Tumor Biology

Inhibition of VEGF-C-induced VEGFR-3 activity and lymphatic endothelial cell function by the tyrosine kinase inhibitor AZD2171

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Abstract

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Solid tumors express a range of growth factors required to sustain their growth and promote their dissemination. Among these factors is vascular endothelial growth factor-A (VEGF-A), the key angiogenic stimulant, and VEGF-C, a primary mediator of lymphangiogenesis. Small molecule tyrosine kinase inhibitors can prevent VEGF signaling activity by targeting the VEGF receptors and are an effective approach to impede tumor progression. The indole-ether quinazoline AZD2171 is a highly potent ATP-competitive inhibitor of VEGFR-2 (KDR) kinase, with additional activity against VEGFR-1 (Flt-1) and -3 (Flt-4), that has been shown in experimental models to prevent VEGF-A-induced angiogenesis and primary tumor growth (Wedge *et al. Cancer Res* 2005;65:4389-4400). For these studies we wished to further assess the ability of AZD2171 to inhibit VEGFR-3 and its associated functions. Upon binding its ligands VEGF-C or -D, VEGFR-3 becomes activated with the resulting signaling cascade eventually translated into increased proliferation, survival and migration of lymphatic and blood vascular endothelial cells. At concentrations of ≤1 nM AZD2171 inhibited VEGFR-3 phosphorylation in porcine aortic endothelial cells selectively expressing the human receptor, and in human dermal microvascular endothelial cells (HDMVECs). In HDMVECs, AZD2171 prevented phosphorylation of signaling molecules downstream of VEGFR-2 and -3, ERK1/2, Akt and CREB, induced by the VEGFR-2 and -3-specific ligands VEGF-E and -C156S, respectively. Additionally, AZD2171 blocked VEGF-E- and -C156S-induced proliferation of both lymphatic and blood vascular endothelial cells at similar concentrations, and prevented ligand-induced endothelial cell cord formation in a Matrigel assay. The effects of AZD2171 on VEGF-C-induced lymphangiogenesis are currently being assessed *in vivo*. These studies, together with previous results, not only demonstrate that AZD2171 may be an effective means of preventing tumor progression by inhibition of VEGFR-2 activity and angiogenesis, but may also prevent further tumor spread by inhibiting VEGFR-3 activity and, consequently, lymphangiogenesis.

Footnotes

- 98th AACR Annual Meeting-- Apr 14-18, 2007; Los Angeles, CA

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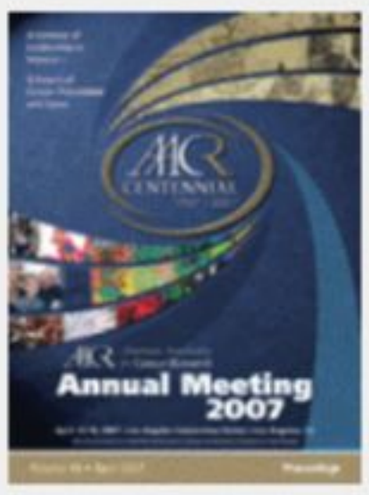

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