Re: Role of Transforming Growth Factor-β Signaling in Cancer

We congratulate Dr. A. B. Roberts and her colleagues (1) for their excellent and timely review on transforming growth factor-β (TGF-β)1 signaling in cancer. Perhaps constraint of space and danger of losing focus has not allowed them to mention an important modulator of TGF-β1 signaling, namely, CD105 (endoglin).

CD105, a homodimeric glycoprotein of 180 kd, was described initially as a leukemia-associated antigen; subsequently, it was identified as the type III receptor for TGF-β1 and TGF-β3. CD105 is preferentially expressed in proliferating vascular endothelial cells, constitutively phosphorylated, and forms heteromeric complexes with TGF-β receptor I and/or receptor II in the presence of ligands TGF-β1 and TGF-β3, implicating its participation in the modulation of TGF-β signaling (Fig. 1). CD105 insufficiency leads to hereditary hemorrhagic telangiectasia type I, an autosomal-dominant disorder characterized by multisystemic vascular dysplasia and recurrent hemorrhage. Unlike betaglycan, which shares high homology with CD105 and presents ligand to the signaling receptors, CD105 antagonizes TGF-β1 signaling in various cell types. For instance, overexpression of CD105 in U937 human myelomonocytic cells, rat myoblasts, and mouse fibroblasts renders these cells refractory to TGF-β1 treatment (2). In human umbilical vein endothelial cells, that strongly express CD105, antisense approach was applied to suppress CD105 gene expression (3). In CD105-deficient cells, wherein both its messenger RNA and protein were considerably reduced, the inhibitory effects of TGF-β1 on cell proliferation, migration, and capillary formation were substantially augmented, implying that the abundant presence of CD105 may shield endothelial cells from the inhibitory action of TGF-β1, thus contributing to angiogenesis. Further evidence came from the CD105 knockout mice, in
which CD105 null mice develop severe defects in angiogenesis and die in utero (4). The abrogation of CD105 gene expression is likely to result in TGF-β malfunction, thus contributing to the lethal consequence, which is further supported by the occurrence of defective vasculogenesis and embryonic lethality in both TGF-β1 null and transgenic mice (5,6).

Overexpression of CD105 in tissues has been linked with angiogenesis. This notion initially came from the observation that monoclonal antibody E9 to CD105 reacted most strongly with the endothelium in various types of tumor tissues but only weakly or not at all with endothelial cells of normal tissues. Subsequently, tissue staining by use of other monoclonal antibodies to CD105 have confirmed the increase of CD105 in blood vessels of many more histologic types of tumor and numerous angiogenic diseases. Recently, expression of CD105 in blood vessels of breast cancer tissues was found to be associated inversely with overall and disease-free survival (7). Furthermore, the levels of soluble CD105 and CD105/TGF-β complexes in the circulation were elevated markedly in breast cancer patients who developed metastasis and/or who died of the disease. In cervical cancer, CD105 reactivity correlated significantly with lymph node metastasis.

In conclusion, there is a compelling evidence that CD105 is essential for angiogenesis, and it has entered the fray as one of the key modulators of TGF-β signaling. Although it is not known how an interaction between the receptor and ligand exactly controls angiogenesis, a discussion on TGF-β involvement in cancer warrants inclusion of this key molecule.

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RESPONSE

We welcome and appreciate the comments of Dr. Li and colleagues regarding the possibility that overexpression of endoglin/CD105 in tumor blood vessels may contribute to tumor angiogenesis. Indeed, this is especially exciting because it begins to define reciprocal relationships between tumor cells and stroma that create an environment permissive for tumor cell growth. Furthermore, it provides potentially a mechanism whereby the endothelial cell can selectively "protect" itself from inhibitory effects of transforming growth factor-β (TGF-β) secreted by the tumor cell, while at the same time allowing suppression of immune surveillance and enhancement of desmoplasia. However, before we embrace this mechanism, we must be cautious to assure that the tumor endothelial cells actually express more endoglin per cell, as distinguished from certain conditions, betaglycan can enhance tumorigenicity. Thus, overexpression of oncogenic, but not wild-type, Ras results in conversion of HD6–4 colon cancer cells from being insensitive to TGF-β to being growth stimulated by TGF-β, giving rise to a more aggressive tumor phenotype. This has been shown to correlate specifically with post-translational modification of betaglycan (6).

Overall, it is clear that the entire TGF-β signaling cascade from secretion of ligand, to activation or sequestration of ligand, to receptors and receptor-modulating proteins (such as endoglin and betaglycan), to the intracellular signaling transducers and modulators, including mitogen-activated protein kinase (MAP) and small mothers against decapentaplegic (Smad) pathways, must all be considered in any analysis of the complex effects of TGF-β on carcinogenesis.

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