Role of Endostatin in Cardiovascular Remodeling
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Tumor growth is accompanied by angiogenesis, and because surgical removal of certain tumors may lead to rapid growth of remote metastases, endogenous angiogenesis inhibitors may be secreted from the tumor. The endogenous angiogenesis inhibitor, angiotatin, was identified in urine in 1994, and a more potent angiogenesis inhibitor, endostatin, was discovered in 1997 in the conditioned media of cultured hemangioblastoma cells. Endostatin is a 20-kDa carboxy-terminal proteolytic fragment derived from the first noncollagenous domain of collagen XVIII. Because tumor growth depends on angiogenesis, endostatin was thought to be a promising factor for inhibiting tumor growth. Indeed, many animal and human tumors have been inhibited by the administration of endostatin in animal studies; however, the results of several clinical studies were disappointing, and the clinical trials of endostatin were terminated at early phase II in the United States. The failure of the clinical studies is attributable, at least in part, to the failure of an appropriate trial design, including administration regimen, patient selection and the establishment of a biologically effective dosage. Only Endostar, a N-terminal modified endostatin, is used in clinical trials in China, although its precise effectiveness is unknown.

In contrast to tumors, angiogenesis may play a beneficial role in ischemic cardiovascular diseases and is a promising strategy for the treatment of ischemic heart disease, including myocardial infarction (MI). Several studies that administered pro-angiogenic genes, bone marrow cells or peripheral blood cells to the ischemic heart are under clinical trial. Further, recent studies of patients with coronary artery disease (CAD) demonstrate that endostatin protein levels correlate significantly with reduced angiogenesis and poorly developed collateral vasculature.

In this issue of the Journal, Isobe et al hypothesized that inhibition of endostatin may improve heart function and mortality by facilitating angiogenesis in CAD. On the contrary, they demonstrated that (1) neutralization of endostatin resulted in higher mortality because of adverse LV remodeling and heart failure in a rat MI model and (2) not only angiogenesis, but also collagen XVIII through its C-terminal domain. The upregulated genes included pro-angiogenesis genes (VEGF-A, MMP-9, HIF-1α), while the downregulated genes included collagen XVIII, which was speculated to be due to the inhibition of downstream focal adhesion kinase activation. Endostatin interferes with vascular endothelial growth factor (VEGF) receptor 2 signaling. In addition, endostatin forms a stable complex with MMP-2 and inhibits its activity by masking the MMP-2 catalytic domain. Endostatin is also known to block the activities of MMP-9 and MMP-13. Endostatin has also been reported as downregulating β-catenin via Wnt signaling pathways, which is important for heart development and remodeling. Recently, gene chip analysis revealed that the expression of 12% of the genes on the chip was significantly altered in response to endostatin treatment. The upregulated genes included pro-angiogenesis genes (VEGF-A, MMP-9, HIF-1α), while the downregulated genes included anti-angiogenic genes such as thrombostatin (TSP)-1, TSP-2, kininogen, and vasostatin. This study suggests that endostatin modifies multiple pathways to inhibit angiogenesis. Isobe et al demonstrated increased fibrosis and the upregulation of MMP-2, MMP-9 and ACE. The upregulation of ACE is a novel finding and suggests that endogenous endostatin may inhibit ACE, leading to inhibition of LV remodeling after MI. Thus, the adverse LV remodeling and heart failure by endostatin neutralization may result not only from a direct effect on angiogenesis, but also from other effects of endostatin inhibition.

Another possibility that should be considered is a direct effect of antibody on collagen XVIII. Antibody was raised against the endostatin sequence in collagen XVIII, so anti-endostatin antibody may block not only secreted endostatin but also collagen XVIII through its C-terminal domain. Collagen XVIII, a component of the basement membrane, is a heparan sulfate proteoglycan and contains 10 collagenous domains that are interrupted and flanked by noncollagenous domains. After endostatin was identified as the C-terminal domain of collagen XVIII, more than 10 extracellular matrix (ECM) protein fragments have been also discovered as endogenous angiogenesis inhibitors, such as tumstatin from...
α3 collagen IV, vastin from α1 collagen VIII and endorepel-
lin from perlecan. The reports suggest that interactions
between endothelial cells and the ECM play key roles in the
regulation of angiogenesis.

Recently, the phenotype of collagen XVIII-deficient
(Coll18a1−/−) mice was reported. The mice demonstrate a
progressive attenuation of vision, with abnormalities in ocu-
lar structures, but surprisingly they do not display increased
angiogenesis in major organs, suggesting that collagen
XVIII/endostatin is not a critical negative regulator of angi-
genesis under basal conditions. However, endothelial cells
isolated from Coll18a1−/− mice show an increased ability to
adhere to fibronectin in vitro, and increased outgrowth of
microvessels from aortic explants of Coll18a1−/− mice has
also been observed. Using Coll18a1−/− mice and apoE−/−
mice, Mouton et al demonstrated that endostatin/collagen
XVIII expression was elevated in the aorta, and that the loss
of collagen XVIII enlarged plaque lesions through enhanced
neovascularization and vascular permeability. Furthermore,
they previously reported that the administration of recom-
binant endostatin reduced plaque growth and intimal neo-
vascularization in apoE−/− mice, suggesting that intimal
neovascularization may promote plaque development. Thus,
in the cardiovascular system, the anti-angiogenesis function
of endostatin may exert cardiovascular protection in some
situations. Isobe et al showed adverse effects of endostatin
inhibition on MI by using neutralizing antibody alone. The
use of Coll18a1−/− mice in MI models will provide defini-
tive evidence regarding the role of endogenous endostatin
in the LV remodeling after MI.

The induction of endogenous collagen XVIII/endostatin
in the MI heart is noteworthy, and this is the first evidence of a
pathophysiological role of endogenous endostatin/collagen
XVIII in LV remodeling and heart failure in MI. In the MI
model, pro-angiogenic factors are also increased to promote
angiogenesis. Thus, induced endogenous endostatin may
inhibit the excessive angiogenesis or cardiac remodeling
induced by these growth factors. Although the precise mecha-

In conclusion, this study provides a novel insight into the
function of endogenous endostatin in MI. Although angi-
genesis is believed to have a beneficial effect on LV remod-
eling after MI, this study suggests a possible adverse effect
of excessive angiogenesis. Furthermore, the results may lead
to a novel approach in treating MI by using endostatin.

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