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The potent, proangiogenic effects of vascular endothelial growth factor (VEGF) have been the focus of many strategies to promote therapeutic angiogenesis. However, the dose-limiting proinflammatory side effects of VEGF (eg, increased vascular permeability, leukocyte adhesion, upregulated adhesion molecule expression) have raised concerns about the clinical utility of VEGF.[1–4] Recently, combinations of VEGF with other growth factors (such as with angiopoeitin-1) have been tested as alternative strategies to promote new vessel growth and limit the edema and inflammation associated with VEGF.[5]

Hepatocyte growth factor (HGF; also known as scatter factor) is a large multidomain protein structurally similar to plasminogen. The receptor for HGF is c-met, a disulphide linked heterodimer with tyrosine kinase activity. HGF is a potent endothelial mitogen, motogen, and morphogen,[6,7] although in contrast to VEGF these effects are not limited to endothelial cells. HGF is induced in skeletal and cardiac muscle after ischemic injury,[8,9] and HGF and its receptor c-met are often overexpressed in various tumors.[10] Administration of HGF, either as a protein or incorporated into an adenoviral vector, has been shown to promote angiogenesis without increased vascular permeability or inflammation.[11–17]

Combining HGF and VEGF results in a much more robust endothelial proliferative response and chemotactic response than either growth factor alone.[18,19] In three-dimensional type I collagen gels, neither HGF nor VEGF alone are sufficient to induce human endothelial cell survival and tubulogenesis, yet the combination of the two growth factors will support these responses.[19] In vivo studies also suggest that combining HGF and VEGF also induces a more robust angiogenic response.[18,19]

Early studies of the proangiogenic actions of HGF attributed the effects of HGF to the induction of VEGF. Van Belle and coworkers suggested that HGF induced VEGF production by surrounding smooth muscle cells.[18] Wojta et al[20] and Gille and coworkers[21] observed that HGF increased the expression of keratinocyte-derived VEGF, and suggested that HGF might induce angiogenesis by a paracrine mechanism. However, other studies suggested that the proangiogenic effects of HGF were independent of VEGF.[22] A recent gene expression profiling study clearly demonstrated that HGF and VEGF signal through discrete pathways in vascular endothelial cells, and moreover, the combination of the two growth factors synergistically induces a number of genes involved in the regulation of the cell cycle.[23]

In this issue of *Circulation Research*, Min and coworkers provide new insights into the potential of growth factor combinations for therapeutic angiogenesis.[24] These authors report that HGF does not alter leukocyte adhesion to endothelial cells and, moreover, markedly reduces the increase in leukocyte adhesion and adhesion molecule expression stimulated by VEGF. Mechanistically, this effect appeared to be mediated by an HGF suppression of VEGF-induced NF-κB signaling. In vivo, HGF decreased VEGF-elicited leukocyte recruitment in a delayed type hypersensitivity model, whereas HGF/VEGF cotreatment markedly increased vascular density compared with either growth factor alone. This study clearly demonstrates that further study of the interactions of HGF and VEGF is warranted. Using this dynamic duo of growth factors to stimulate new vessel growth without the complications of inflammation and edema offers an exciting new direction for therapeutic angiogenesis.

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KEY WORDS: therapeutic angiogenesis ■ leukocytes ■ inflammation ■ antiinflammatory ■ HGF ■ VEGF