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Review

Vascular endothelial growth factors and receptors: Anti-angiogenic therapy in the treatment of cancer

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ABSTRACT

Vascular endothelial growth factors (VEGFs) are critical regulators of vascular and lymphatic function during development, in health and in disease. There are five mammalian VEGF ligands and three VEGF receptor tyrosine kinases. In addition, several VEGF co-receptors that lack intrinsic catalytic activity, but that indirectly modulate the responsiveness to VEGF contribute to the final biological effect. This review describes the molecular features of VEGFs, VEGFRs and co-receptors with focus on their role in the treatment of cancer.

Contents

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1. Vascular endothelial growth factors (VEGFs)

There are five structurally related mammalian VEGF ligands (VEGFA, VEGFB, VEGFC, VEGFD and placenta growth factor; PLGF). A parapox virus open reading frame encodes a related molecule denoted VEGFE (Ogawa et al., 1998), and several snake venom-derived VEGF-related proteins are denoted VEGFFs (Yamazaki et al., 2005). The VEGFs are disulfide-bonded homodimers, although VEGFA and PLGF heterodimers have also been described (DiSalvo et al., 1995).

Each VEGF ligand occurs as several different variants either due to alternative splicing or due to processing. The variants bind differently to both VEGFRs and to co-receptors and therefore induce different biological responses, such as angiogenesis, lymphangiogenesis, permeability, inflammatory cell recruitment and fatty acid uptake (see Table 1). Co-receptor-binding isoforms such as VEGFA165 mediate pro-angiogenic responses, whereas VEGFA121 and VEGFA (xxx)b isoforms that do not interact with co-receptors, may exert anti-angiogenic effects (Nowak et al., 2008) (Table 1). The VEGFs are produced by many different cell types and typically act locally, in a paracrine manner. However, VEGFA is produced in endothelial cells and may act in an autocrine manner on VEGFRs expressed in the same cell (Lee et al., 2007a).

Gene targeted mice lacking expression of different VEGF ligands have demonstrated the critical role of VEGFs in vessel function. The most striking effects are seen for VEGFA, where embryos succumb already when one allele is deleted (Carmeliet et al., 1996; Ferrara et al., 1996). VEGFA is critical for development of endothelial cells during embryogenesis and for organization of the vasculature. It is also required for survival of endothelial cells in healthy tissues. VEGFA produced by endothelial cells may act in an autocrine manner to stimulate vessel survival, as shown in studies of recombinant mice specifically lacking endothelial-produced VEGFA; interestingly, VEGFA produced by adjacent cells cannot compensate for endothelial VEGFA (Lee et al., 2007a). VEGFA was the first of the VEGF ligands to be identified and it remains the most studied. It was originally also denoted VPF, vascular permeability factor (Senger et al., 1983). An essential feature of VEGFA is its sensitivity to hypoxia. Hypoxia-inducible factor (HIF) is a powerful regulator of VEGFA expression in growing tissues, in physiological or pathological processes (Shweiki et al., 1992). Antibodies that bind VEGF and thereby prevent its binding to VEGFRs, inhibit angiogenesis, and have been exploited clinically in pathologies characterized by excess angiogenesis, such as cancer and retinopathy (Ferrara, 2005), as discussed in detail below.

The VEGFs bind to three structurally related receptor tyrosine kinases, VEGFR1, VEGFR2 and VEGFR3. In addition, a number of co-receptors that lack intrinsic catalytic activity bind VEGF and modulate the effect of the VEGFRs. Such co-receptors

Table 1
Mammalian VEGF ligands including selected isoforms and processed variants, their functions and binding properties to VEGF receptors and co-receptors.

VEGF ligands	VEGFR binding	NRP binding	HS/H binding*	Biological function
VEGFA165	VEGFR1, VEGFR2	NRP1, NRP2	Exon 6	Angiogenesis (permeability, survival, migration of EC)
VEGFA121	VEGFR1, VEGFR2	NRP1**	No	Angiogenic/anti-angiogenic***
VEGFA145	VEGFR1, VEGFR2	NRP2	Exon 6	Angiogenesis
VEGFA189	VEGFR1, VEGFR2	NRP1	Exon 6	Angiogenesis
VEGFA(xxx)b	VEGFR1, VEGFR2	No	No	Anti-angiogenic
VEGFB	VEGFR1	NRP1	VEGFB167 (not isoform VEGFB186)	Fatty acid uptake in EC of the heart
VEGFC (processed)	VEGFR3, (VEGFR2)	NRP2	No	Lymphangiogenesis
VEGFD (processed)	VEGFR3, (VEGFR2)	NRP2	Yes	Lymphangiogenesis
PlGF	VEGFR1	NRP1, NRP2 (only isoform PLGF2)	PlGF2 (not isoform PlGF1)	Inflammatory cell recruitment

For further details on VEGF ligands and their biochemical and biological properties, see (Koch et al., 2011).
* Abbreviations: EC, endothelial cells; HS, heparan sulfate; H, heparin.
** VEGFA121 binds NRP1 but does not bridge to VEGFRs (Pan et al., 2007b).
*** VEGFA121 has been described as anti-angiogenic (Nowak et al., 2008).