Vascular Permeability Factor/Vascular Endothelial Growth Factor and the Significance of Microvascular Hyperpermeability in Angiogenesis

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1 Introduction

Vascular permeability factor/vascular endothelial growth factor (VPF/VEGF) was originally discovered in the late 1970s because of its capacity to increase the permeability of microvessels to plasma and plasma proteins (DVORAK et al. 1979a,b). Using plastic-embedded, light microscopic sections and, subsequently, immunohistochemistry, we noted that transplantable tumors growing in guinea pigs and rodents exhibit substantial deposits of fibrin in their stroma. Fibrin results from the clotting of fibrinogen, a 340kDa plasma protein which, under normal circumstances, is retained almost quantitatively within the blood vasculature. For fibrin to be deposited outside of blood vessels in tumor stroma, it was necessary that two requirements be met; namely, (1) that microvessels be abnormally hyperpermeable to permit the escape of fibrinogen and other plasma proteins necessary for blood clotting and (2) that there be a mechanism in place for activating the clotting system. In fact, both requirements were found to be met in tumors. The microvessels supplying tumors were hyperpermeable to fibrinogen and other plasma proteins, and both tumor cells and host stromal cells were capable of initiating extravascular coagulation via the tissue-factor pathway. Encouraged by these findings, we initiated a search for a tumor product that could account for tumor-vessel hyperpermeability. A potent vascular permeabilizing protein was soon found in serum-free tumor culture supernatants (DVORAK et al. 1979a,b) and was subsequently purified to homogeneity and given the name vascular permeability factor (VPF) (SENGGER et al. 1983, 1986, 1987, 1990).

Several years later, our collaborators at the Monsanto Company found that, in addition to enhancing vascular permeability, VPF was also a selective mitogen for cultured vascular endothelial cells (CONNOLLY et al. 1989). Independently, investigators in California isolated an endothelial cell mitogen from pituitary cell cultures and gave this protein the name vascular endothelial growth factor (VEGF) (FERRARA and HENZEL 1989; GOSPODAROWICZ et al. 1989; LEUNG et al. 1989). Subsequent experiments determined that the vascular permeabilizing and the endothelial cell mitogenic activities were mediated by the same molecule, hence the designation of this molecule as VPF/VEGF (KECK et al. 1989; CLAUSSE et al. 1990; CONN et al. 1990a,b; FERRARA et al. 1992; KOCH et al. 1994).

In addition to its vascular permeabilizing activity, VPF/VEGF exerts a number of other important actions on vascular endothelium. Many of these are discussed elsewhere in this volume and in several reviews (DVORAK et al. 1992, 1995; FERRARA et al. 1992; SENGGER et al. 1993; ALON et al. 1995; BROWN et al. 1997a; WATANABE and DVORAK 1997; WATANABE et al. 1997). Increased microvascular permeability is the earliest biological activity detected following interaction of tissues with VPF/VEGF, becoming evident within a matter of seconds to a few minutes. In contrast, changes in endothelial cell shape, adhesion, migration, altered messenger ribonucleic acid (mRNA) and protein expression, cell division and protection from apoptosis and senescence develop more slowly over a period of hours to days to weeks.