News Release

Title

An anti-angiogenic isoform of VEGF-A contributes to impaired vascularization in peripheral artery disease.

Key Points

- Clinically, peripheral artery disease (PAD) is widespread in the elderly and in diabetic patients. It results from insufficient blood flow associated with impaired blood vessel growth (referred to as the process of angiogenesis) to the lower limbs.
- Clinical PAD is shown to be associated with elevated expression of an anti-angiogenic VEGF-A splice isoform (VEGF-A_{165}b).
- In a murine model of PAD, treatment with an isoform-specific neutralizing antibody reversed the impaired revascularization phenotype caused by metabolic dysfunction.
- VEGF-A_{165}b may be new pharmacological target to treat limb ischemia in patients with PAD.

Summary

Ryosuke Kikuchi, Ph.D. (Department of Medical Technique), Tadashi Matsusita, MD, Ph.D. (Department of Clinical Laboratory) in Nagoya University Hospital (Director: Naoki Ishiguro, MD, Ph.D.), Toyoaki Murohara, MD, Ph.D. (Department of Cardiology) in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, Ph.D.), Kenneth Walsh, Ph.D. (Molecular Cardiology and Whitaker Cardiovascular Institute, Boston University School of Medicine) and their collaborators investigated the role of VEGF-A_{165}b in peripheral artery disease. They showed that clinical PAD is associated with elevated a rare anti-angiogenic isoform of VEGF-A (VEGF-A_{165}b), and a corresponding reduction of the more common pro-angiogenic VEGF-A_{165}a isoform.
In a murine model of PAD, delivery of VEGF-A_{165}b inhibited revascularization of ischemic hind limbs. Conversely, treatment with an isoform-specific neutralizing antibody reversed the impaired revascularization phenotype caused by metabolic dysfunction. Therefore, VEGF-A_{165}b may be new pharmacological target to treat limb ischemia in patients with PAD. This work was published online in *Nature Medicine* on November 2, 2014.

Research Background

Disability attributable to PAD is rising due to an aging population and an increase in the prevalence of metabolic diseases. Lower extremity ischemia in PAD is painful, disabling, causes non-healing ulcers, and results in 200,000 amputations per year in the United States alone.
PAD thus represents a major unmet clinical need afflicting approximately 10 million people in the United States. Limb ischemia induced by arterial obstructive lesions is exacerbated by

insufficient angiogenesis and collateral vessel formation, processes regulated by VEGF-A. Paradoxically, VEGF-A levels are reported to be elevated in patients with advanced PAD. Further, clinical interventions to promote therapeutic angiogenesis by VEGF-A delivery have had limited efficacy in PAD. It is therefore not yet clear why collateralization and angiogenesis are insufficient in patients with PAD, despite raised VEGF-A levels.

Research Results

Consistent with previous reports, we observed higher levels of circulating VEGF-A in PAD patients compared to controls using an ELISA that does not discriminate between different VEGF-A isoforms. Consistent with the ELISA data, higher levels of total VEGF-A were detected in the serum of PAD patients. However, using reagents to specifically measure levels of various forms of VEGF-A revealed that levels of the pro-angiogenic hVEGF-A_{165}a isoform were reduced in PAD patients relative to healthy control subjects, whereas levels of the hVEGF-A_{165}b isoform were higher in the PAD cohort.

In a murine model of PAD, diet-induced and genetic forms of obesity led to impaired revascularization. These conditions were found to be associated with elevated mVEGF-A_{165}b. When these mice were treated with anti-VEGF-A_{165}b neutralizing antibody, they showed significant improvements in the revascularization of their ischemic limbs.

Research Summary and Future Perspective

In summary, we showed that a unique VEFGF-A isoform, referred to as VEGF-A_{165}b, is expressed in clinical and experimental settings that are associated with impaired vascularization (Figure 1). Using isoform-specific antibodies, we provide evidence that the circulating VEGF-A in PAD patients is predominantly comprised of the variant VEGF-A_{165}b isoform. In murine experimental models we establish the presence mVEGF-A_{165}b and demonstrate that this isoform impairs revascularization in a model of PAD. Conversely, acute immunological neutralization of mVEGF-A_{165}b promotes revascularization of ischemic tissue under conditions where the process of regenerative angiogenesis is impaired.

These findings support the concept that VEGF-A_{165}b may be new pharmacological target to treat limb ischemia in patients with PAD.

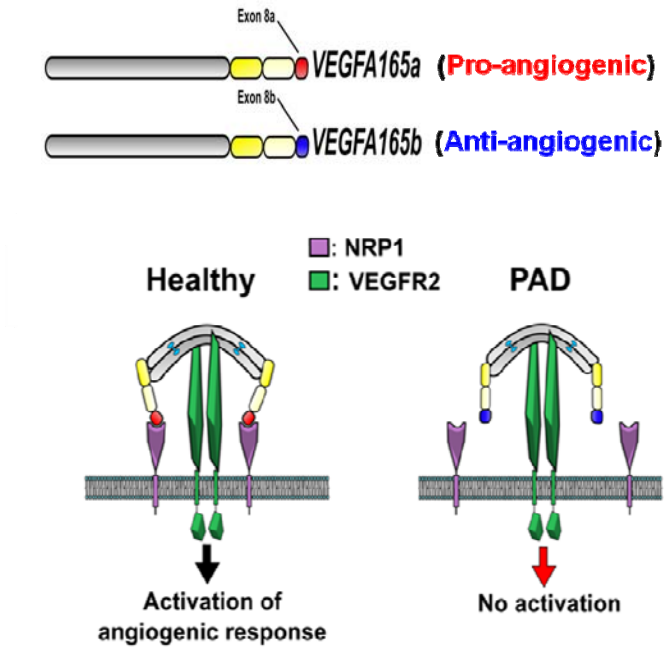

Figure 1.

Kikuchi R, Nakamura K, MacLauchlan S, Doan TM, Shimizu I, Fuster J, Katanasaka Y, Yoshida S, Qiu Y, Yamaguchi P, T, Matsushita T, Murohara T, Gokce N, Bates OD, Hamburg NM, Walsh K.
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