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Delivery of cancer therapeutics to extracellular and intracellular targets: Determinants, barriers, challenges and opportunities☆

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ABSTRACT

Advances in molecular medicine have led to identification of worthy cellular and molecular targets located in extracellular and intracellular compartments. Effectiveness of cancer therapeutics is limited in part by inadequate delivery and transport in tumor interstitium. Parts I and II of this report give an overview on the kinetic processes in delivering therapeutics to their intended targets, the transport barriers in tumor microenvironment and extracellular matrix (TME/ECM), and the experimental approaches to overcome such barriers. Part III discusses new concepts and findings concerning nanoparticle–biocorona complex, including the effects of TME/ECM. Part IV outlines the challenges in animal-to-human translation of cancer nanotherapeutics. Part V provides an overview of the background, current status, and the roles of TME/ECM in immune checkpoint inhibition therapy, the newest cancer treatment modality. Part VI outlines the development and use of multiscale computational modeling to capture the unavoidable tumor heterogeneities, the multiple nonlinear kinetic processes including interstitial and transvascular transport and interactions between cancer therapeutics and TME/ECM, in order to predict the *in vivo* tumor spatiokinetics of a therapeutic based on experimental *in vitro* biointerfacial interaction data. Part VII provides perspectives on translational research using quantitative systems pharmacology approaches.

Contents

Abbreviations: Ago2, argonaute 2; CDE, clathrin-dependent endocytosis; CIE, clathrin-independent endocytosis; CPP, cell penetrating peptides; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; ECM, extracellular matrix; EPR, enhanced permeability and retention; ERC, endosome recycling compartment; IFP, interstitial fluid pressure; ILV, intraluminal vesicle; MVB, multivesicular bodies; NP, nanoparticles; PD1, cytotoxic T cell programmed death-1 membrane receptor; PDL1 and PDL2, PD1 ligands; RES, reticuloendothelial system; RISC, RNA induced silencing complex; RNAi, RNA interference; siRNA, short interfering RNA; TME, tumor microenvironment.

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1. Introduction

Advances in molecular genetics and medicine, nanotechnology and pharmaceutical sciences have broadened the scope of cancer therapeutic targets. In addition to tumor cells, components in the tumor microenvironment (TME) have emerged as clinically important targets. TME is a complex strcuture comprising cells, blood vessels, cytokines and extracellular matrix (ECM). The three major cell types in TME are fibroblasts, inflammatory/immune cells, and endothelial cells; these cells secrete or express cytokines and chemokines that interact with tumor cells [1]. ECM proteins, primarily collagen and fibronectin, are synthesized and deposited by fibroblasts, and represent a major fraction of larger tumors. Classes of cancer therapeutics include the traditional small molecules, macromolecules (e.g., proteins, antibodies), bioconjugates, viral vectors, and nanoparticle (NP) carriers (e.g., liposomes, micelles, and polymeric NP) [2]. These agents target tumor vasculature (e.g., anti-angiogenics), tumor interstitium (e.g., diagnostics or therapeutics targeting extracellular proteins), cell membrane (e.g., antibodies), and intracellular compartments such as the cytosol (e.g., RNAi, drugs targeting cytosolic proteins) [3–5] and nucleus (e.g., DNA gene vectors, DNA-active drugs) [6,7]. Their utility depends on their ability to reach their sites of action [8], which in turn is partly determined by TME and ECM. The goals of this report are to outline the processes and determinants of the delivery, transport and residence of cancer therapeutics and their NP carriers in solid tumors. The unique challenges and opportunities for nanomedicines, RNAi gene therapeutics and immune checkpoint therapy are also discussed.

As most cancer therapeutics are administered by intravenous injections, this review will focus on the transfer from blood to target sites. For the orally active agents such as tyrosine kinase inhibitors, additional processes governing the transport into the systemic blood, including absorption from the gastrointestinal tract and hepatic first pass elimination, are additional considerations.

This review comprises seven parts. Part I outlines the transfer processes of cancer therapeutics from the injection site to tumor interstitium, and Part II the processes from interstitium to cellular and intracellular targets; the barriers for delivery and the approaches to overcome these barriers are summarized. Part III discusses the interactions of therapeutics with components of TME and ECM, e.g., formation of NP biocorona. Part IV outlines the challenges in animal-to-human translation of cancer nanotherapeutics. Part V is a review of immune checkpoint inhibitors, the newest therapeutic group with demonstrated clinical benefits in cancer patients, and a discussion of the potential roles of TME/ECM in determining their treatment