Advanced Drug Delivery Reviews 64 (2012) 353–365

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

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

Delivery of molecular and cellular medicine to solid tumors ☆

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ARTICLE INFO

Article history:
Received 23 October 1996
Accepted 20 March 1997
Available online 13 September 2012

Keywords:
Tumor microcirculation
Angiogenesis
Blood flow
Vascular permeability
Diffusion and convection
Receptor-ligand binding
Interstitial pressure
Lymphatics
Cell adhesion and deformation
Cancer detection and treatment

ABSTRACT

To reach cancer cells in a tumor, a blood-borne therapeutic molecule or cell must make its way into the blood vessels of the tumor and across the vessel wall into the interstitium, and finally migrate through the interstitium. Unfortunately, tumors often develop in ways that hinder each of these steps. Our research goals are to analyze each of these steps experimentally and theoretically, and then integrate the resulting information in a unified theoretical framework. This paradigm of analysis and synthesis has allowed us to obtain a better understanding of physiological barriers in solid tumors, and to develop novel strategies to exploit and/or to overcome these barriers for improved cancer detection and treatment.

Contents

1. Introduction

Cancer is the second leading cause of death in the United States and in many industrialized countries [1]. After the primary tumor has been surgically removed and/or sterilized by radiation, the residual disease is usually managed with a variety of systemic therapies (Table 1). For these therapies to be successful, they must satisfy two requirements: (a) the relevant agent must be effective in the in vivo orthotopic microenvironment of tumors, and (b) this agent must reach the target cells in vivo in optimal quantities. The goal of our research is to examine the latter issue – the delivery of diagnostic and therapeutic agents to solid tumors and normal host tissues.

All conventional and novel therapeutic agents can be divided into three categories – molecules, particles and cells (Table 1). A blood-borne molecule or particle that enters the tumor vasculature reaches cancer cells via distribution through the vascular compartment, transport across the microvascular wall, and transport through the interstitial compartment. For a molecule of given size, charge, and configuration, each of these transport processes may involve diffusion and convection. In addition, during the journey the molecule

☆ PII of original article: S0169-409X(97)00027-6. The article was originally published in *Advanced Drug Delivery Reviews* 26 (1997) 71–90.

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http://dx.doi.org/10.1016/j.addr.2012.09.011

Table 1
Systemic therapy of cancer.

Therapy	Agent		
	Molecules	Particles	Cells
Radiotherapy	×	×	
Chemotherapy	×	×	
Immunotherapy	×	×	×
Gene therapy	×	×	×
Hyperthermia	×		
Phototherapy	×	×	

Agents used in various conventional and novel therapies can be divided in three categories: molecules, particles, and cells.

may bind nonspecifically to proteins or other tissue components, bind specifically to the target(s), or be metabolized [2]. Although lymphokine-activated killer (LAK) cells (lymphocytes activated by the lymphokine interleukin-2) or tumor-infiltrating lymphocytes (TIL) are capable of deformation, adhesion, and migration, they encounter the same barriers that restrict their movement in tumors. Some of these physiological parameters are also important for heat transfer in normal and tumor tissues during hyperthermic treatment of cancer [3].

The overall aim of our research is to develop a quantitative understanding of each of the abovementioned steps involved in the delivery of various agents. More specifically, our goals are to understand: (1) how angiogenesis takes place and what determines blood flow heterogeneities in tumors; (2) how blood flow influences the metabolic microenvironment in tumors, and how microenvironment affects the biological properties of tumors (e.g., vascular permeability; cell adhesion); (3) how material moves across the microvascular wall; and (4) how it moves through the interstitial compartment and the lymphatics. In addition, we are examining the role of cell deformation and adhesion in the delivery of cells. Following analysis of these processes for molecules, particles and cells, we integrate this information in a unified framework for scale-up from mice to men (Fig. 1). In this article, I will briefly describe various experimental and theoretical approaches used in our lab, our recent findings in these six areas, and finally, how we have taken some of these concepts from bench to bedside for potential improvement in cancer detection and treatment.

2. Experimental and theoretical approaches

We have utilized five approaches to gain insight into the pathophysiology of solid tumors:

(a) A tissue-isolated tumor which is connected to the host's circulation by a single artery and a single vein [4,5]. This technique was originally developed by P.M. Gullino at the National Cancer Institute in 1961 for rats [6]; we have recently adapted it to mice [7,8] and humans [9].
(b) A modified Sandison rabbit ear chamber [10,11], a modified Algire mouse dorsal chamber [12,13], and a cranial window in mice and rats [14]. The ear chamber has the advantage of superior optical quality and the mice of working with immunodeficient and genetically engineered animals [15,16]. Recently we have developed a quantitative angiogenesis assay using these windows to study the physiology of vessels induced by individual growth factors [17](Fig. 2). We also perfuse single vessels of tumors in these windows [18]. We also utilize two acute preparations: liver and mesentery.
(c) In vitro methods to assess the deformability, adhesion and permeability of normal and neoplastic cells [19–22], as well as measurements of adhesion molecules' expression in intact monolayers [23](Fig. 3).

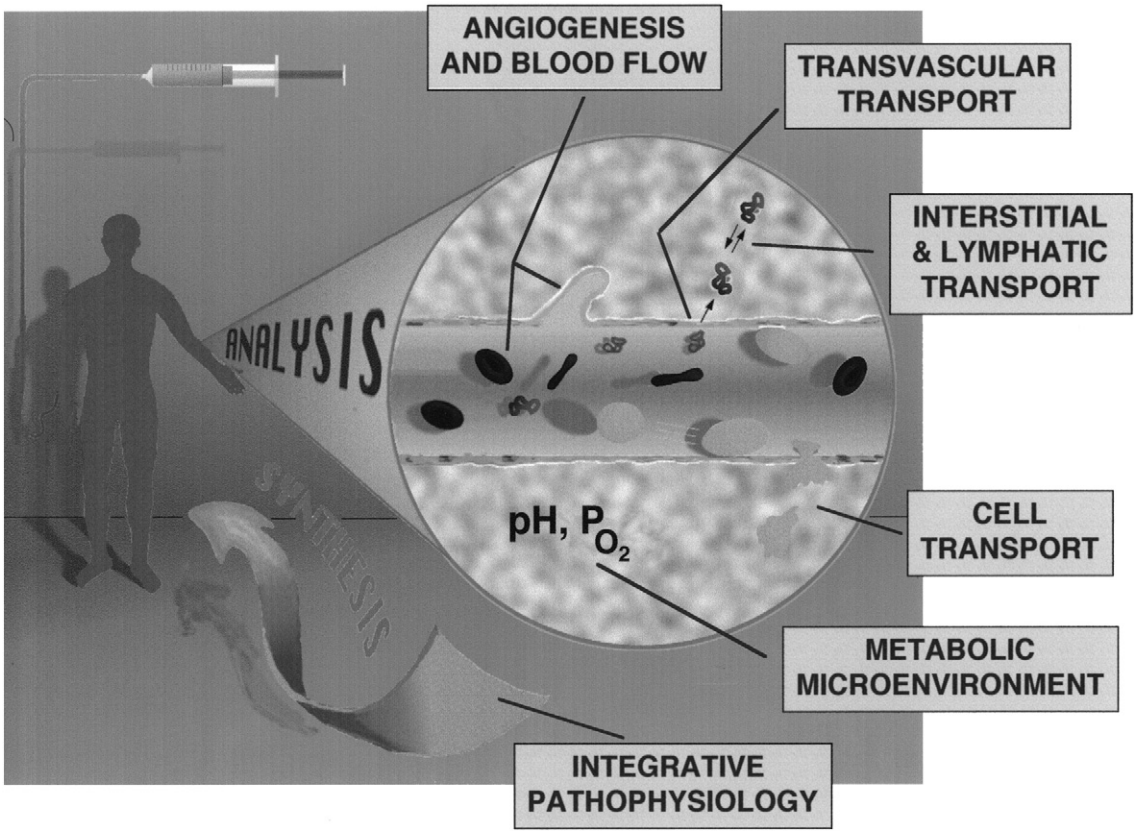

Fig. 1. Quantitative understanding of various steps involved in the delivery of therapeutic agents is studied by analyzing the underlying processes and then integrating the resulting information in a unified framework. More specifically, our goal is to develop a quantitative understanding of (a) angiogenesis and blood flow; (b) metabolic microenvironment; (c) transvascular transport; (d) interstitial and lymphatic transport; (e) cell transport, and (f) systemic distribution and interspecies scale-up.