Chapter 17
Nitric Oxide in Tumor Angiogenesis

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Keywords: nitric oxide, nitric oxide synthase (NOS), COX-2

Abstract: Nitric oxide (NO), produced from L-arginine by NO synthases (NOS), is a short-lived molecule required for many physiological functions and contributing to different pathological conditions. In the last decade, we and others contributed to demonstrate that NO stimulates angiogenesis and mediates the effect of different angiogenic molecules. In human tumors, NOS expression and activity correlate with tumor growth and aggressiveness through angiogenesis stimulation and regulation of angiogenic factor expression. Interrelations among the NOS pathway, prostanoids and tyrosine kinase receptors have been reported in regulating tumor progression and malignancy. Drugs affecting the NOS pathway may be foreseen as anti-tumor strategies able to reduce edema, inhibit angiogenesis and facilitate the delivery of chemotherapeutic agents. Recent developments include research on NOS gene polymorphisms which might become useful biomarkers for predicting cancer susceptibility as well as the role of NO in chemopreventive strategies.

Nitric Oxide: Synthesis and Roles

The discovery in 1987 that nitric oxide (NO) accounted for the bioactivity of the endothelium-derived relaxing factor (EDRF) [1,2] rapidly led to a burst of information on the physiological and pathological roles of this molecule. Although known for its role in vasorelaxation, neurotransmission, inhibition of platelet aggregation, and immune defense, NO also acts as an intracellular messenger for various cells in the body. Moreover, its up- or down-regulation is documented in different pathological conditions.

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Role of NO in Angiogenesis

Starting from the observation that angiogenesis is accompanied by vasodilation and that many angiogenic molecules possess vasodilating properties, the existence of a close molecular/biochemical link among vasodilation, NO production and angiogenesis has been established [8]. The critical role played by the eNOS during all the steps of the angiogenesis process has also been firmly illustrated [9,10]. Several evidences suggest a stimulatory role of NO in angiogenesis. NO and cGMP increase the replication of endothelial cells [10]. Angiogenesis elicited in vivo by the vasoactive molecules substance P and prostaglandin E was blocked by systemic NOS inhibition [8]. Similarly, NOS inhibitors and genetic models of NOS knocking-out showed reduced neovascularisation and wound healing in different tissues [5, 11–13].

NO is the final mediator of angiogenesis stimulated by vascular endothelial growth factor (VEGF) [14], the major factor implicated in therapeutic angiogenesis and tumor neovascularization. Functional eNOS is required for endothelial cell migration and proliferation induced by this growth factor [14–16], as well as for its vasorelaxing properties [17]. Stimulation of eNOS by VEGF is mediated by several mechanisms. First is up-regulation of eNOS mRNA and protein [18]. Second, eNOS can be activated through increased association with heat-shock protein 90 (Hsp90) [19], activation of phosphatidylinositol-3OH-kinase (PI3K)/protein kinase B (PKB/Akt), leading to phosphorylation of eNOS [20], and activation of mitogen-activated protein kinase (MAPK)/phospholipase C-γ, leading to increased phosphatidylinositol triphosphate and intracellular calcium ions [21].

Hsp90 seems crucial also for the intracellular activity of NO, since it is complexed with both eNOS and soluble guanylate cyclase (sGC) in endothelial cells [22,23]. sGC derived cGMP is the intracellular mediator of neovessel formation [10,14,15,24] (Fig. 17.1).

NO acts as an autocrine regulator of endothelial cell function/survival. In microvascular endothelium, exogenous administered and endogenously produced NO up-regulates the expression of the endogenous angiogenic factors fibroblast growth factor (FGF-2) [25–27].

The concept of the proangiogenic role of NO, however, is not univocal. Depending on the angiogenesis model, the species, the drugs used and their concentrations, opposing results have been reported in the literature. In fact, NO behaves as an antiangiogenic mediator in the chick chorioallantoic membrane model, acting as an endogenous brake to control tissue vascularization [28].

Fig. 17.1. Intracellular cross talk between eNOS signaling and VEGF receptor activation.