

Research Progress of Prostate Stem Cell Antigen in Bladder Cancer Treatment

Jinmei Li^{1,2†}, Runfen Cheng^{3†}, Bingjuan Zhou^{1,2}, Zhiqiang Zhang⁴, Qiongli Zhai^{3*}, Jinku Zhang^{1,2*}

¹Department of Pathology, Baoding First Central Hospital, Baoding 071000, Hebei Province, China

²The Key Laboratory of Molecular Pathology and Early Diagnosis of Tumor in Hebei Province, Baoding 071000, Hebei Province, China

³Department of Pathology, Cancer Hospital of Tianjin Medical University, National Clinical Medical Research Center of Cancer, Tianjin Key Laboratory of Cancer Prevention and Treatment, Tianjin Clinical Medical Research Center of Malignant Cancer, Tianjin 300060, China

⁴Department of Thoracic Surgery, Baoding First Central Hospital, Baoding 071000, Hebei Province, China

[†]These authors contributed equally to this work as first authors

***Corresponding author:** Jinku Zhang, zjkbk@sina.com; Qiongli Zhai, zhaiqiongli@126.com

Copyright: © 2022 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract: In order to study the application effect of prostate stem cell antigen in the treatment of bladder cancer, several literatures have been reviewed in this paper, including the predisposition factors of bladder cancer, clinical treatment methods, progress of prostate stem cell antigen, and nanomaterial probe. This paper presents a feasible method of using luminescent nanomaterials (anti-UCNPs) as biological probes.

Keywords: Bladder cancer; Prostate stem cells; Nanoprobes

Online publication: September 28, 2022

1. Introduction

Bladder cancer is a malignant tumor that occurs in the epithelium of the bladder mucosa. It is the most common tumor of the urinary system in China and one of the ten most common tumors in humans. Although bladder cancer may occur in patients of any age, the overall incidence of bladder cancer shows an increasing trend with age, in which the age with the highest incidence is between 40 and 70 years old. Among them, urothelial carcinoma is the most common type of bladder cancer, accounting for more than 80% of all bladder malignancies. Bladder cancer is commonly referred to as bladder urothelial carcinoma, which is also known as bladder transitional cell carcinoma.

2. Predisposing factors for bladder cancer

The pathogenesis of bladder cancer is relatively complex, and the pathogenesis is still unclear. There are many factors that lead to bladder cancer.

2.1. Gene mutation

In terms of molecular biology, the occurrence of bladder cancer is a process involving multi-gene damage and mutation. This multi-step, multi-gene pathological process ^[1-2] involves the activation of proto-

oncogenes, the inactivation of tumor suppressor genes, and many other gene mutations. Oncogenes related to bladder cancer mainly include the RAS gene family (N-RAS, K-RAS, and H-RAS), CCND1 gene, ERBB2 gene, MYC gene, MDM2 gene, FGFR3 gene, *etc.* The mutation of these genes initiates cell proliferation signal and causes abnormal regulation of cell proliferation and apoptosis, which may lead to tumor formation.

2.2. Smoking

In the research on the risk factors of bladder cancer, smoking is the most significant, in which the ratio of bladder cancer among smokers and non-smokers is 2.57 to 1. About 35% of women and 50% of men with bladder cancer are associated with smoking ^[3-4]. The smoke released from tobacco burning contains a large amount of polycyclic aromatic hydrocarbons and aromatic amines, such as benzopyrene and 4-aminobiphenyl, which are highly carcinogenic. Nitrosamines and aromatic compounds can activate oncogenes, which may cause DNA damage and sequence changes, and eventually lead to cancer.

2.3. Occupational exposure

Some chemical carcinogens include benzidine, β -naphthylamine, 4-aminobisphenyl, *etc.* Other common industrial chemicals include dyes, leather, textiles, plastics, rubber, printing, paint, *etc.* Bladder cancer may occur as a result of the activation of oncogenes or the inactivation of tumor suppressor genes ^[5-7].

2.4. Other factors

Virus (such as human papillomavirus) infection, bladder calculi, bladder diverticulum, schistosomiasis-associated cystitis, and other chronic infections of the bladder may lead to a series of pathological effects, including chronic inflammation. This will eventually cause epigenetic modifications, thus affecting the transformation and invasion of host cells and metastasis, as well as increasing the probability of bladder cancer ^[8-10]. A prospective meta-analysis showed that poor dietary habits, such as habitually high salt intake, increase the risk of bladder cancer. Psychosocial factors may also increase the probability of bladder cancer by changing the body's hormone levels and the components of the immune system through the central nervous system.

3. Treatments for bladder cancer

3.1. Surgical treatment

In western medicine, surgical resection of lesions, in particular standard complete resection, remains the first choice for the treatment of bladder cancer. Standard complete resection involves a thorough and systematic clearing of lymph nodes depending on the number and group of lymph nodes. It reduces the false negative rate of sentinel lymph node biopsy and the need for more comprehensive treatment postoperatively; furthermore, it improves the probability of patient survival and the prognosis of patients with bladder cancer, which are largely dependent on the initial surgical removal of tumor cells in addition to the amount and size of residual lesions. Surgical skills and surgical equipment are updated. It is possible to effectively and quickly remove primary and metastatic lesions of bladder cancer through surgical treatment. The treatment effect and patient satisfaction with primary cytoreductive surgery have improved year by year, along with the survival rate. However, surgery is predominantly suitable for patients with early-stage bladder cancer. For patients who have been diagnosed with advanced bladder cancer at the first visit, it is often challenging to achieve the expected therapeutic effect if surgery is performed, and indicators such as patient prognosis and five-year survival rate are also not ideal ^[11-13].

3.2. Radiotherapy and chemotherapy

In radiotherapy, radiation is used to kill cancer cells, whereas in chemotherapy, chemotherapy drugs are used to inhibit the proliferation and metastasis of cancer cells. Both, radiotherapy and chemotherapy have become the main treatment methods since they have an established cell-killing effect on tumor cells. Radiotherapy is used in patients whose hormone levels in the body have not been reduced to normal levels after surgery or who still have tumor residues in their bodies. The main methods include conventional radiation therapy and stereotactic radiation therapy, in which the most commonly used method is Gamma (γ) Knife radiosurgery. However, the disadvantage of radiotherapy is that the onset of the effect is slow, whereby it may take 1 to 2 years to see satisfactory results after treatment. The effect from radiotherapy is not ideal in terms of the need to quickly relieve compression of nearby structures. There are also some patients who are unresponsive to radiotherapy, and complications such as radiation necrosis of brain tissue, hair loss, and tumor hemorrhage may occur; in severe cases, death may even occur; in other patients, tumor growth becomes more rapid and disordered following radiotherapy; hence, conventional radiotherapy may not be able to control tumor growth and proliferation in such patients. The commonly used chemotherapeutic drugs in clinical practice include alkylating agents, such as cisplatin, as well as topotecan, gemcitabine, oral etoposide, decitabine, and doxorubicin liposome. The anti-tumor mechanism for groups of molecules with deoxyribonucleic acid (DNA) protein in biological macromolecules, such as amino, hydroxyl, and other negative valence molecular groups, that form covalent bonding material, results in the combination of molecules, which causes the inability to exercise cell metabolism. The inability of cells to carry out normal metabolism would eventually affect cell growth and proliferation, resulting in tumor cell death. These agents are usually converted into electron-deficient active intermediate. The mechanism by which chemotherapeutic drugs work is by covalently binding with electronic groups, such as amino groups, sulfhydryl groups, hydroxyl groups, carboxylic acid groups, phosphate groups, *etc.*, contained in the biological macromolecules (DNA, RNA, and proteins) of cells, and undergoing alkylation reaction, which renders these cellular components inactive in cellular metabolism. However, the incidence of side effects from chemotherapy is high, and the inhibition of the hematopoietic function of the bone marrow as well as the damage to the body's own tissues are significant. While removing and shrinking tumor cells, these agents may also cause harm to the human body. Treatment may be discontinued due to adverse reactions [14,15].

3.3. Other treatments

With the development of molecular biotechnology, biological therapy represented by molecular targeted therapy has become the development direction in the field of oncology. Studies have shown that epidermal growth factor receptor (EGFR) plays an important role in bladder cancer that is associated with angiogenesis and the upregulation of VEGF, basic fibroblast growth factor (bFGF), interleukin (IL)-8, and other vascular growth factors. It is known to play a crucial role in the occurrence and development of bladder cancer. In terms of the pathogenesis of bladder cancer, molecular targeted drugs such as gefitinib and erlotinib have been clinically studied with regard to their actions on the above targets. In addition, gene therapies such as tumor suppressor gene, antisense gene, immune gene, and gene knockout therapies have been developed.

4. Prostate stem cell antigen

Prostate stem cell antigen (PSCA), which has 30% homology with stem cell antigen 2 (SCA2), was first discovered in LAPC-4 mouse, an animal model of human prostate cancer in 1998. PSCA belongs to the Thy-1/Ly-6 family of glucosyl inositol (glycosylphosphatidylinositol, GPI), which is one of the anchored cell surface antigen members, consisting of 123 amino acids, with an amino-terminal signal sequence, a

carboxyl-terminal sugar containing 3 introns, 2,269 base pairs, a phosphatidylinositol anchoring sequence, and N-glycosylation sites. Its specific function is unclear, but since it is an anchored membrane protein, studies have shown that PSCA is involved in cell signal transduction and intercellular adhesion, both of which play important roles in functions of stem cell, including progenitor cell self-renewal (anti-apoptotic) and proliferation [16,17]. PSCA was first found to be specifically expressed on the surface of prostate epithelium and was identified and isolated as a tumor antigen overexpressed in prostate cancer tissue. The expression of PSCA was found to be significantly increased in more than 80% of prostate cancers, in which its expression level is similar to that of prostate cancer. Its differentiation and stage were found to be significantly correlated, and its expression was found to be higher in hormone-independent prostate cancer and prostate cancer metastases. Subsequent studies have confirmed that PSCA can also be expressed in normal epithelial cells of bladder, kidney, skin, esophagus, stomach, placenta, and other organs and tissues. Its expression is upregulated in bladder cancer, renal cell carcinoma, pancreatic cancer, hydatidiform mole, and ovarian mucinous carcinoma.

5. Nanomaterial probes

In recent years, the development of nanotechnology has provided more opportunities for the establishment of new tumor diagnosis and treatment methods [18–22]. In magnetic resonance imaging (MRI), photoacoustic imaging (PAI), computed tomography (CT), positron emission tomography (PET), fluorescence imaging, and other diagnostic methods, as well as in photothermal therapy (PTT), photodynamic therapy (PDT), and immunotherapy, a variety of nanoscale materials have been used as contrast agents for imaging and therapeutic agents, all of which have shown good imaging and therapeutic effects. Among them, imaging-guided treatment methods that combine the imaging and therapeutic functions of nanoparticles have garnered widespread attention. With appropriate imaging technologies, it is possible to identify the location and size of tumors accurately and determine the biodistribution of therapeutic drugs in the body, which can assist in achieving accurate treatment and improving the treatment effect.

As a commonly used investigation method, MRI, with its excellent features of high resolution and good contrast, is an effective non-invasive imaging technique, especially for demarcating the tumor site. There are two types of nanomaterials that are considered to be good contrast agents for MRI: one of them is polymer nanoparticles doped with gadolinium ions, iron ions, or copper ions, while the other is magnetic nanoparticles, with iron (II, III) oxide (Fe_3O_4) as a representative. In contrast, although PAI has not been widely used in clinical work, its advantages are outstanding. PAI, as its name suggests, is a biomedical imaging technique that combines the principles of ultrasound (US) and optical imaging. Since it inherits the principles of optical and ultrasound imaging techniques, PAI can provide both, strong optical contrast and high ultrasound resolution of deep tissues. PAI provides structural information of tumors, enables a clear diagnosis of tumors, and allows the monitoring of tumor progression and treatment outcomes. Meanwhile, compared with other biomedical imaging technologies, optical imaging systems have several advantages, including low cost, simple structure, and no harmful ionizing radiation. An ideal contrast agent for PAI must be able to absorb near-infrared (NIR) light and have a high molar extinction coefficient as well as high stability. Small molecule organic dyes, precious metal nanoparticles, carbon nanoparticles, polymer nanoparticles, *etc.* are all good contrast agents for PAI. At the same time, these contrast agents can act as photothermal reagents, converting light energy into heat energy, and killing cancer cells by utilizing the low thermal tolerance of cancer cells, thereby realizing PTT. By incorporating basic elements with MRI functions into nanoparticles with NIR light absorption ability, nanoparticles with multiple functions of MRI, PAI, and PTT can be obtained, thereby realizing tumor PTT guided by multimodal imaging.

We developed a luminescent nanomaterial (anti-UCNP) as a biological probe through (1) BCMab1 monoclonal antibody modified rare earth upconversion luminescent nanomaterials cytotoxicity

experiments, (2) anti-UCNPs stem cell targeted binding test, (3) anti-UCNPs combined with cancer cell luminescence effect test, (4) animal model toxicity test, (5) animal *in vivo* imaging test, *etc.*

The research results are as follows:

- (1) a multimodal nanomaterial with hydrophilicity and dispersibility has been developed following the loading of the hollow mesoporous silica-coated upconversion nanocrystals with ruthenium complexes in the cavity structure; having good water solubility, extremely low biological toxicity, and high stability, as well as being a multi-functional nanoprobe that integrates sensing and imaging, the nanomaterial is suitable for use in biological fields, such as cell imaging, small animal imaging, and magnetic resonance imaging;
- (2) NaYF₄:Yb,Er and NaYF₄:Yb,Tm upconverting nanocrystals, which are coated with a layer of sodium gadolinium fluoride (NaGdF₄), have been synthesized for potential magnetic resonance imaging functions; a simple grafting method was used to modify the polyhedral oligomeric silsesquioxane (POSS) on the surface of the upconversion material to achieve good hydrophilicity, high biocompatibility, and low toxicity of the upconversion material;
- (3) the activation and functionalization of the surface groups of upconversion luminescent materials as well as the preparation of upconversion fluorescent contrast agents (collectively known as UCNC-Anti, UCNC-Er-Anti, UCNC-Tm-Anti, and UCNC-Er, Tm-Anti) by covalent linkage of the activated groups with BCMab1 and CD44 monoclonal antibodies were carried out; their imaging mechanisms were then studied; rare earth upconversion luminescent nanomaterials (anti-UCNPs) coupling BCMab1 with CD44 monoclonal antibodies should have good cytocompatibility and low toxicity;
- (4) the upconversion luminescence *in vivo* imaging system can be used to detect rare earth upconversion luminescence nanomaterials modified by BCMab1 and CD44 monoclonal antibodies with high luminescence efficiency and bladder cancer specificity *in vivo*;
- (5) rare earth upconversion luminescent nanomaterials modified by BCMab1 and CD44 monoclonal antibodies can be used as probes for detecting bladder cancer, tracking lymph node metastasis in bladder cancer, and comprehensively evaluating the overall effect of nanoprobe targeting bladder cancer stem cells curative effect.

6. Conclusion

In conclusion, there are various factors that lead to the occurrence of bladder cancer. Those of which have been confirmed include gene mutation, smoking, occupational exposure, and other factors. Surgery, radiotherapy, and chemotherapy are the main treatment methods; however, nanomaterials are now also being used to identify the progress of bladder cancer cells.

Funding

This research received financial support from the Key Laboratory of Molecular Pathology and Early Diagnosis of Tumor in Hebei Province, the Beijing-Tianjin-Hebei Basic Research Cooperation Special Project (2019), “Visual Stem Cell Targeted Tumor Therapy Techniques for Precise Diagnosis and Treatment of Tumors” (Project Number: 19JCZD-JC65800[Z]).

Disclosure statement

The authors declare no conflict of interest.

References

- [1] Zhang Z, Zhang W, Mao W, et al., 2022, Research Progress on Biomarkers of Response to Immunotherapy for Advanced Bladder Cancer. *Shandong Medicine*, 62(02): 93–96.
- [2] Che W, Sun Y, Tan Z, et al., 2021, Research Progress on FGFR3 Gene Mutation and Targeted Drug Therapy for Bladder Cancer. *Life Science*, 33(09): 1133–1142.
- [3] Luo L, Luan H, Zheng H, et al., 2022, Study on the Disease Burden of Prostate Cancer, Bladder Cancer and Kidney Cancer Attributable to Smoking in China from 1990 to 2019. *Chinese Journal of Evidence-Based Medicine*, 22(05): 530–536.
- [4] Nie S, 2021, Smoking: A High Risk Factor for Bladder Cancer. *Family Medicine. Happy Health*, 2021(10): 82.
- [5] Yang J, Dong X, Qiao X, et al., 2020, Urine Urothelial Carcinoembryonic Antigen 1 Gene Expression and Significance in Bladder Cancer Patients. *Chinese Journal of Practical Diagnosis and Treatment*, 34(11): 1099–1102.
- [6] Xu H, Li K, Liang Y, et al., 2019, Incidence and Trend Analysis of Bladder Cancer in Guangzhou from 2004 to 2016. *China Oncology*, 28(12): 913–917.
- [7] Song Y, 2019, Association of Single Nucleotide Polymorphism rs762551 with Risk and Prognosis of Bladder Cancer, Shandong University.
- [8] Cai Z, 2021, Research on Abnormal Changes in DNA Copy Number as a Molecular Marker for Prognostic Judgment of Bladder Cancer, Molecular Mechanism and Significance of the Interaction Between Viral Mirna and Host in Epstein-Barr Virus-Related Epithelial Malignant Tumors, Peking Union Medical College.
- [9] Zhang S, 2021, The Effect of SAPCD2 Gene on the Proliferation and Apoptosis of Bladder Cancer T24 Cells, Kunming Medical University.
- [10] Zhang C, 2021, Functional Study of Circular RNA circPGM5 in Regulating Bladder Cancer Cell Progression, Wannan Medical College.
- [11] Wang F, Wang D, Zhou Y, 2021, Effects of Transurethral Bipolar Plasma Resection for Bladder Cancer on Intraoperative Blood Loss, Operation Time and Catheter Indwelling Time. *Hebei Medicine*, 43(24): 3752–3754 + 3758.
- [12] Liang Y, Shen M, Chen J, 2021, Clinical Study of Radical Cystectomy for Well-Differentiated T1 Bladder Cancer. *Zhejiang Trauma Surgery*, 26(06): 1038–1039.
- [13] Ma Y, Shan Z, Guo L, et al., 2021, Clinical Effect Analysis of Multi-Technology Fusion Surgery in the Treatment of Non-Muscle Invasive Bladder Cancer. *Modern Journal of Genitourinary Oncology*, 13(06): 330–335.
- [14] Urological Oncology Collaborative Group of China Cancer Hospital, 2022, Chinese Consensus on Multidisciplinary Diagnosis and Treatment of Bladder Cancer and Bladder Preservation Therapy. *Chinese Journal of Oncology*, 44(03): 209–218.
- [15] Wu R, Bai Y, Tang Y, et al., 2021, Research Progress of Molecular Typing to Guide the Treatment of Muscle-Invasive Bladder Cancer. *Journal of Clinical Urology*, 36(08): 668–671.
- [16] Shang G, Liu J, Yu H, et al., 2020, Expression and Detection of Prostate Stem Cell Antigen and Its Single-Chain Antibody-Alkaline Phosphatase Fusion Protein. *Journal of Anhui Medical University*, 55(12): 1968–1971.
- [17] You X, Xiang Z, Yi C, et al., 2020, Research Progress of Chimeric Antigen Receptor-Modified T Cells in the Treatment of Prostate Cancer. *Tianjin Medicine*, 48(10): 1020–1024.

- [18] Xue S, Zhang H, 2021, Research Progress of Nanomaterial-Assisted Diagnosis and Treatment of Bladder Cancer. *Journal of Community Medicine*, 19(22): 1382–1386.
- [19] Tao K, 2021, Application of Targeted Multifunctional Nanomaterials in Bladder Cancer Diagnosis and Treatment, Jilin University.
- [20] Wang X, Gu H, 2021, Research Progress of Nanomedicine for Bladder Cancer Perfusion Therapy. *Ion Exchange and Adsorption*, 37(02): 183–192.
- [21] Li D, 2020, Study on the Effect of New Nanomaterial Graphene Quantum Dots on Bladder Cancer T24 Cells In Vitro. Qingdao University.
- [22] Xu K, Wang H, 2015, Application of Nanomaterials in Bladder Cancer. *Journal of Urology (Electronic Edition)*, 7(04): 1–3 + 7.

Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.