Computers in Biology and Medicine 58 (2015) 118–129

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Modeling and simulation of a low-grade urinary bladder carcinoma

Svetlana Bunimovich-Mendrazitsky [a], Vladimir Pisarev [b,c,d], Eugene Kashdan [e,*]

[a] Department of Computer Science and Mathematics, Ariel University, Ariel 40700, Israel
[b] V.A. Negovsky Research Institute for General Reanimatology, 25 Petrovka, Bldg. 2, Moscow 107035, Russian Federation
[c] D. Rogachev Federal Clinical Research Center for Children Hematology, Oncology and Immunology, 1 Samory Mashela St., Moscow 117198, Russian Federation
[d] University of Nebraska Medical Center, Omaha, NE 68198, USA
[e] School of Mathematical Sciences, University College Dublin, Belfield, Dublin 4, Ireland

ARTICLE INFO

Article history:
Received 11 October 2013
Accepted 26 December 2014

Keywords:
Bladder cancer
Angiogenesis
Cellular automata
Nonlinear diffusion-absorption equation
Hybrid model

ABSTRACT

In this work, we present a mathematical model of the initiation and progression of a low-grade urinary bladder carcinoma. We simulate the crucial processes affecting tumor growth, such as oxygen diffusion, carcinogen penetration, and angiogenesis, within the framework of the urothelial cell dynamics. The cell dynamics are modeled using the discrete technique of cellular automata, while the continuous processes of carcinogen penetration and oxygen diffusion are described by nonlinear diffusion–absorption equations. As the availability of oxygen is necessary for tumor progression, processes of oxygen transport to the tumor growth site seem most important. Our model yields a theoretical insight into the main stages of development and growth of urinary bladder carcinoma with emphasis on the two most common types: bladder polyps and carcinoma *in situ*. Analysis of histological structure of bladder tumor is important to avoid misdiagnosis and wrong treatment. We expect our model to be a valuable tool in the study of bladder cancer progression due to the exposure to carcinogens and the oxygen dependent expression of genes promoting tumor growth. Our numerical simulations have good qualitative agreement with *in vivo* results reported in the corresponding medical literature.

1. Introduction

Bladder cancer (BC) represents an increasing health problem worldwide. It is estimated that around 400,000 new cases are diagnosed annually and 150,000 people die directly from BC each year. The highest incidence of BC occurs in the industrialized and developed countries in Europe, North America, and Northern Africa. According to the current statistics urinary bladder carcinoma is the fourth most common new cancer in men and ninth in women [1].

A number of risk factors have been strongly linked to the development of BC. Roughly 20% of all BC cases have been related to occupational exposure to chemicals and dye, mostly in industrial areas processing paint, metal, and petroleum products. Tobacco smoking is the main BC risk factor, accounting for at least 30% of BC cases. Epidemiological and experimental evidence has also implicated environmental carcinogens in the aetiology of BC. Exposure to arsenic in drinking water has been recognized as a cause of BC, for instance, in a study of long-term impact of arsenic pollution observed in Chile. BC mortality was significantly higher in affected regions more than 20 years after cessation of pollution [2].

The first model of carcinogen penetration and BC initialization was proposed by Kashdan and Bunimovich-Mendrazitsky [3]. It was based on the evidence of BC origins and the biological properties of the urothelium and included a porous medium type equation to model carcinogen penetration combined with the cellular automata (CA) simulation of cell dynamics. In [3], the authors assumed that the tissue was well oxygenated and the angiogenesis had not started. Thus it was aimed to simulate the BC initiation and the first steps of the superficial polyp growth. However, it laid a basis of the high fidelity model presented in this paper that reproduces the state and behavior of multiple mechanisms involved in BC development. In this work, we introduce continuous oxygen and nutrient diffusion, and address hypoxia as one of the regulating factors in the cell cycle for both normal and cancerous cells. In order to simulate tumor growth beyond its initial stages we embed in the model a mechanism responsible for the development of the neovascular network providing tumor cells with additional oxygen and nutrients necessary for their continuous proliferation (a process known as *angiogenesis*).

Our research is based on the hypothesis that BC development is a multiscale multilevel process. The “building blocks” of our model

* Corresponding author.
E-mail addresses: svetlanabu@ariel.ac.il (S. Bunimovich-Mendrazitsky), vpisarev@gmail.com (V. Pisarev), ekashdan@maths.ucd.ie (E. Kashdan).

http://dx.doi.org/10.1016/j.compbiomed.2014.12.022
0010-4825/

are: (i) carcinogen penetration into the urothelium and (ii) oxygen diffusion, influenced by (iii) angiogenesis. Our approach to BC modeling corresponds with the multiscale studies of brain gliomas [4] and colorectal cancer [5] that eventually led to novel therapeutic strategies to treat these diseases.

The first goal of this work is to analyze various tumor development scenarios leading to angiogenesis. The second goal is to provide a basis for BC therapy personalization through the simulation of BC progression under various conditions. In the numerical experiments presented in this paper, we discuss a number of scenarios involving low-grade urothelial carcinomas such as superficial bladder polyp and carcinoma *in situ* (CIS). However, our model is not limited to these cases and it could simulate the invasive form of BC in conjunction with the model of tumor invasion.

The mathematical model of invasive BC is based on the interaction (and the competition) between the matrix metalloproteinases (MMP), produced by the cancerous cells, and the tissue inhibitors of metalloproteinases (TIMP), secreted by the tissue to confront the tumor progression, was introduced and studied in [6]. The paper is organized as follows: In Section 2, we present general information about the BC and the biological background of our model. After which we provide the reader with the model framework, divided into three consecutive sections: (a) The CA model of the urothelial cell dynamics (Section 3). (b) Continuous processes, which correspond to oxygen diffusion and carcinogen penetration (Section 4). (c) Modeling angiogenesis (Section 5). Section 6 is dedicated to numerical simulations and a discussion of a number of scenarios leading to tumor development and progression. We conclude our paper in Section 7.

2. Biological background

2.1. Normal urothelium

A human bladder consists of the following layers: bladder lumen, urothelium, lamina propria, muscle and fat [7,8] as sketched in Fig. 1.

The urothelium is a highly specialized layer of epithelial cells lining the bladder. It has to maintain a tight barrier against urea and other toxins, while accommodating large changes in bladder volume. The epithelial cells of the urothelium form part of an integrated network, which plays a major role in bladder sensory system. It is responsible for local circulation of blood and removal of pathogens. Under normal conditions the urothelium has a very low cell turnover rate. However, when the urothelium is damaged it has to repair itself rapidly [7,9]. The balance between the cell proliferation and differentiation controls the cell replacement process.

The urothelium is composed of three to six layers of cells including basal cells, intermediate cells and superficial (umbrella)

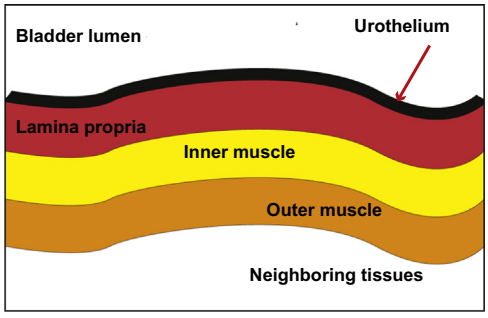

Fig. 1. The structure of human bladder.

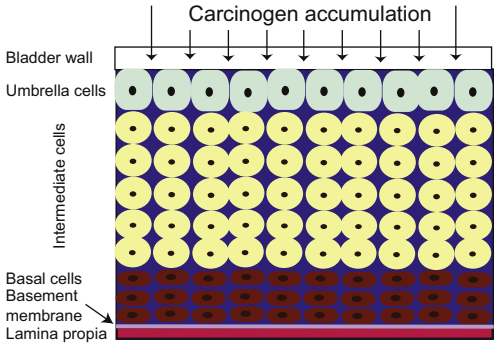

Fig. 2. The structure of the urothelium. (Reproduced with publisher permission [3].)

cells (Fig. 2). Basal cells are germinal in nature and approximately 5–10 μm in diameter. The basal cells are the only cells in a normal urothelium that could proliferate and move between layers after differentiation (if needed). The basal cells replace dead intermediate and umbrella cells by accepting the phenotype corresponding to each layer [7]. The cell replacement process is discussed in more detail in Section 3. The layer containing basal cells includes rare normal stem cells, which have a potential to initiate tumor growth [10,11]. It has been well established that tumor-initiating cells (stem cells or stem-like cells), originating from normal stem cells or from cells, which have transformed back from differentiated cells due to mutations, are responsible for initiation, control and metastatic spread of numerous tumors including urothelial cancer (see review in [11]). Accumulation of carcinogenic mutations in normal stem cells due to continuous action of environmental carcinogenic compounds is crucial to initiate and drive the carcinogenesis due to the altered expression of genes, affecting key signaling pathways of the cell. Most recent studies have demonstrated that abnormal overexpression, even of one protein in stem cells, within the basal urothelium in mice might generate an invasive lesion resembling all patterns of human bladder carcinoma *in situ* [12].

Intermediate cells are superficial to the basal cells and larger than them (about 20 μm in diameter). The luminal surface of the urothelium is formed by the umbrella cells (the largest epithelial cells in the body, between 100 μm and 200 μm in diameter [8]). The bladder urothelium shrinks (20–50%) during the urination process. When the bladder fills the number of cell layers reduces as the cells flatten to accommodate the stretching of the bladder wall [13].

As with any epithelial tissue, the normal (healthy) urothelium obtains oxygen and nutrients through diffusion from the capillary network located in the lamina propria and is separated from the urothelium by the basement membrane [3,7].

2.2. BC classification and grading

The most recent 2004 WHO classification distinguishes four grades of urothelial tumors in accordance with their malignancy (from low to high) [7]:

1. Urothelial papilloma.
2. Urothelial neoplasm of low malignant potential.
3. Papillary urothelial carcinoma, low-grade.
4. Papillary urothelial carcinoma, high-grade.

In this work, we model the low-grade papillary urothelial carcinoma. However, our approach is not limited to this type of