versatile particles regarding their size and functionality. The easily modifiable surface characteristic of dendrimers enables them to be simultaneously conjugated with several molecules including therapeutic drugs, targeting ligands and/or other components to increase cancer specificity (Wang and Thanou).

Viruses have been explored as nano-containers for specific targeting applications. Interestingly, there exists a subset of viruses with natural affinity for receptors of malignant cells that could be exploited for nanotechnology applications. For example, the canine parvovirus (CPV) utilizes transferrin receptors (TfRs), which are over-expressed by a variety of tumour cells, for binding and entry into canine and human cancer cells (Singh et al.).

Other nanodevices have also been used in cancer therapy such as gold NPs. Gold NPs are inorganic metal particles used for targeting tumours (Loo et al.; von Maltzahn et al.). When studied *in vivo* in mice, gold NPs were "stealthed" with PEG and shown to accumulate preferably at the tumour site due to the highly permeable, poorly organized vascular networks common in neoplastic tumours. Then, laser treatment of the bulk tissue selectively heats and destroys the nanoshell tumour regions within the tissue, while leaving **healthy surrounding tissue** intact (Feng et al.).

4. CHALLENGES AND FUTURE DIRECTIONS

The National Cancer Institute (NCI) has recognized the potential that nanotechnology holds for cancer prevention, earlier detection, and prognosis at premalignant stages and treatment. Assays that detect, accurately and quickly quantify, the presence of cancer-related biomarkers simultaneously on single tumour sections or small tumour specimens will be enabled by applying nanotechnology strategies.

Multifunctionality is the main advantage of NPs compared to conventional technological approaches. The future of nanodevices in clinical oncology will be passing by successful clinical application of radiolabeled multifunctional nanoplateforms, to allow combination of both molecular therapies and multimodality targeted molecular imaging. In addition, it is required that nanodevices allow specific *in vivo* drug delivery, without systemic toxicity, and that the dose delivered can be accurately measured noninvasively over time (Cai et al.). Concerning cancer treatment, future areas of nanotechnology innovation include the development of bioresponsive and self-regulated delivery systems. The most important innovations are taking place in drug delivery, which involves the development of new NPs formulations to improve drug bioavailability at specific sites and over a defined period of time, owing to an optimized therapy.

Although various radiolabeled nanocarriers have been effective in detecting and treating cancer in animal models (Kaijzel et al.), further preclinical, clinical and toxicity assays will be important for effective application in human patients.

Another important expectative of applying nanotechnology in medicine is the possibility to obtain a tailor-made therapy.

In the near future, nanotechnology will bring an important set of research tools and clinically helpful devices. The NCI expects new commercial applications in the pharmaceutical industry that will include new drug delivery systems and therapies. Finally, a shift from the possible to the potential will be made when nanorobots such as neuroelectronic interfaces and cell-repair machines are available (Banerjee and Mukesh).

5. CONCLUSION

Several nanoscale carriers (e.g., polymeric, lipidic and gold NPs, dendrimers, quantum dots) have been developed for the targeted delivery of cancer diagnostic and therapeutic agents. In addition, nanotechnology will enable earlier detection of cancer stages which will greatly improve disease prognostic. The current approaches for cancer treatment are still limited to surgical resection, radiation, and chemotherapy. These traditional strategies are highly invasive, nonspecific, often associated with traumatic side effects and toxicity, to both tumour and healthy cells. The promises of nanotechnology in cancer research lies on the potential to overcome these drawbacks. Advances in nanoimaging and nano drug delivery will drive the future of tailor-made and targeted cancer therapy. There are some nanodevices already available in clinical practice, which can concomitantly improve the efficacy and decrease the toxicity of currently existing drugs. NPs are able to detect, diagnosis, imaging, transport and controlled drug release, promoting target-specific tumour cell destruction, allowing greater efficacy with lower drug concentrations, more sensitive diagnosis, early detection requiring minimal amount of tissue and monitoring the progress of therapy over time.

6. REFERENCES

- Aaron, Jesse, et al. "Plasmon Resonance Coupling of Metal Nanoparticles for Molecular Imaging of Carcinogenesis *in vivo*." *Journal of Biomedical Optics* 12.3 (2007): 034-007.
- Banerjee, Hirendra N., and Verma Mukesh. "Application of Nanotechnology in Cancer." *Tech-nology in Cancer Research and Treatment* 7.2 (2008): 149-54.
- Cai, Weibo, et al. "Applications of Gold Nanoparticles in Cancer Nanotechnology." *Nanotech-nology, Science and Applications* 1 (2008): 17-32.
- Chan, Warren C., and Shuming Nie. "Quantum Dot Bioconjugates for Ultrasensitive Noniso-topic Detection." *Science* 281.5385 (1998): 2016-18.
- Chen, Xiaolan, et al. "Using Aptamer-Conjugated Fluorescence Resonance Energy Transfer Nanoparticles for Multiplexed Cancer Cell Monitoring." *Analytical Chemistry* 81.16 (2009): 7009-14.
- Choi, Young-Eun, Ju-Won Kwak, and Joon W. Park. "Nanotechnology for Early Cancer Detec-tion." *Sensors* 10.1 (2010): 428-55.
- Copland, John A., et al. "Bioconjugated Gold Nanoparticles as a Molecular Based Contrast Agent: Implications for Imaging of Deep Tumors using Optoacoustic Tomography." *Molecular Imaging & Biology* 6.5 (2004): 341-49.
- Fan, Yi, et al. "Detection of MicroRNAs Using Target-Guided Formation of Conducting Polymer Nanowires in Nanogaps." *Journal of the American Chemical Society* 129.17 (2007): 5437-43.
- Fanciullino, Raphaele, and J. Ciccolini. "Liposome-Encapsulated Anticancer Drugs: Still Wait-ing for the Magic Bullet?" *Current Medicinal Chemistry* 16.33 (2009): 4361-73.
- Fang, Zhichao, and Shana O. Kelley. "Direct Electrocatalytic mRNA Detection Using PNA-Nanowire Sensors." *Analytical Chemistry* 81.2 (2009): 612-17.
- Feng, Yusheng, et al. "Nanoshell-Mediated Laser Surgery Simulation for Prostate Cancer Tre-atment." *Engineering with Computers* 25.1 (2009): 3-13.
- Ferrandina, Gabriella, et al. "Pegylated Liposomal Doxorubicin in the Management of Ova-rian Cancer." *Clinical Medicine Insights: Therapeutics* 2 (2010): 261-70.
- Gao, Xiaohu, et al. "In Vivo Cancer Targeting and Imaging with Semiconductor Quantum Dots." *Nature Biotechnology* 22 (2004): 969-76.
- Jokerst, Jesse V., et al. "Nano-bio-chips for High Performance Multiplexed Protein Detection: Determinations of Cancer Biomarkers in Serum and Saliva Using Quantum Dot Bioconjugate Labels." *Biosensors & Bioelectronics* 24.12 (2009): 3622-29.
- Kaijzel, Eric L., Gabri van der Pluijm, and Clemens W. Lowik. "Whole-Body Optical Imaging in Animal Models to Assess Cancer Development and Progression." *Clinical Cancer Research* 13.12 (2007): 3490-97.

Kang, Keon W., et al. "Doxorubicin-Loaded Solid Lipid Nanoparticles to Overcome Multidrug Resistance in Cancer Therapy." *Nanomedicine* 6.2 (2010): 210-13.

Kateb, Babak, et al. "Nanoplatfoms For Constructing New Approaches to Cancer Treatment, Imaging, and Drug Delivery: What Should Be the Policy?" *Neuroimage* (2010) (in press).

Kwangjae, Cho, et al. "Therapeutic Nanoparticles for Drug Delivery in Cancer." *Clinical Cancer Research* 14.5 (2008): 1310-16.

Lee, Hyun-Seung, et al. "Electrical Detection of VEGFs for Cancer Diagnoses Using Anti-Vascular Endothelial Growth Factor Aptamer-Modified Si Nanowire FETs." *Biosensors & Bioelectronics* 24.6 (2009): 1801-5.

Lee, Jae-Hyun, et al. "Artificially Engineered Magnetic Nanoparticles for Ultra-sensitive Molecular Imaging." *Nature Medicine* 13 (2007): 95-99.

Liu, Xiong, et al. "A One-Step Homogeneous Immunoassay For Cancer Biomarker Detection Using Gold Nanoparticle Probes Coupled With Dynamic Light Scattering." *Journal of the American Chemical Society* 130.9 (2008): 2780-82.

Liu, Yongjing, et al. "Nanogram Per Milliliter-Level Immunologic Detection of Alpha-Fetoprotein with Integrated Rotating-Resonance Microcantilevers for Early-Stage Diagnosis of Hepatocellular Carcinoma." *Biomedical Microdevices* 11.1 (2009): 183-91.

Loo, Christopher, et al. "Nanoshell-Enabled Photonics-Based Imaging and Therapy of Cancer." *Technology in Cancer Research & Treatment* 3.1 (2004): 33-40.

Mani, Vigneshwaran, et al. "Ultrasensitive Immunosensor for Cancer Biomarker Proteins using Gold Nanoparticle Film Electrodes and Multienzyme-particle Amplification." *ACS Nano* 3.3 (2009): 585-94.

Medarova, Zdravka, et al. "In Vivo Imaging of siRNA Delivery and Silencing in Tumors." *Nature Medicine* 13 (2007): 372-77.

Miele, Eveline, et al. "Albumin-Bound Formulation of Paclitaxel (Abraxane ABI-007) in the Treatment of Breast Cancer." *International Journal of Nanomedicine* 4 (2009): 99-105.

Mirsaidov, U., et al. "Nanoelectromechanics of Methylated DNA in a Synthetic Nanopore." *Biophysical Journal* 96.4 (2009): L32-L34.

Nasongkla, Norased, et al. "Multifunctional Polymeric Micelles as Cancer-Targeted, MRI-Ultrasensitive Drug Delivery Systems." *Nano Letters* 6.11 (2006): 2427-30.

Nie, Shuming, et al. "Nanotechnology Applications in Cancer." *Annual Review Biomedical Engineering* 9 (2007): 257-88.

Pathak, Priya, and V. K. Katiyar. "Multi-Functional Nanoparticles and Their Role in Cancer Drug Delivery – A Review." *Journal of Nanotechnology Online* 3 (2007): 1-17.

Peng, Gang, Elena Trock, and Hossan Haick. "Detecting Simulated Patterns of Lung Cancer Biomarkers by Random Network of Single-Walled Carbon Nanotubes Coated with Nonpolymeric Organic Materials." *Nano Letters* 8.11 (2008): 3631-35.

Shi, Xiangyang, et al. "Multifunctional Dendrimer-Modified Multiwalled Carbon Nanotubes: Synthesis, Characterization, and *In Vitro* Cancer Cell Targeting and Imaging." *Biomacromolecules* 10.7 (2009): 1744-50.

Singh, Pratik, et al. "Canine Parvovirus-Like Particles, a Novel Nanomaterial For Tumor Targeting." *Journal of Nanobiotechnology* 4.2 (2006): 4-2.

Vishwakarma, Kirti, M. Ramrakhiani, and O. P. Vishwakarma. "Nanotechnology: A Boon for Medical Science." *International Journal of Nanotechnology and Applications* 2.1 (2008): 69-73.

von Maltzahn, Geoffrey, et al. "Computationally Guided Photothermal Tumor Therapy Using Long-Circulating Gold Nanorod Antennas." *Cancer Research* 69.9 (2009): 3892-900.

Wang, M., and Maya Thanou. "Targeting Nanoparticles to Cancer." *Pharmacological Research* 62.2 (2010): 90-9.

Wang, Xu, et al. "Application of Nanotechnology in Cancer Therapy and Imaging." *CA Cancer Journal for Clinicians* 58 (2008): 97-110.

Yong, Ken-Tye, et al. "Preparation of Gold Nanoparticles and Their Applications in Anisotropic Nanoparticle Synthesis and Bioimaging." *Plasmonic* 4.2 (2009): 79-93.