Drug Resistance Updates 25 (2016) 26–37

Contents lists available at ScienceDirect

Drug Resistance Updates

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

Role of the tumor stroma in resistance to anti-angiogenic therapy

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ARTICLE INFO

Article history:
Received 3 December 2015
Received in revised form 9 February 2016
Accepted 17 February 2016

Keywords:
Angiogenesis
Tumor
Stroma
Anti-angiogenic therapy
Resistance

ABSTRACT

Several angiogenesis inhibitors are currently used in the clinic for treatment of cancer. While anti-angiogenesis treatment can improve treatment outcome, the overall benefit on patient survival is still rather limited. This is partially explained by intrinsic or acquired resistance of tumor cells to angiostatic drugs. In addition, it has become evident that extrinsic mechanisms are also involved in resistance to angiostatic therapy. Most of these extrinsic mechanisms reside in the tumor stroma, which is composed of different cell types, including endothelial (progenitor) cells, smooth muscle cells, pericytes, (myo)fibroblasts, immune cells and platelets. In the current review, we describe the role of these stromal cells in the resistance to anti-angiogenic drugs and discuss possible strategies to overcome resistance and enhance the efficacy of angiostatic therapy.

1. Introduction

The identification of angiogenesis as a prerequisite for the outgrowth of solid tumors boosted the field of angiogenesis research (Folkman, 1971). This has resulted in the identification of many different angio-stimulatory factors and pathways that can be targeted for therapeutic purposes (Griffioen and Molema, 2000; Carmeliet and Jain, 2011; Potente et al., 2011). Indeed, numerous angiogenesis inhibitors have been developed, several of which are approved for clinical use and have improved the treatment of cancer (Meadows and Hurwitz, 2012; Jain et al., 2006). However, the enthusiasm for angiostatic therapy has been hampered due to the limited beneficial effect of these anti-angiogenic agents on patient survival (Jayson et al., 2016). Continuous preclinical and clinical research has shown that this modest efficacy can partly be attributed to the induction of resistance (Jayson et al., 2016). For example, it has been shown that resistance to angiostatic therapy involves growth factor redundancy. This refers to the ability of tumor cells to express and secrete multiple angio-stimulatory growth factors. The production of growth factors other than those blocked by angiostatic drugs would allow tumor cells to evade the therapy (Thijssen et al., 2007). Other mechanisms of resistance to anti-angiogenic therapy involve the sequestration of drugs in intracellular vesicles (Gotink et al., 2011; Adar et al., 2012; Zhitomirsky and Assaraf, 2015, 2016; Nowak-Sliwinska et al., 2015) or a switch to the dependency on different types of vascularization, such as vessel cooption (Leenders et al., 2004) or vasculogenic mimicry (van der Schaft et al., 2005; Paulis et al., 2010). While it can be argued whether some of these

Abbreviations: Ab, antibody; ACT, adoptive cell therapy; ANG, angiopoietin; ATP, adenosine triphosphate; BMDC, bone marrow derived cell; CA4P, combretastatin A phosphate; CAF, cancer-associated fibroblast; CCL2, C-C motif ligand 2; CD, cluster differentiation antigen; CEC, circulating endothelial cell; CSF-1, colony stimulating factor-1; CSF-1R, colony stimulating factor-1 receptor; CXCL2, C-X-C motif ligand 2; CXCR, C-X-C chemokine receptor; DC, dendritic cells; dRB, 2-deoxy-D-ribose-1-phophate; EC, endothelial cell; ECM, extracellular matrix; EGF, epidermal growth factor; EPC, endothelial progenitor cell; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; HLA-DR, human leukocyte antigen-DR; ICAM, intracellular adhesion molecule; IGF, insulin-like growth factor; IL, interleukin; mbKitL, membrane-bound KIT ligand; MCP-1, monocyte chemoattractant protein-1; MDSC, myeloid derived suppressor cell; MMP, matrix metalloproteinase; MMTV-PyMT, mouse mammary tumor virus- polyoma middle T-antigen; NF-κB, nuclear factor kappa B; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDGF, platelet derived growth factor; PI3K, PI3 kinase; PNET, pancreatic neuroendocrine tumor; pSTAT5, phosphorylated Signal Transducer and Activator of Transcription 5; RCC, renal cell carcinoma; RIP-Tag2, rat insulin promoter- large T-antigen 2; SCF, stem cell factor; SDF1, stromal-derived factor 1; TAM, tumor-associated macrophages; TAN, tumor-associated neutrophils; TEM, TIE2 expressing macrophages; TGFβ, transforming growth factor beta; TKI, tyrosine kinase inhibitor; TNFα, tumor necrosis factor alpha; TP, thymidine phosphorylase; VCAM, vascular cell adhesion molecule; VEGFR, vascular endothelial growth factor receptor; VLA-4, very late antigen-4.

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http://dx.doi.org/10.1016/j.drup.2016.02.002
1368-7646/

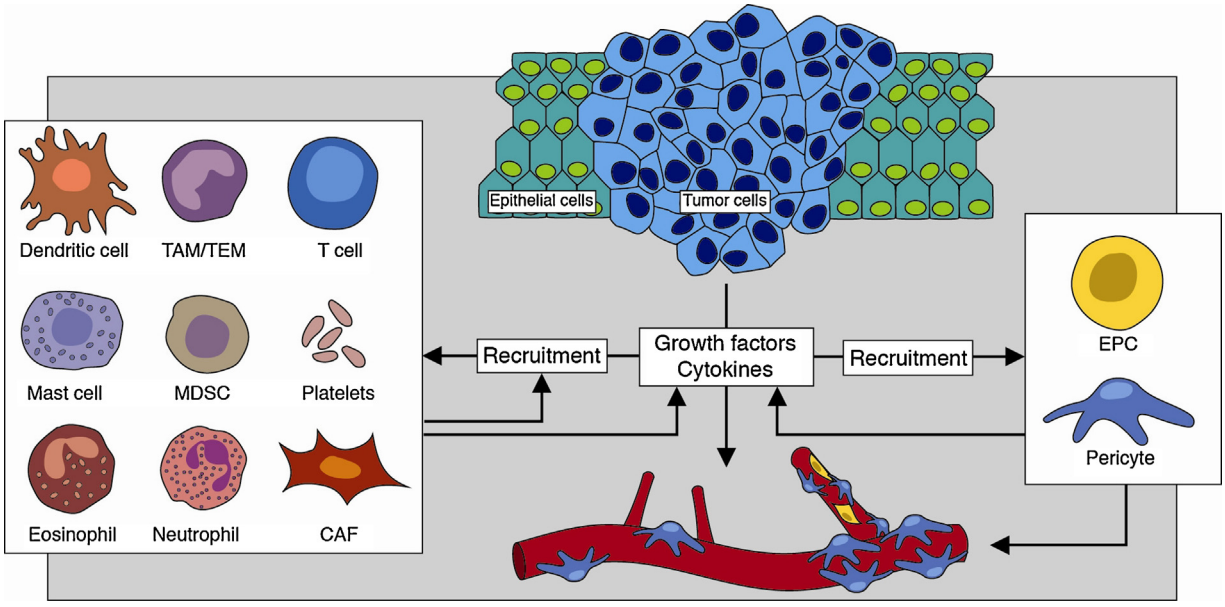

Fig. 1. Cell types involved in resistance to anti-angiogenic therapy. Tumor cells secrete growth factors and cytokines in response to anti-angiogenic therapy. This leads to the recruitment of endothelial cells, myeloid cells, lymphoid cells, pericytes and cancer-associated fibroblasts supporting both tumor growth and tumor angiogenesis.

mechanisms represent a more compensatory mechanism rather than actual resistance, it is evident that tumor cells exploit different mechanisms to evade angiostatic therapy. Apart from such acquired or intrinsic escape mechanisms it has also become apparent that several extrinsic mechanisms are involved in resistance to angiostatic therapy. Most, if not all, of these mechanisms reside in the tumor stroma, which consists of a plethora of different cell types, including endothelial cells, smooth muscle cells, pericytes, (myo)fibroblasts, immune cells and platelets. It has been proposed that insight in the contribution of these non-cancerous cells to malignant progression could help to better tackle tumor growth (Egeblad et al., 2010). Consistently, it is becoming increasingly evident that the cells in the stromal compartment of tumors not only provide a target for cancer treatment but also play an important role in resistance to therapy (van Beijnum et al., 2015; Bergers and Hanahan, 2008; Vasudev and Reynolds, 2014).

Here, we review the presence of different resistance mechanisms to anti-angiogenic drug therapy mediated by cells in the tumor stroma (Fig. 1). Different strategies to overcome resistance conveyed by these cell types are discussed.

2. Endothelial cells

Endothelial cells (ECs), i.e., cells that line the luminal side of blood vessels, are considered the main target cells for angiostatic therapy. Not only because they are easily accessible for blood-borne compounds but also because ECs are key in blood vessel growth (Griffioen and Molema, 2000; Potente et al., 2011). Moreover, ECs are considered to be a homogeneous and genetically stable cell population, which is less prone to develop drug resistance. However, morphological analyses and gene expression studies revealed that considerable heterogeneity exists within the EC population, both in healthy and diseased tissues (Aird, 2012; Jain and Booth, 2003). In addition, cytogenetic abnormalities, such as aneuploidy, have been observed in tumor endothelial cells (Hida et al., 2004, 2015). While the latter suggests genetic instability, it has been suggested that these abnormalities can occur through horizontal transfer of genomic material between ECs and tumor cells (Streubel et al., 2004; Ehnfors et al., 2009). Nevertheless, acquiring traits from genetically unstable cells might induce drug resistance. On the other hand, while evidence has been found that tumor endothelial cells can be resistant to chemotherapeutics or tyrosine kinase inhibitors (Tran et al., 2002; Huang et al., 2013, 2014; Xiong et al., 2009), it has not been elucidated whether this is related to the genomic signature of tumor endothelial cells. Rather, resistance of ECs to anti-angiogenic treatment appears to be related to increased expression of multidrug resistance proteins like P-glycoprotein (Pgp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2), that serve as cellular efflux pumps (Akiyama et al., 2012; Huang et al., 2014). In addition, it has been shown that induction of the anti-apoptotic protein survivin by VEGF can also confer resistance to chemotherapy upon ECs (Tran et al., 2002). A more recent study linked altered receptor glycosylation to resistance to anti-VEGF treatment. It was found that different VEGF receptor 2 glycosylation allowed the glycan-binding protein galectin-1 to maintain receptor signaling (Croci et al., 2014). This extended beyond classical resistance caused by growth factor redundancy as the presence of receptor specific growth factor was not required (Croci et al., 2014). Consistently, other galectin family members have been associated with the angiogenic activity of ECs (Thijssen et al., 2006, 2013). Thus, ECs might become resistant to angiostatic therapy by alterations in the glycosylation machinery.

Altogether, most studies suggested that resistance of ECs to angiostatic treatment mainly involves intrinsic response mechanisms rather than genomic alterations. This provides opportunities to overcome drug resistance and warrants further studies into the molecular pathways that drive the mechanisms of resistance in ECs. Regarding the latter, it appears more feasible to target proteins that are expressed on tumor EC in response to activation rather than those that cause activation (Thijssen et al., 2007; van Beijnum and Griffioen, 2005). We and others have performed expression screens to identify such tumor endothelial cell markers (TEMs) (St Croix et al., 2000; van Beijnum et al., 2006) which has resulted in unexpected targets for angiostatic therapy like vimentin and HMGB1 (van Beijnum et al., 2006, 2013). Further research is required to confirm that targeting such TEMs are less prone to the development of drug resistance.

3. Myeloid cells

Myeloid cells are derived from common hematopoietic progenitor cells in the bone marrow and include, amongst others,