Editorial

Is it the primetime for endoglin (CD105) in the clinical setting?

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See article by Jerkic et al. [12] (pages 845–854) in this issue.

Initial studies carried out at the beginning of the past century identified increased vascularity as a common feature associated with tumor growth; based on these morphological observations, it was then demonstrated that local tumor growth and distant metastasis of neoplastic cells are strictly dependent on adequate blood supply. The latter was subsequently shown to be provided by blood vessels neoformed from pre-existing ones whose growth is directly promoted by neoplastic cells through the local release of angiogenic factors. Altogether, these observations provided a strong scientific rationale to hypothesize the clinical use of an anti-angiogenic approach based on therapeutic tools able to inhibit molecularly characterized regulators of angiogenesis as an effective strategy to treat cancer [1,2]. Nevertheless, among a large array of novel therapeutic agents with anti-angiogenic activity tested in the clinical setting in the past decade, the humanized version of a murine anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb) (bevacizumab) is the only such agent that has received approval for the treatment of metastatic colorectal cancer in association with chemotherapy [2]; thus, plenty of room is still available for the clinical development of new therapeutic compounds that interfere with tumor-associated angiogenesis.

The two major anti-angiogenic strategies utilized so far in the clinical setting of human malignancies involve the inhibition of pro-angiogenic factors (e.g., VEGF) and therapy with endogenous inhibitors of angiogenesis such as endostatin and angiostatin [3]. However, direct targeting of endothelial cells lining tumor-associated blood vessels is emerging as an alternative, highly attractive approach to cut down blood supply to neoplastic cells in the tumor mass. In this respect, the prospective use of therapeutic mAbs directed to cell-surface antigens present or over-expressed on tumor-associated endothelia [4] is strongly supported by the significant clinical results we are experiencing with solid and hemopoietic human malignancies utilizing therapeutic mAbs that recognize different tumor-associated antigens [5]. The great advantage of therapeutic mAb stems from their generally pleiotropic mechanism of action that can combine the delivery of therapeutic agents at tumor sites and the transduction of growth inhibitory and/or pro-apoptotic intracellular signals, with direct killing of target cells through the activation of immunologic mechanisms, such as antibody-dependent cell-mediated cytotoxicity and/or complement-mediated cytotoxicity [6]. On the other hand, their efficient binding to cell surface molecules expressed on neoplastic cells requires that therapeutic mAbs reach the target tissue that is in most cases away from the bloodstream, and thus, difficult to be adequately reached by these large-sized therapeutic agents. Thus, to overcome this limitation of therapeutic mAbs, their ideal target(s) have to be expressed on cells directly exposed to the bloodstream, such as endothelial cells. Along this line, different markers of resting, activated, and/or proliferating endothelial cell are under active investigation as potential molecular targets for antibody-based anti-angiogenic therapy [4,7]. Among the most promising members of this growing “family” of novel therapeutic targets is endoglin (CD105), a homodimeric transmembrane glycoprotein over-expressed on endothelial
cells of angiogenic tumor blood vessels [8] that is part of the TGF-β receptor complex and modulates cellular responses to TGF-β implicated in the early steps of angiogenesis [9].

The main evidence supporting the crucial role of CD105 in angiogenesis is derived from the demonstration that CD105 knockout mice show defective vascular development leading to death during early gestation [10], and that mutations in CD105 gene associate to hereditary hemorrhagic telangiectasia type (HHT)-1, a dominant-inherited disease characterized by arterio-venous malformations and bleeding in humans [11]. Expanding on this latter aspect and utilizing endothelial cells derived from an animal model of HHT-1 (CD105+/− adult mice), Jerkic et al. [12] demonstrate in the present issue of Cardiovascular Research that normal levels of CD105 are mandatory for their physiologic angiogenic activity. In fact, CD105+/− endothelial cells showed reduced proliferation and migration, increased basal or TGF-β1-mediated collagen synthesis, impaired capillary tube formation, reduced endothelial nitric oxide-synthase activity and VEGF secretion, and reduced blood vessel formation in vitro and/or in vivo [12]. These pieces of evidence, along with a large bulk of pre-existing literature data, clearly identify a key functional role for CD105 in the physiologic generation of blood vessels and strongly support the idea that CD105 is an adequate target to disrupt the development of tumor-associated angiogenesis.

Confirming its great potentiality as therapeutic target in human malignancies, different in vitro and in vivo studies have recently demonstrated that naked, radiolabeled or immunotoxin-conjugated anti-CD105 mAb specifically localized in the areas of major vascularization within the tumor mass inhibited proliferation of micro- and macro-vascular endothelial cells, efficiently radiolabeled spontaneous or grafted tumors, and induced a long-lasting suppression of tumor growth and metastasis in different human and murine tumor models [13,14]. Furthermore, among different pan-endothelial markers, staining for CD105 more efficiently assessed intra-tumor microvascular density and showed a stronger correlation with patients’ prognosis, providing additional, though indirect, support to the usefulness of CD105 for therapeutic targeting of cancer [13].

Altogether, the large body of available data on the biology of CD105 in human solid and hemopoietic malignancies and on the functional activity of distinct anti-CD105 mAb (Fig. 1) undoubtedly indicate that CD105 is now ready to go into its clinical evaluation for the treatment of human cancer. Along this line, a human/mouse chimeric antibody of the IgG1 isotype that shows pharmacokinetic parameters comparable to those reported for other therapeutic mAbs currently utilized for cancer treatment has been recently generated and is planned to be used in clinical trials [15].

The next few years promise to be a very exciting time for those who have been enthusiastically exploring the therapeutic potential of CD105 for the treatment of human cancer!

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