Comment on Kärrkäinen et al, page 4468

Lymphangiogenesis factors: a target for therapy?

Arjan W. Griffioen  MAASTRICHT UNIVERSITY

In this issue of Blood, Kärrkäinen and colleagues demonstrate, using a VEGF-D transgenic mouse model, that overexpression of human VEGF-D induces a pro-angiogenic phenotype, increases regeneration after ischemic injury, and also induces the formation of tumors.

Vascular endothelial cell growth factor D (VEGF-D) was identified in the mid-1990s as a c-fos–induced growth factor sharing structural and functional characteristics with VEGF-C and displaying lymphangiogenic properties through activation of the lymph vasculature receptor VEGFR-3.1,2 In humans, VEGF-D binds to VEGFR-3 as well as to VEGFR-2, of which the latter is the receptor for VEGF-transducing signals leading to formation of blood vessels. The study by Kärrkäinen et al., which reports the generation of human VEGF-D transgenic mice using a method based on perivitelline oocyte injection of a lentiviral vector expressing the growth factor, provides new insight into the biology of VEGF-D.3 The transgenic mice, constitutively expressing VEGF-D in many organs, clearly demonstrate a proangiogenic phenotype with enhanced blood vessel capillary density in muscle tissue while a lack of increased numbers of lymphatic capillaries suggest no effect on lymphangiogenesis. The enhanced healing capacity of transgenic mice after ischemic injury was also suggested to be mainly due to VEGFR-2 signaling and enhanced blood vessel formation. These results are consistent with earlier studies where knockout approaches were used, demonstrating that VEGF-D does not have a major lymphangiogenesis function.4 This study by Kärrkäinen et al., as well as studies by others, may suggest the potential for growth factor therapy of isch-emic diseases. In addition, discussions on the use of therapeutic lymphangiogenesis for diseases with associated lymphedema after surgery or radiotherapy are ongoing. Although this is an attractive approach, (lymph)-angiogenic growth factors can enhance vascular permeability, which may pose an additional problem.

In the present study, it was observed that mice with human VEGF-D incorporated in their genome developed spontaneous tu-
mors in epithelia with a preference for induction of mammary gland adenocarcinomas. This interesting and unexpected finding may limit the therapeutic use of VEGF-D. Therapeutic intervention by neutralization of VEGF-D for diseases characterized by excessive angiogenesis, such as cancer, may therefore be a more promising approach. Indeed, inhibition of metastatic spread, microhemorrhage, and collapse of tumor vessels has been described in mice injected with blocking monoclonal antibodies5 or soluble VEGFR-3.6

Although it was reported before that VEGF-D can facilitate tumor growth and support metastasis formation, probably due to enhanced vessel/tumor cell interaction surface, it is very interesting to question how VEGF-D can give rise to spontaneous tumors. It suggests that either the growth factor itself can transform normal epithelial cells into tumor cells — a hypothesis that is currently considered unlikely — or that normal epithelial cells are continuously challenged by genetic or epigenetic alterations, having more chance to result in tumor cells (normally a very rare event) when a more angiogenic environment is available. In the latter situation, tumor growth may be supported by better supply of oxygen and nutrients, by enhanced vascular permeability, a beneficial cytokine/chemokine milieu, or by a changed adhesion molecule profile. Another possibility is the VEGF-D–mediated generation of an immune-privileged situation. Indeed, VEGF-D has been reported to contribute, in a concerted action with other angiogenic growth factors, to endothelial cell anergy and subsequent escape from immune surveillance.7 All these conditions are supportive for an anti–VEGF-D strategy to intervene with tumor growth. Such an approach would potentially have the same problems as current anti–VEGF strategies in the clinic,8 such as induction of drug-induced resistance, but this may be overcome by combining different strategies of therapy. The paper by Kärrkäinen et al definitely underscores the importance of VEGF-D in the regulation of angiogenesis and suggests an opportunity for the development of new and innovative medical technology for cancer and other human diseases.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Conflict-of-interest disclosure: The author declares no competing financial interests.

vascular endothelial cell growth factor D (VEGF-D) was identified in the mid-1990s as a c-fos–induced growth factor sharing structural and functional characteristics with VEGF-C and displaying lymphangiogenic properties through activation of the lymph vasculature receptor VEGFR-3.1,2 In humans, VEGF-D binds to VEGFR-3 as well as to VEGFR-2, of which the latter is the receptor for VEGF-transducing signals leading to formation of blood vessels. The study by Kärrkäinen et al., which reports the generation of human VEGF-D transgenic mice using a method based on perivitelline oocyte injection of a lentiviral vector expressing the growth factor, provides new insight into the biology of VEGF-D.3 The transgenic mice, constitutively expressing VEGF-D in many organs, clearly demonstrate a proangiogenic phenotype with enhanced blood vessel capillary density in muscle tissue while a lack of increased numbers of lymphatic capillaries suggest no effect on lymphangiogenesis. The enhanced healing capacity of transgenic mice after ischemic injury was also suggested to be mainly due to VEGFR-2 signaling and enhanced blood vessel formation. These results are consistent with earlier studies where knockout approaches were used, demonstrating that VEGF-D does not have a major lymphangiogenesis function.4 This study by Kärrkäinen et al., as well as studies by others, may suggest the potential for growth factor therapy of ischemic diseases. In addition, discussions on the use of therapeutic lymphangiogenesis for diseases with associated lymphedema after surgery or radiotherapy are ongoing. Although this is an attractive approach, (lymph-)angiogenic growth factors can enhance vascular permeability, which may pose an additional problem.

In the present study, it was observed that mice with human VEGF-D incorporated in their genome developed spontaneous tu-
mors in epithelia with a preference for induction of mammary gland adenocarcinomas. This interesting and unexpected finding may limit the therapeutic use of VEGF-D. Therapeutic intervention by neutralization of VEGF-D for diseases characterized by excessive angiogenesis, such as cancer, may therefore be a more promising approach. Indeed, inhibition of metastatic spread, microhemorrhage, and collapse of tumor vessels has been described in mice injected with blocking monoclonal antibodies or soluble VEGFR-3.6 Although it was reported before that VEGF-D can facilitate tumor growth and support metastasis formation, probably due to enhanced vessel/tumor cell interaction surface, it is very interesting to question how VEGF-D can give rise to spontaneous tumors. It suggests that either the growth factor itself can transform normal epithelial cells into tumor cells — a hypothesis that is currently considered unlikely — or that normal epithelial cells are continuously challenged by genetic or epigenetic alterations, having more chance to result in tumor cells (normally a very rare event) when a more angiogenic environment is available. In the latter situation, tumor growth may be supported by better supply of oxygen and nutrients, by enhanced vascular permeability, a beneficial cytokine/chemokine milieu, or by a changed adhesion molecule profile. Another possibility is the VEGF-D–mediated generation of an immune-privileged situation. Indeed, VEGF-D has been reported to contribute, in a concerted action with other angiogenic growth factors, to endothelial cell anergy and subsequent escape from immune surveillance. All these conditions are supportive for an anti–VEGF-D strategy to intervene with tumor growth. Such an approach would potentially have the same problems as current anti–VEGF strategies in the clinic, such as induction of drug-induced resistance, but this may be overcome by combining different strategies of therapy. The paper by Kärrkäinen et al definitely underscores the importance of VEGF-D in the regulation of angiogenesis and suggests an opportunity for the development of new and innovative medical technology for cancer and other human diseases.

Conflict-of-interest disclosure: The author declares no competing financial interests.
REFERENCES


2. Achen MG, Jeltsch M, Kukk E, et al. Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4). Proc Natl Acad Sci USA. 1998;95:548-553.


Lymphangiogenesis factors: a target for therapy?

Arjan W. Griffioen