Journal of Controlled Release 261 (2017) 10–22

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Review article

Exploiting passive nanomedicine accumulation at sites of enhanced vascular permeability for non-cancerous applications

Mikhail Durymanov[a], Tatiana Kamaletdinova[b], Sarah E. Lehmann[a], Joshua Reineke[a,*]

[a] Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, South Dakota State University, 1055 Campanile Avenue, Brookings, SD 57007, USA

[b] Department of Molecular Genetics of Intracellular Transport, Institute of Gene Biology, Russian Academy of Sciences, Ul. Vavilova, 34/5, 119334 Moscow, Russia

ARTICLE INFO

Keywords:
Nanomedicine delivery
Passive accumulation
Vascular permeability
Inflammation

ABSTRACT

Over the past few decades, enhanced permeability of tumor vasculature was actively exploited for targeted delivery of anticancer nanomedicines resulting in numerous pharmaceutical products. Formation of new immature and leaky vessels along with inflammatory remodeling of existing vessels accompany development of numerous diseases beyond cancer and present an opportunity for passive accumulation of intravenously administered nanomedicines in many pathological tissues. To date, applications of non-cancerous enhanced permeation have been relatively unexploited as target tissues and may create new therapy and prevention technologies for many disorders. Herein, we summarize the current knowledge on the nature of enhanced vascular permeability in multiple non-cancerous pathological tissues. We also discuss the clinical status of nanotherapeutics with selectivity based on passive accumulation in non-cancerous target tissues, their challenges, and prospects.

1. Introduction

Drug administration by the intravenous route enables the rapid systemic distribution of therapeutics throughout the body. Biodistribution and pharmacokinetics of intravenously injected drugs are determined by convection and diffusion transport processes and are dependent on molecular mass and size of the drugs/drug carriers. In cancer, the link between drug accumulation in solid tumors and drug hydrodynamic size is reflected by the enhanced permeation and retention (EPR) effect, described in 1986 [1]. Through this mechanism the use of nanoparticles and carriers of high molecular weight can be beneficial for improved accumulation of therapeutics in tumor tissue due to leaky fenestrated tumor vessels, and thin, or absent, basement membranes. Vessel permeability for such nanovehicles in healthy (non-leaky) tissues is significantly lower. The resulting selectivity of nanomedicines together with sustained drug release allows a reduced injected dose of drug and minimizes unwanted side effects.

Enhanced vascular permeability is a feature that extends beyond tumors with discontinuous endothelium in newly formed and immature vessels to also include other pathological tissues with dysfunctional vasculature. Loss of endothelium integrity can result in abnormal angiogenesis as, for example, may be the case in rheumatoid arthritis [2], atherosclerosis [3] and obesity [4]. Although neovascularization mechanisms in diseased tissues are poorly understood, hypoxia and inflammation are critical factors that govern formation of new vessels. Besides angiogenesis, inflammatory processes are involved in the remodeling of existing vessels and are responsible for enhanced permeability. Although both abnormal angiogenesis and vessel remodeling usually occur in diseased tissues, their contribution might be different depending on the extent of chronicity. As a rule, vessel remodeling mostly contributes in vascular permeability during acute inflammation (for example, in initial stages of myocardium infarction [5] or bacterial abscesses [6]), whereas in some chronic diseases the contribution of pathological angiogenesis becomes predominant. In either case, vascular permeability provides a good opportunity to target non-cancerous pathological tissues using nanomedicines.

Here we describe the nature of vascular permeability in numerous non-cancerous pathological tissues and provide an overview of nanotherapeutics, in which delivery to these tissues is based on exploiting enhanced vessel permeability. Furthermore, we discuss advantages and challenges of different nanomedicines as well their current status in clinical translation.

* Corresponding author at: Dr. Joshua Reineke, Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, South Dakota State University, 1055 Campanile Avenue, Avera Health Science Building, Brookings, SD 57007, USA.
E-mail address: joshua.reineke@sdstate.edu (J. Reineke).

http://dx.doi.org/10.1016/j.jconrel.2017.06.013
Received 24 March 2017; Received in revised form 13 June 2017; Accepted 14 June 2017
Available online 16 June 2017
0168-3659/ © 2017 Elsevier B.V. All rights reserved.

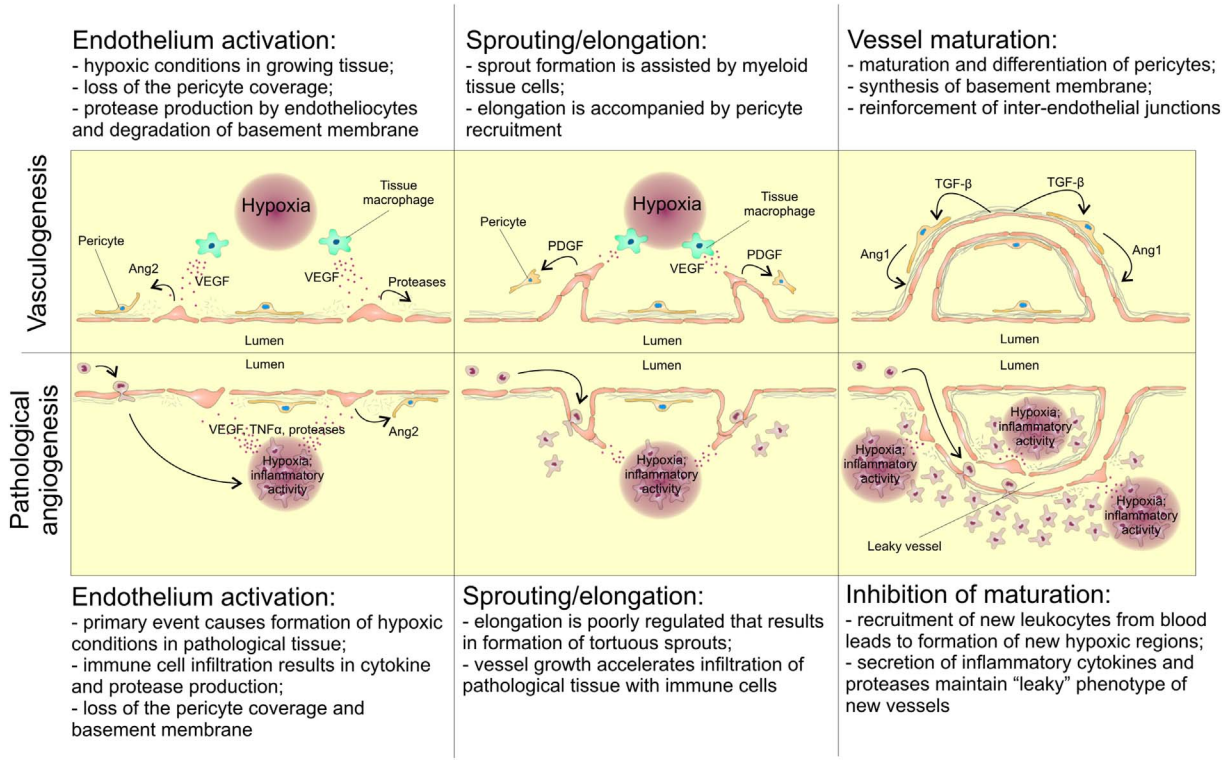

Fig. 1. Differences and similarities between developmental and pathological angiogenesis via sprout formation. Hypoxia plays the central role in both developmental and pathological angiogenesis, although in the latter case the role of inflammation is also significant. Formation of hypoxic centers in pathological tissues is a result of some primary events which are always associated with immune cell recruitment to the site of lesion; for example, proliferation of synoviocytes and macrophage infiltration of the synovium in rheumatoid arthritis; tumor growth and immune response in cancer; macrophage migration to the atherosclerotic plaque, etc. As compared with developmental angiogenesis, vessel sprouts in pathological angiogenesis stay leaky and immature. Angiogenic processes in different disorders often accelerate infiltration of pathological tissue with new immune cells leading to development of disease and may cause formation of new hypoxic centers.

2. EPR-like effect in diseases associated with abnormal angiogenesis

Vascular growth plays a very important role in the development of many chronic diseases. Despite different characteristics of pathogenesis, there are some common features of angiogenesis in unhealthy tissues. As in the case of normal tissue growth, pathological neovascularization is a hypoxia-driven process [7,8]. Appearance of hypoxic areas in different diseases could be associated with immune system activity that will be discussed below for some examples. Hypoxic conditions promote activation of hypoxia-inducible transcription factors HIF-1 and HIF-2 resulting in expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and other mitogenic molecules produced by cells in hypoxic regions [9,10], resulting in loss of intercellular junctions between endotheliocytes in adjacent blood vessels [10,11]. Moreover, VEGF induces release of angiopoietin 2 (Ang-2) from the Weibel-Palade bodies of endothelial cells [12], that leads to local loss of pericyte coverage, degradation of basement membrane with matrix-degrading enzymes, and endothelial cell sprouting (Fig. 1). VEGF-signaling provides elongation of sprout vessels by way of endothelial cell proliferation and, partially, lumen formation. The resulting nascent vascular network is leaky and very unstable. Maturation of newly formed vessels in healthy tissues is provided by platelet-derived growth factor B (PDGF-B) and transforming growth factor (TGFβ) mediated recruitment of lining cells (smooth muscle cells and pericytes), basement membrane formation, and recovery of Ang-1 expression resulting in reinforcement of endothelial intercellular junctions and barrier function [13]. It should be noted that inflammatory cells can also contribute to both normal and abnormal angiogenesis by producing cytokines and pro-angiogenic molecules including VEGF, tumor necrosis factor alpha (TNFα), PDGF, etc. [14] However, in pathological tissues the process of vessel maturation can be significantly slowed by activity of inflammatory cells in sites of neovascularization resulting in permeable and disorganized vascular network. There are numerous immune cell subsets that contribute to abnormal angiogenesis including monocytes/macrophages, neutrophils, natural killers (NK cells), T-cells, and dendritic cells, among others [15]. It is important to emphasize that the spectrum of cytokines secreted by inflammatory and stromal cells in different pathological tissues retain formation of new permeable vasculature, but hinder their maturation. This characteristic of pathological angiogenesis is crucial for recruitment of new leukocytes from circulation, maintenance of inflammation, and progression of disease.

2.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a complex autoimmune disease, associated with chronic inflammation of the synovial membrane surrounding the joint cavity, followed by localized destruction of cartilage and bone tissues. The initial step is characterized by extensive proliferation of macrophage- and fibroblast-like synoviocytes as well as excessive migration of immune cells (predominantly T cells and monocytes) to the synovium leading to hypertrophy [2,16]. Increase in the synovium width from 2 to 3 cell layers to several cell layers promotes hypoxia and HIF signaling activation [2]. Thus, hypoxic conditions along with production of pro-inflammatory cytokines up-regulate VEGF and bFGF resulting in induction of angiogenesis [2,17]. Angiogenesis combined with inflammation lead to failure of the blood-joint barrier function. This results in an enhanced permeability confirmed by electron microscopy of vascular morphology [18] (Fig. 2a). Thus, enhanced leakiness of the synovial blood vessels serves as the rationale for exploiting therapies based on intravenous administration of nanomedicines. Since the pathogenesis of RA is not fully understood, current treatment aims to achieve prolonged remission. Conventional therapies

Download English Version:

https://daneshyari.com/en/article/5433415

Download Persian Version:

https://daneshyari.com/article/5433415

Daneshyari.com