

Advances in the bladder cancer research using 3D culture models

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Conflict of interest: The authors do not have any possible conflicts of interest.

Abbreviation used: 2D, two-dimensional; 3D, three-dimensional; NMIBC, Non-muscle invasive bladder cancer; MIBC, muscle-invasive bladder cancer; UICC, The Union for International Cancer Control; TURBT, Transurethral removal of bladder tumor; ADM, Adriamycin; HCPT, hydroxycamptothecin; BCG, Bacillus Calmette-Guérin vaccine; GC, Gemcitabine plus cisplatin; MVAIC, methotrexate, vinblastine, doxorubicin, and cisplatin; MVP, methotrexate, vinblastine, cisplatin; FANFT, n-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide; BBN, N-butyl-N-(4-hydroxybutyl) nitrosamine; MNNU, N-methyl-N-nitrosourea; BOPN, N-butyl-N-(3-carboxypropyl) nitrosamine; DLP, digital-light processing; QdMA, gelatin methacryloyl; PDT, patient-derived gliomas.

Received: October 21, 2022; Revision received: January 31, 2023; Accepted: February 28, 2023; Published: May 30, 2023

ABSTRACT

Bladder cancer represents the most common malignancy of the urinary system, posing a significant threat to patients' life. Animal models and two-dimensional (2D) cell cultures, among other traditional models, have been used for years to study various aspects of bladder cancer. However, these methods are subject to various limitations when mimicking the tumor microenvironment *in vivo*, thus hindering the further improvement of bladder cancer treatments. Recently, three-dimensional (3D) culture models have attracted extensive attention since they overcome the shortcomings of their traditional counterparts. Most importantly, 3D culture models more accurately reproduce the tumor microenvironment in the human body because they can recapitulate the cell-cell and cell-extracellular matrix interactions. 3D culture models can thereby help us gain deeper insight into the bladder cancer. The 3D culture models of tumor cells can extend the culture duration and allow for co-culturing with different cell types. Study of patient-specific bladder cancer mutations and subtypes is made possible by the ability to preserve cells isolated from particular patients in 3D culture models. It will be feasible to develop customized treatments that target relevant signaling pathways or biomarkers. This article reviews the development, application, advantages, and limitations of traditional modeling systems and 3D culture models used in the study of bladder cancer and discusses the potential application of 3D culture models.

Keywords: bladder cancer, cell culture, 3D culture models, 3D bioprinting

1. BACKGROUND

Bladder cancer is a malignant tumor resulting from the uncontrolled proliferation of abnormal cells in the bladder. It is one of the commonest malignant tumors of the urinary system. According to the World Health Organization, nearly 430,000 patients are diagnosed with bladder cancer and more than 165,000 died of the cancer annually [1]. An epidemiological report released in 2019 stated that the incidence rate and mortality rate of bladder cancer rank among the top ten in China [2].

Bladder cancer presents a severe threat to public health due to its high recurrence rate and mortality rate. The current "one-size-fits-all" approach is not, by many, deemed the best strategy

since it does not consider the potential impact of patient-specific genetic variations on drug response. Therefore, it is essential to develop new treatments. 2D cell cultures are primarily used in basic and clinical research of drugs. Cell culture is an essential technique employed in drug development, providing a simple, rapid, and economical way. 2D cell culture is a valuable technique for cell-based research, but it has limitations. Practically, all cells in the *in vivo* environment are surrounded by extracellular matrix and other cells. Therefore, 2D cell culture sometimes provides unreliable data that may misrepresent *in vivo* responses. Currently, the standard procedure of compound screening in new drug development starts with the test based on 2D cell culture, followed by animal tests and clinical trials. Only

How to cite this article: Gu YX, Lu Y, Xiong YQ, Zhan XP, Liu TB, Tang M, Xie A, Liu XQ, Fu B. Advances in the bladder cancer research using 3D culture models. *Bladder* 2023;10:e21200005. DOI: 10.14440/bladder.2023.856

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Table of Contents Advances In Bladder Research

1. Understanding the eBook Advances In Bladder Research
 - The Rise of Digital Reading Advances In Bladder Research
 - Advantages of eBooks Over Traditional Books
2. Identifying Advances In Bladder Research
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Advances In Bladder Research
 - User-Friendly Interface
4. Exploring eBook Recommendations from Advances In Bladder Research
 - Personalized Recommendations
 - Advances In Bladder Research User Reviews and Ratings
 - Advances In Bladder Research and Bestseller Lists
5. Accessing Advances In Bladder Research Free and Paid eBooks
 - Advances In Bladder Research Public Domain eBooks
 - Advances In Bladder Research eBook Subscription Services
 - Advances In Bladder Research Budget-Friendly Options
6. Navigating Advances In Bladder Research eBook Formats

- ePub, PDF, MOBI, and More
- Advances In Bladder Research Compatibility with Devices
- Advances In Bladder Research Enhanced eBook Features
- 7. Enhancing Your Reading Experience
 - Adjustable Fonts and Text Sizes of Advances In Bladder Research
 - Highlighting and Note-Taking Advances In Bladder Research
 - Interactive Elements Advances In Bladder Research
- 8. Staying Engaged with Advances In Bladder Research
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Advances In Bladder Research
- 9. Balancing eBooks and Physical Books Advances In Bladder Research
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Advances In Bladder Research
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Advances In Bladder Research
 - Setting Reading Goals Advances In Bladder Research
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Advances In Bladder Research
 - Fact-Checking eBook Content of Advances In Bladder Research
 - Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development
 - Exploring Educational eBooks
- 14. Embracing eBook Trends
 - Integration of Multimedia Elements
 - Interactive and Gamified eBooks

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