Cancer Letters ■■ (2015) ■■–■■

Contents lists available at ScienceDirect

Cancer Letters

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

Mini-review

Recapitulation of complex transport and action of drugs at the tumor microenvironment using tumor-microenvironment-on-chip

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ARTICLE INFO

Keywords:
Drug transport
Targeted delivery
Stromal tissue
Microfluidics
Nanoparticles

ABSTRACT

Targeted delivery aims to selectively distribute drugs to targeted tumor tissues but not to healthy tissues. This can address many clinical challenges by maximizing the efficacy but minimizing the toxicity of anti-cancer drugs. However, a complex tumor microenvironment poses various barriers hindering the transport of drugs and drug delivery systems. New tumor models that allow for the systematic study of these complex environments are highly desired to provide reliable test beds to develop drug delivery systems for targeted delivery. Recently, research efforts have yielded new *in vitro* tumor models, the so called tumor-microenvironment-on-chip, that recapitulate certain characteristics of the tumor microenvironment. These new models show benefits over other conventional tumor models, and have the potential to accelerate drug discovery and enable precision medicine. However, further research is warranted to overcome their limitations and to properly interpret the data obtained from these models. In this article, key features of the *in vivo* tumor microenvironment that are relevant to drug transport processes for targeted delivery were discussed, and the current status and challenges for developing *in vitro* transport model systems were reviewed.

Introduction

Many promising anti-cancer drug candidates have been identified in the last several decades. However, only a handful have exhibited therapeutic efficacy on human patients. This is largely due to the limited delivery of drugs to target tumors, which can result in unwanted accumulation of compounds to non-targeted healthy tissues and organs, and ultimately lead to systemic toxicity. Targeted delivery, which aims to selectively distribute drugs to targeted tumor tissues but not to healthy tissues, can address many of these difficulties. Such targeted delivery, however, is very difficult to achieve [1]. The term "targeted" used in this article refers to the preferential delivery of drugs to the tumor site. It should be distinguished from "targeted therapy," which refers to drugs interfering with specific molecular targets in cancers.

Recent developments in the field of nanotechnology enables the synthesis of a wide variety of **n**ano**p**articles (NPs), whose size and surface properties can be designed to serve as effective vehicles for targeted delivery. These nanostructures include liposomes, polymer micelles, dendrimers, drug nanocrystals, magnetic nanoparticles, gold nanoparticles/nanoshells, nanorods, nanotubes, and drug–polymer conjugates (all of which will be collectively referred to as NPs). Research aimed at controlling the size and surface properties of these NPs to be responsive to the tumor microenvironment has been performed as reported elsewhere [2–5]. Even though improvements in the delivery efficacy have been shown, the majority of administered NPs fail to reach target tumors. One of the biggest benefits of using NP formulations is to avoid non-aqueous solvents for administering hydrophobic drugs to patients, resulting in fewer side effects, while maintaining the same efficacy. The success of Abraxane® (nanoparticle albumin-bound paclitaxel) and Doxil® (PEGylated liposome formulation), in large part, relies on delivering anticancer drugs without using organic solvents. In order to maximize the therapeutic outcomes, however, drug accumulation as well as penetration into the targeted tumors should be improved. The challenge before us is to achieve effective delivery to the cancer cells since it is significantly hindered by various barriers engendered by the complex **t**umor **m**icro**e**nvironment (TME).

After being administered into a patient's bloodstream, the drugs (for brevity, the term "drug" is used to refer both drug and drug delivery system including NPs) are thought to be subjected to complex and multi-faceted transport processes prior to reaching the cancer

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http://dx.doi.org/10.1016/j.canlet.2015.12.003
0304-3835/

Please cite this article in press as: Bumsoo Han, Chunjing Qu, Kinam Park, Murray Korc, Stephen F. Konieczny, Recapitulation of complex transport and action of drugs at the tumor microenvironment using tumor-microenvironment-on-chip, Cancer Letters (2015), doi: 10.1016/j.canlet.2015.12.003

cells as reviewed previously [6–10]. These include – i) blood flow-driven transport to the tumor vasculature, ii) transvascular transport (i.e., extravasation), iii) interstitial transport, and iv) cellular uptake and metabolism as illustrated in Fig. 1. Excess drugs often occupy the interstitial space or are transported through the lymphatic vessels. These transport phenomena are governed by diffusion and convection processes, and the significance of each process is dependent on both drugs and the biophysical conditions of TME. The drug dependent properties are the size and surface properties, and the TME dependent ones include leakiness of the blood vessel wall, interstitial fluid pressure gradient, and the **e**xtra**c**ellular **m**atrix (ECM) microstructure within the tumor interstitium. These processes and physiological conditions are highly dynamic, interconnected and vary spatiotemporally.

Besides these biophysical barriers, the TME also poses biochemical and biological complexities. Typically, tumor tissues consist of cancerous cells as well as stromal components that consist of various stromal cells including **c**ancer-**a**ssociated **f**ibroblasts (CAF), diverse immune and inflammatory cell types and rich extracellular matrix components, such as type I collagen [11,12]. In addition to the highly heterogeneous cancer cell populations, i.e. intra-tumoral heterogeneity, the complex stromal tissue acts as a repository for various growth factors and cytokines that can dramatically influence tumor growth and drug response. The TME is also a hypoxic environment. Thus, it is important to understand the TME to design and develop effective targeted drug delivery systems. New tumor models that allow for the systematic study of these complex environments are highly desired and will provide reliable test beds to characterize and optimize the design of drugs.

Several tumor models are available, but they do not adequately address this challenge. Conventional static *in vitro* systems, including cell suspensions and cell monolayers, are not sufficient to study these complex *in vivo* transport processes because the model systems lack dynamic interactions among the cells, ECM, interstitial fluid and drugs. Animal models can provide a TME with all of these dynamic interactions, but such models are limited to systematically studying the effects of these dynamic interactions. Recently, research efforts have yielded new *in vitro* tumor models, the so called **t**umor-**m**icroenvironment-**o**n-**c**hip (T-MOC), that recapitulate certain characteristics of the TME. Although various configurations have been developed, T-MOCs are basically microfluidic platforms where cancer cells are cultured within the ECM under perfusion conditions. These new models show benefits over other conventional tumor models, and have the potential to accelerate drug discovery and patient-specific personalized treatment planning. However, the TME is extremely complex and there remain significant limitations to overcome. In this article, key features of the *in vivo* TME that are relevant to drug transport processes for targeted delivery are reviewed, and the current status and challenges for developing transport model systems are discussed.

Tumor microenvironment: a complex and chaotic bed for tumor growth

The tumor microenvironment is a complex and adverse environment for drug transport and action. It comprises a highly heterogeneous mixture of tumor and stromal cells embedded in an extracellular matrix that also includes cytokines, growth factors, inflammatory cells and macrophages. Together, the TME poses multifaceted barriers including biological, chemical and physical hindrances to drug transport and actions. These barriers are highly dynamic and often interconnected. Their interactions and relative significance with respect to drug delivery and therapeutic efficacy vary drastically depending on the cancer type, stage and organs. The current difficulty in developing new anticancer drugs and drug delivery systems partly stems from the lack of a clear understanding of the delicate interplay of these barriers at the TME [13–15]. Thus, instead of providing a generic description on these hindrances, it is more relevant to collectively discuss the interplays that are associated with one type of cancer. Here, our discussion will be focused on pancreatic cancer and its associated TME unless mentioned otherwise.

Pancreatic **d**uctal **a**deno**c**arcinoma (PDAC) is a significant clinical challenge due to its poor prognosis and extremely low (7%) five-year survival rate [16]. Its extensive TME presents many key features relevant to discussing the hindrances and resistance of drug transport and actions. One of the most notable characteristics of PDAC is its marked desmoplasia. The desmoplastic stroma of PDAC is composed of CAFs, various immune and inflammatory cell types and a dense extracellular matrix [11,12], as illustrated in Fig. 1. Moreover, PDAC is poorly vascularized and has extremely high **i**nterstitial **f**luid **p**ressure (IFP) [17–19]. In this complex 3D TME, highly intricate and multifaceted interactions occur among **p**ancreatic **c**ancer **c**ells (PCC), CAFs, **t**umor-**a**ssociated **m**acrophages (TAMs) and other

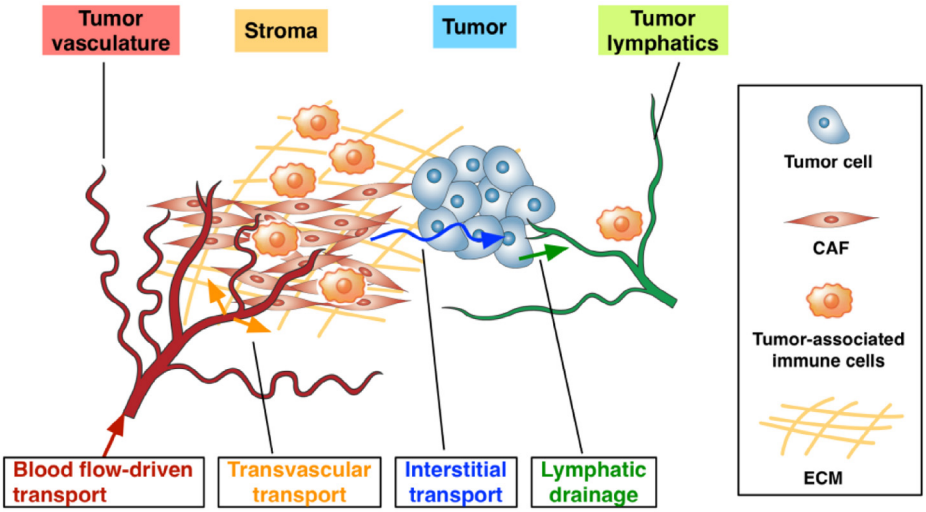

Fig. 1. Complexity of the tumor microenvironment. TME poses multi-faceted barriers to drugs transport owing to the dense stromal tissue, which is composed of collagens, fibronectin, and hyaluronan, an abundance of cancer-associated fibroblasts, and aberrant interactions between infiltrating tumor-associated immune cells, cancer cells, and CAFs.

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