Vascular endothelial growth factor: molecular underpinning from development of vasculature to development of disease

CELLULAR PHYSIOLOGY of vascular endothelial growth factor (VEGF) was the focus of a featured topic session presented during the Experimental Biology meeting, April 15–18, 2000, under the aegis of the American Physiological Society. The success of this venue was ensured by two factors. First, the physiology of VEGF represents a “hot” topic in vascular biology. Second, the speakers, all of whom are major contributors to the field of VEGF physiology, provided a balanced state-of-the-art review of biochemistry, cell biology, signaling, and pathophysiology of the growing family of endothelial growth factors.

Discovered in the late 1970s as a secretory product of tumor cells and characterized as a potent vascular permeability factor (VPF) (5), VEGF was soon found to play a physiological role in angiogenesis (4) and, thus, set the stage for the exciting drama in vascular biology of the 1990s.

The dichotomy in terminology (VPF/VEGF) reflects well on paradoxical effects of this growth factor, its role in the disease processes (Ref. 2, see p. C1358 in this issue), and emerging paradigms in therapeutic trials to suppress or enhance its action. Tissue oxygenation provides a physiological surveillance of VEGF production and receptor expression (Ref. 1, see p. C1367 in this issue). A number of other stimuli include fibroblast growth factor-4, keratinocyte growth factor, epidermal growth factor, platelet-derived growth factor, insulin-like growth factor-1, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, ovarian steroids, interleukin (IL)-1β and IL-6, and oncogenic ras. Von Hippel-Lindau gene product, IL-10, and IL-13 inhibit VEGF production, whereas receptors are downregulated by TNF-α and TGF-β. Intracellular signaling of VEGF is accomplished via changes in phospholipase C activity, cytosolic calcium concentration, phosphorylation of several tyrosine kinases, and generation of nitric oxide and prostacyclin, which lead to the mitogenic, motogenic, and permeabilizing effects as well as the vasoprotective action (Ref. 6, see p. C1375 in this issue) of VEGF.

The role of VEGF in diverse pathological conditions, such as tumor angiogenesis, retinal neovascularization, development of collateral circulation, rheumatoid arthritis, ovarian hyperstimulation syndrome, endometriosis, leakage of blood-brain barrier, and brain edema, to name a few, has been established (2). There have been fledgling attempts to harness accumulated knowledge for use in either suppressing or enhancing effects of VEGF (3). These include VEGF gene therapy and use of recombinant VEGF for therapeutic angiogenesis in ischemic heart disease, peripheral vascular disease, and Burger’s disease and for prevention of restenosis of coronary arteries and arteriovenous fistulas. On the other hand, attempts to suppress angiogenesis have led to the synthesis of several potentially useful molecular tools, such as antibodies against VEGF, soluble extracellular domain of receptors 1 and 2, VEGF antisense oligonucleotides (University of California, Los Angeles), carbamethoxytriazole (National Cancer Institute), 4-anilinoquinazoline (Zeneca Pharm), SU-5416 and SU-6668 (Sugen), and arginine-rich anti-VEGF peptide (Pohang University, Korea), to name a few. The future will decide whether the present great expectations associated with such therapies have met the high requirements for efficacy and safety.

REFERENCES


Michael S. Goligorsky
Department of Medicine, Division of Nephrology
State University of New York at Stony Brook
Stony Brook, NY 11794-8152
June 2001, Volume 280