Critical Reviews in Oncology/Hematology 100 (2016) 177–189

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

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

Significance and therapeutic implications of endothelial progenitor cells in angiogenic-mediated tumour metastasis

Valentina Flamini, Wen G. Jiang, Jane Lane, Yu-Xin Cui*

Cardiff China Medical Research Collaborative, School of Medicine, Cardiff University, UK

Contents

ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form
30 November 2015
Accepted 15 February 2016

Keywords:
Tumour
Endothelial progenitor cell
Interaction
Angiogenesis
Metastasis

ABSTRACT

Cancer conveys profound social and economic consequences throughout the world. Metastasis is responsible for approximately 90% of cancer-associated mortality and, when it occurs, cancer becomes almost incurable. During metastatic dissemination, cancer cells pass through a series of complex steps including the establishment of tumour-associated angiogenesis. The human endothelial progenitor cells (hEPCs) are a cell population derived from the bone marrow which are required for endothelial tubulogenesis and neovascularization. They also express abundant inflammatory cytokines and paracrine angiogenic factors. Clinically hEPCs are highly correlated with relapse, disease progression, metastasis and treatment response in malignancies such as breast cancer, ovarian cancer and non-small-cell lung carcinoma. It has become evident that the hEPCs are involved in the angiogenesis-required progression and metastasis of tumours. However, it is not clear in what way the signalling pathways, controlling the normal cellular function of human BM-derived EPCs, are hijacked by aggressive tumour cells to facilitate tumour metastasis. In addition, the actual roles of hEPCs in tumour angiogenesis-mediated metastasis are not well characterised. In this paper we reviewed the clinical relevance of the hEPCs with cancer diagnosis, progression and prognosis. We further summarised the effects of tumour microenvironment on the hEPCs and underlying mechanisms. We also hypothesized the roles of altered hEPCs in tumour angiogenesis and metastasis. We hope this review may enhance our understanding of the interaction between hEPCs and tumour cells thus aiding the development of cellular-targeted anti-tumour therapies.

1. Introduction

The endothelial progenitor cells (EPCs) are a subtype of stem cells that reside within a stem cell niche in the bone marrow and are required in some repairing processes, such as

* Corresponding author.
E-mail address: cuiy7@cf.ac.uk (Y.-X. Cui).

http://dx.doi.org/10.1016/j.critrevonc.2016.02.010

myocardial ischemia and infarction, limb ischemia and wound healing. In particular they are defined by co-expression of the markers of CD34, CD309 (VEGFR-2/KDR) and CD133. Notably, CD133 is expressed in the most primitive EPCs and lost during maturation to endothelial cells, in which other markers are expressed, such as vascular endothelial cadherin and von Willebrand factor. The frequency of $CD34^+$ cells which also express CD309 and CD133 in peripheral blood in healthy individuals is around $0.4 \pm 0.2\%$ of the total $CD34^+$ population (0.002% of total mononuclear cells). Cord blood and foetal liver-derived $CD34^+$ cells contain $1.4 \pm 0.5\%$ and $1.2 \pm 0.3\%$ $CD133^+/CD309^+$ cells, respectively (Hristov and Weber, 2004; Peichev et al., 2000). In normal physiological conditions EPCs are quiescent but in response to a vascular injury, they acquire the ability to circulate in the peripheral blood, proliferate and differentiate into mature endothelial cells. In response to a gradient of growth factors and cytokines released by the damaged site, EPCs are able to migrate and home to the local endothelium, contributing to neovasculature (Peichev et al., 2000; Asahara and Kawamoto, 2004). There are no systematic studies on the physiological variation of EPCs but it has been proved that their number may varies in pathological conditions. For example, the level of circulating EPCs is lower in diabetic and vascular disease patients than in healthy people (Fadini et al., 2006; Vasa et al., 2001) and rises after an acute myocardial infarction and in some malignancies (Nowak et al., 2010a; Massa et al., 2005). EPCs are activated not only by a vascular injury, but also in the sites where the oxygen level is low such as foetal liver, umbilical cord blood and tumour tissues (Asahara and Kawamoto, 2004). EPC isolation and enumeration is made difficult by the low number of cells in peripheral blood, methodological issues and a lack of consensus on phenotypic identification. Despite this, EPCs can be isolated from peripheral blood through three general approaches and using specific methodologies to enrich their number. In the first approach EPCs are isolated by cultivation of mononuclear peripheral blood cells (PBMCs) in fibronectin-coated plates. After 2–3 weeks, the adherent cells that are able to ingest acetylated low density lipoprotein (acLDL) and to bind specific lectins are classified as EPCs. Circulating EPCs may be also purified using monoclonal antibodies and fluorescence activated cell sorting (FACS). Finally, EPCs may be obtained using two different *in vitro* colony forming assays, the colony forming unit-Hill (CFU-Hill) and endothelial colony forming cells (ECFC) assays (Yoder and Ingram, 1796). In this review, we summarised the clinical relevance of EPCs in cancer. In particular, we evaluated the possible biomarker value of EPCs in cancer, and explored how tumour microenvironment may regulate the activation, mobilisation and homing of EPCs. We also highlighted the internal and external stresses which contribute to the interaction of tumour cells and EPCs. We further proposed possible therapeutic strategies by targeting tumour-associated EPCs to halt tumour angiogenesis and metastasis.

2. Significance of EPCs in angiogenic-mediated tumour metastasis

Although the mechanisms that regulate the migration of cancer cells from the primary to secondary organs have been widely studied, some aspects of this multistep process are still unclear (Hoshino et al., 2015). Stem cells are recruited to the tumour site to enhance new blood vessel formation by secreting angiogenic molecules and/or by trans-differentiation into endothelial-like cells, such as dendritic cell precursors, circulating mesenchymal stem cells (MSCs) and a subset of adult peripheral blood leukocytes functions as endothelial cell progenitors (Coukos et al., 2005; Harraz et al., 2001; Xu and Li, 2014). Haematopoietic precursor cells from the bone marrow, including EPCs, appear to be activated on specific sites before the tumour cells get there, contributing to the formation of a "pre-metastatic niche", in which non-cancer cells promote metastasis development. Changes in the level of circulating EPCs in patients with cancers can indicate treatment response as well as the grade of the malignancy. Thus, the number or functional alteration of EPCs in peripheral blood of cancer patients may be used as a biomarker to evaluate the risk of metastasis and raises the possibility that targeting circulating progenitors may have a therapeutic value.

2.1. Clinical relevance of EPCs in cancer

The condition in which a region of the body is deprived of an adequate oxygen supply is called "hypoxia". During embryonic development, where the level of oxygen is low, EPCs contribute to the physiological vasculogenesis of the embryo (Schmidt et al., 2007). In adults, EPCs can be activated by a vascular injury or hypoxia and play an important role in neo-vasculogenesis, the formation of new vessels during post-natal life (Ceradini et al., 2004). In normal conditions, EPCs are mobilized from the bone marrow in response to paracrine factors released by the injured tissues, such as Vascular Endothelial Growth Factor (VEGF) and Stromal cell-Derived Factor 1 (SDF-1). When the wound is repaired, the physiological state is established again and EPCs are not recruited anymore. In pathologic states such as tumour aggression, when a chronic state of hypoxia and/or inflammation occurs, the EPCs are constitutively activated and play a double role: from one side, they contribute to the tumour sprouting thanks to their ability to form new vessels. On the other side by releasing paracrine secretions of pro-angiogenic growth factors, they contribute to maintaining an inflammatory state, one of the essential biological characteristics for tumour growth and progression (Hanahan and Weinberg, 2011). It has been shown that hypoxia itself is good for growth and survival of stem and progenitor cells, inducing a "protective" autophagy and moderate apoptosis during times of cellular stress. However, if the exposure to low oxygenation in tissues becomes a chronic state, the result is a major apoptosis and destructive necrosis (Sharma and Wu, 2013).

It has been demonstrated that EPCs are mobilized from the bone marrow in different types of malignancies, such as hepatocellular carcinoma, lung, pancreatic and breast cancer (Yu et al., 2007; Nowak et al., 2010b; Starzynska et al., 2013; Ono et al., 2014; Buchanan et al., 2012). Several studies have shown that in different types of cancers, the EPC level is very high in both tissues and peripheral blood of cancer patients compared to those of healthy donors. For instance, the increase of EPCs in peripheral blood of hepatocellular carcinoma patients was observed (Yu et al., 2007). In patients with Non-Small-Cell Lung Carcinoma (NSCLC) and Small Lung Carcinoma (SLC) the number of circulating EPCs increases in proportion to the disease progression, and there appears a correlation between circulating EPC concentration and the stage of the malignancy (Nowak et al., 2010b). If further studies can confirm this finding, it may be possible to consider the EPCs from peripheral blood as non-invasive biomarkers for the monitoring of tumour progression, in concert with other tumour-specific biomarkers already available. Studies also suggested a possible application of circulating EPCs as predictors of the malignancy grade of some tumours. In fact, a decrease of circulating EPCs has been observed in patients who respond well to anticancer treatments. Circulating EPCs have also been proposed to be prognostic and predictive biomarkers for gastric cancer patients treated with chemotherapy (Ahn et al., 2010). Indeed there is a reduction of EPC levels in breast cancer patients after cytotoxic therapy (Kuo et al., 2012). The level of EPCs in blood can be distinguished from healthy donors, NSLC patients who responded well to the treatment (chemotherapy/radiotherapy) and NSLC patients who did not