European Polymer Journal 72 (2015) 507–513

Contents lists available at ScienceDirect

European Polymer Journal

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

Polymeric hydrogels as artificial extracellular microenvironments for cancer research

Kyung Min Park [a,*], Sharon Gerecht [a,b]

[a] Department of Chemical and Biomolecular Engineering, Johns Hopkins Physical Sciences – Oncology Center and Institute for NanoBioTechnology, Johns Hopkins University, Baltimore, MD 21218, United States
[b] Department of Materials Science and Engineering, Johns Hopkins University, Baltimore, MD 21218, United States

ARTICLE INFO

Article history:
Received 4 March 2015
Received in revised form 23 May 2015
Accepted 27 June 2015
Available online 29 June 2015

Keywords:
Polymeric hydrogels
Engineered tumor models
Cancer research

ABSTRACT

An emerging trend in cancer research is to design *in vitro* tissue culture models that can accurately guide clinical trials to improve their therapeutic outcomes. Particularly, recent studies in cancer research have focused on utilizing three-dimensional (3D) microenvironments to precisely mimic *in vivo* conditions as a new tool to gain mechanistic understanding that will lead to the discovery of novel target therapeutics. In order to create 3D tumor microenvironments *in vitro*, polymeric hydrogel materials have been widely used as an artificial microenvironment due to their tunable properties and structural similarity to native extracellular matrices. In this review, we discuss how polymeric hydrogels may serve as 3D artificial tumor microenvironments to study cancer. Furthermore, we review the most recent approaches to integrate hydrogel materials and micro/nano-fabrication techniques, such as microfluidic devices and 3D printing techniques, for cancer research.

1. Introduction

Cancer is a leading cause of death worldwide. Despite tremendous advances in medical science and technology, universally effective cancer treatments therapies have remained elusive. Additional motivation for the urgency and importance of cancer research is revealed through the ever increasing number of new cancer cases each year. In fact, it has been estimated that nearly 14.5 million cancer patients are alive in United States alone and 585,720 US residents will die from some form of cancer in 2014 [1]. The number of people dying of cancer in worldwide is being predicted to increase dramatically from 8.2 million in 2012 to 14.6 million in 2035 [1]. It is expected that the economic burden of cancer worldwide will increase significantly in the future due to growing and aging of the population and emerging therapeutics for improvements in survival following cancer diagnosis [2]. While there are many therapeutic and diagnostic tools to detect and treat cancer, these approaches fail to effectively treat the broad spectrum of cancer that exists today. The development of innovative platforms to discover new drugs and their carriers is essential for effective cancer therapies. An emerging trend in cancer research is to develop preclinical models that can accurately guide clinical trials to reduce costs and to improve the therapeutic effects of novel treatments, in hopes that a wider range of patients may be treated, and treated effectively.

* Current address: Division of Bioengineering, Incheon National University, 119 Academy-ro, Yeonsu-gu, Incheon 406-772, Republic of Korea (K.M. Park). Address: Department of Chemical and Biomolecular Engineering, Johns Hopkins Physical Sciences – Oncology Center and Institute for NanoBioTechnology, Johns Hopkins University, Baltimore, MD 21218, United States (S. Gerecht).
E-mail addresses: kmpark@inu.ac.kr (K.M. Park), gerecht@jhu.edu (S. Gerecht).

http://dx.doi.org/10.1016/j.eurpolymj.2015.06.030
0014-3057/

One of the most prevalent approaches in development of preclinical disease models is to recapitulate the complex *in vivo* microenvironment. Growing evidence has demonstrated that the tumor microenvironment plays a critical role in tumor progression and metastasis, both of which have been associated with poor clinical outcomes [3]. In particular, a variety of parameters have been implicated as important factors in tumor development and the metastatic process, including tumor-derived abnormal angiogenesis, extracellular matrix (ECM) components and their remodeling, mechanical properties, oxygen tension, and three-dimensional (3D) architecture [3–6]. It follows that these are among the most important predictors of metastatic potential in patients with cancers, although the underlying mechanisms for this correlation remain to be completely characterized. Importantly, with an enhanced understanding of these processes, new therapeutic strategies may be developed.

Most *in vitro* cancer research has been conducted in a two-dimensional (2D) manner using adherent cell culture. However, it has become clear that these approaches have severe limitations in precisely reflecting the 3D complex microenvironments *in vivo*, where cells naturally exist. In fact, cancer cell behavior within the microenvironment are regulated by cell to cell and cell to matrix interactions, as well as chemotactic signaling, which are each essential for tumor progression and metastasis [3]. While 2D culture systems have provided important insights in basic cancer biology, these same systems may have misleading results that lead to poor outcomes in clinical trials. Thus, recent works in cancer research have focused on utilizing 3D microenvironments to precisely mimic *in vivo* conditions and provide new tools for better understanding of cancer progression and metastasis, while also leading to improved clinical outcomes in cancer treatment.

In order to create 3D tumor microenvironments *in vitro*, polymeric hydrogel materials have been widely used due to their tunable properties and structural similarity to native ECMs [7–9]. Various kinds of hydrogel materials, derived from natural, synthetic, and semi-synthetic polymers, have been utilized to generate preclinical models for studying basic cancer biology and screening newly developed drugs and carriers for cancer research. Recently, many investigators have endeavored to develop advanced platforms by integrating polymeric hydrogels with emerging techniques, including nano/micro fabrication and 3D printing.

2. Tumor microenvironments *in vivo*

Tumor deployment and metastasis is a complex, multistep process consisting of migration and invasion at primary sites, intravasation and survival in the blood circulation, and finally extravasation and metastasis to other organs [10]. It is commonly recognized that tumor microenvironments play a pivotal role in regulating tumor progression and metastasis, by presenting myriad biochemical, mechanical, and architectural properties [3,11]. These properties include excess ECM production and abnormal ECM remodeling, mechanical strength, oxygen tension, and pathological angiogenesis as well as cancer–stromal cell interactions. In fact, many studies have demonstrated that these properties affect tumor growth [12], migration [13], proliferation [3], and drug resistance [11]. Thus, in order to develop accurate tumor models these parameters should be incorporated and considered. In this section, we will briefly discuss these components of tumor microenvironments and how they play a role in cancer progression.

The most important parameter to be considered when designing a preclinical tumor model is the pathologically abnormal ECM production and ECM remodeling in the tumor microenvironment, which is composed of a variety of ECMs at higher concentration and varying modification compared to normal tissues, including collagen molecules that are critical in regulating cancer cell behavior [14,15]. The excess production of collagen and its modification occurs in tumorigenic microenvironments, resulting in architectural changes. Specifically, in the tumor ECM, collagen I is modified and organized by upregulation of the relevant gene expression (*e.g.*, lysyl oxidase, prolyl hydroxylase, and PLOD2). Recently, it has been found that this increase in collagen density and its structural modification promotes cancer development and metastasis [14–16]. These abnormal processes not only induce changes interstitial flow in tumor–stromal microenvironments, but also alter solid stresses of tumors, such as increased stiffness of the tumor microenvironment [17–19]. In addition to collagen modification, it is well known that matrix metalloproteinases (MMPs), which degrade various ECM proteins, are upregulated in tumor niches, leading to tumor growth, tissue remodeling, tumor invasion, and metastasis [20]. In general, the MMPs play a critical role in tissue remodeling associated with various physiological or pathological processes [21,22]. Thus, inhibitions of collagen production and modification, as well as inhibition of MMP secretion have both attracted attention as therapeutic targets for the cancer treatment [23,24].

Related set of potential parameters to be considered are the biomechanical cues, which typically differ from those of normal tissue. Importantly, the elasticity of the tumor ECM is stiffer than normal tissue through enhanced collagen stabilization and crosslinking as we discuss above [25]. This increased mechanical strength contributes to tumor development, by regulating cellular adaptation to solid stress through cell–matrix interactions. In fact, in the tumor microenvironment both cancer and stromal cells sense and perceive external mechanical stress, which results in changes in their phenotype and gene expression. Recent studies have demonstrated that increased matrix strength caused by deregulated ECM production has been implicated in regulating cancer cell behavior, resulting in tumor malignancy.

In addition to matrix stiffness, oxygen has been implicated as an important signaling molecule that regulates cancer cell activities. As the tumor mass rapidly increases, regional hypoxia develops and pathological angiogenesis occurs due to the tremendous dependency on oxygen for cell survival. In fact, intratumoral oxygen deprivation, defined as hypoxia, is a hallmark of cancer and has been associated with the resistance of conventional therapeutics (*e.g.*, chemo- and radio-therapy),