Biochimica et Biophysica Acta 1846 (2014) 26–39

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Role of endothelial progenitor cells in cancer progression

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ARTICLE INFO

Article history:
Received 29 October 2013
Received in revised form 19 February 2014
Accepted 27 March 2014
Available online 4 April 2014

Keywords:
Endothelial progenitor cells
Cancers
Hematological malignancies
Vasculogenesis

ABSTRACT

Tumor-associated neovasculature is a critical therapeutic target; however, despite significant progress made in the clinical efficacy of anti-vessel drugs, the effect of these agents remains transient: over time, most patients develop resistance, which inevitably leads to tumor progression. To develop more effective treatments, it is imperative that we better understand the mechanisms involved in tumor vessel formation, how they participate to the tumor progression and metastasis, and the best way to target them.

Several mechanisms contribute to the formation of tumor-associated vasculature: i) neoangiogenesis; ii) vascular co-option; iii) mosaicism; iv) vasculogenic mimicry, and v) postnatal vasculogenesis. These mechanisms can also play a role in the development of resistance to anti-angiogenic drugs, and could serve as targets for designing new anti-vascular molecules to treat solid as well as hematological malignancies. Bone marrow-derived endothelial progenitor cell (EPC)-mediated vasculogenesis represents an important new target, especially at the early stage of tumor growth (when EPCs are critical for promoting the "angiogenic switch"), and during metastasis, when EPCs promote the transition from micro- to macro-metastases. In hematologic malignancies, the EPC population could be related to the neoplastic clone, and both may share a common ontogeny. Thus, characterization of tumor-associated EPCs in blood cancers may provide clues for more specific anti-vascular therapy that has both direct and indirect anti-tumor effects. Here, we review the role of vasculogenesis, mediated by bone marrow-derived EPCs, in the progression of cancer, with a particular focus on the role of these cells in promoting progression of hematological malignancies.

Contents

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http://dx.doi.org/10.1016/j.bbcan.2014.03.005
0304-419X/

1. Introduction

Vasculogenesis was first described as a phenomenon occurring in early embryogenesis, and was believed to not occur in adult tissues [1–3]. In 1997, Asahara et al. [4] purified a population of circulating cells that displayed properties of endothelial cells (ECs) as well as progenitor cells, and identified these cells as 'endothelial progenitor cells' (EPCs); these cells can differentiate into ECs *via* the process of postnatal vasculogenesis, as described *in vitro*, as well as *in vivo*, in a model of hind limb ischemia [4]. Ashara's report comprised the first demonstration that vasculogenesis contributes to vascular remodeling, as well as to *de novo* formation of vessels in postnatal life. In 1998, Shi et al. [5] suggested that vasculogenesis may have physiological and pathological roles in healthy and disease states in adults. Here we examine the role of EPCs and vasculogenesis in the progression of cancer, with particular attention to how they promote the progression of hematological malignancies.

1.1. Characteristics of circulating EPCs and their contribution to angiogenesis

Circulating EPCs reside in the bone marrow (BM), in close association with hematopoietic stem cells (HSCs) and the surrounding BM stromal milieu [6,7]. EPCs are derived from hemangioblasts, which are precursor cells that give rise to both EPCs and HSCs [8]. EPCs have the capacity to proliferate, migrate and differentiate into ECs [9]. Mobilization of EPCs may occur in response to low oxygenation in tissues (for example in response to tissue ischemia after myocardial infarction) or in response to tumor growth, leading to increased angiogenesis [9]. Mobilization of EPCs is followed by vasculogenesis, which occurs when circulating EPCs are recruited in response to factors secreted by ischemic tissues and by inflammatory and tumor cells, resulting in the generation of new vessels in injured or pathological tissues [7]. It has been hypothesized that once EPCs are recruited to tumor sites, they can sustain neovessel formation *via* paracrine secretion of pro-angiogenic growth factors [10]; also that these cells provide structural support by being directly incorporated into the lumens of sprouting nascent vessels [11,12]. However, the extent to which EPCs contribute to blood vessel formation in postnatal life (vasculogenesis) is controversial. The number of BM-derived EPCs incorporated into tumor neovessels reportedly ranges from significant to undetectable, even when the same tumor models are used by different investigators [13]. For instance, EPC contributions as high as 50% [14,15] to as low as 5%–20% [16–19], and in some cases even undetectable [20–24], have been reported. These differences are likely based on a number of technical and experimental variables. The use of non-standardized methodologies (flow cytometry or *in vitro* methods) for the quantification of circulating EPCs add to the uncertainty [25]. We believe that many of these problems could be rectified if we had markers to specifically identify the putative EPC population (including circulating and resident EPCs). None of the markers currently used for such identification are restricted to EPCs: all antigens or combinations of antigens used for this purpose are also expressed by circulating HSCs and progenitor cells, circulating mature ECs, platelets/EC-derived vesicles, and some subsets of circulating hematopoietic-derived monocyte/myeloid cells (Table 1) [26,27]. Thus, in the absence of unique antigens to identify the EPCs, it is possible that cells that were previously identified as circulating EPCs actually represent circulating hematopoietic-derived cells, which express both hematopoietic and endothelial cell markers [25,27]: these include "vasculogenic monocytes", or Tie2-expressing monocytes, neutrophils, dendritic cell (DC) precursors, and Gr1+CD11b+ "myeloid-derived suppressor cells [MDSCs]"). All of these hematopoietic-derived cell subsets reportedly also have pro-vasculogenic activities, further supporting the possibility that prior studies that labeled cells as EPCs may have included several BM-derived cell populations of hematopoietic origin, thereby explaining most of the controversies in the field [28]. Note that such miscategorization is not surprising, because EPCs and hematopoietic progenitor cells are derived from a common precursor, the hemangioblast — thus at early stages of differentiation, EPCs and hematopoietic-derived cells may share phenotypic as well as functional characteristics, and may both have the capacity to contribute to neovessel formation in the presence of proper stimuli.

Circulating EPCs differ from circulating mature ECs (CECs). CECs are randomly detached from vessel walls, and enter the circulation subsequent to vascular injury [29]. Also, when EPCs are exposed to angiogenic factors, they give rise to highly proliferative endothelial colonies, whereas similarly exposed CECs can only generate endothelial monolayers, which have a limited proliferative capacity due to their terminally differentiated phenotype [30,31]. Finally, when circulating EPCs are recruited to inflammatory or tumor sites, they differentiate into mature ECs and integrate into nascent neovessels, while CECs lack this ability.

Table 1
Principal surface markers used to characterize circulating endothelial progenitor cells (EPCs) and comparison of their expression in adult hematopoietic stem cells and mature endothelial cells.

Markers	Name	Adult hematopoietic stem cells	Circulating endothelial progenitor cells	Endothelial cells
CD34	-Hematopoietic Progenitor Cell Antigen CD34	Positive	Positive	Positive
VEGFR2 (KDR)	-Fetal liver kinase 1 (FLK1) -CD309	Positive (a subpopulation)	Positive	Positive
CD45	-Leukocyte common antigen (LCA)	Positive	Positive, or dim positive, or negative	Negative
CD133	-Prominin-1 -AC133	Positive	Positive, or negative	Negative
CXCR4	C–X–C chemokine receptor type 4 (CXCR-4) -fusin -CD184	Positive	Positive	Positive
VE-Cadherin	-Cadherin 5, type 2 -CD144	Negative	Positive, or negative	Positive
CD31	-Platelet endothelial cell adhesion molecule (PECAM-1)	Positive	Positive	Positive
CD146	-Melanoma cell adhesion molecule (MEL-CAM) -MUC-18	NR	Positive, or negative	Positive
Tie-2	-Tunica Interna Endothelial Cell Kinase -TEK Tyrosine Kinase -VMCM1	Positive	Positive	Positive
CD14	-Myeloid cell-specific leucine-rich glycoprotein	Negative	Negative	Negative
CD105	-Endoglin (END) -FLJ41744 -HHT1 -ORW1	Positive	Positive	Positive

NR: not reported.