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EC-specific chemotaxis receptor: a double-edged sword

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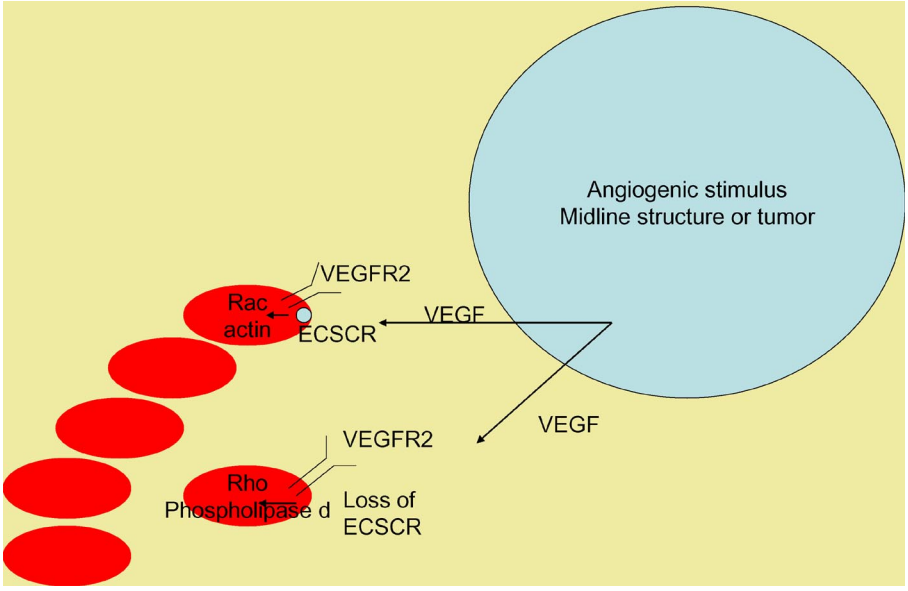
ECSCR is an orphan receptor with no previously determined function. In the report by Verma and colleagues in this issue of *Blood*, ECSCR is finally associated with a function. Using embryonic zebrafish, Verma and colleagues demonstrate that ECSCR is required for optimal migration of endothelial cells to the midline. Blockade of ECSCR leads to decreased migration of endothelial cells to the midline, and increased resistance to apoptosis. Chemical blockade of VEGFR2 (flk/kdr) leads to a phenocopy of the ECSCR phenotype, and down-regulation of ECSCR leads to down-regulation of phosphorylation of VEGFR2, but not VEGFR1.



Proposed model of ECSCR serving as a molecular switch. In the presence of ECSCR, VEGF induces a rac-reactive oxygen-notch chemotactic pathway. In the absence of ECSCR, alternative survival pathways are activated (rho, phosholipase D).

A dual function of endothelial cell–specific chemotaxis receptor (ECSCR) is implicated from the findings of Verma et al.[1] First, the presence of ECSCR is required for optimal phosphorylation of VEGFR2 and migration. Thus, blockade of ECSCR may lead to a more specific blockade of angiogenesis, without the decreased numbers of angioblasts seen in VEGF inhibitor treated animals. Thus, a specific target is presented through ECSCR blockade. The second finding is that cells lacking ECSCR are more susceptible to apoptotic stimuli. This suggests that migrating endothelial cells are highly susceptible to apoptotic stimuli. The nature of apoptotic stimuli that can cause apoptosis of ECSCR need further elucidation. In addition, exploration of whether ECSCR confers increased apoptosis in the presence of extracellular matrix, as seen in vivo, needs to be ascertained.

Migration of endothelial cells through a vascular gradient, as a vascular cord or tumor, is the rate-limiting step in angiogenesis. Several signaling processes are implicated in this process, including VEGF-notch signaling, as well as reactive oxygen-rac signaling.[2,3] Hemangiomas are clonal neoplasms of endothelium that have demonstrated responsiveness to VEGF, and have a reactive oxygen–rac-notch signaling pathway.[4,5] This has been demonstrated not only in endothelium, but in solid tumors as well. The presence of notch activation in the presence of increased reactive oxygen-Akt has been defined as the reactive oxygen– driven tumor, in which Akt is activated, NFκB is activated by superoxide, and p16 is lost.[6] Interestingly, blockade of NADPH oxidases leads to down-regulation of notch activity as observed through down-regulation of the notch target Nrarp.[7] ECSCR likely is a mediator of reactive oxygen–induced angiogenesis, and residual angiogenesis that occurs in the absence of ECSCR may be due to rho or phospholipase D signaling.[8]

What are the implications of these findings? Tumors can be viewed as midline structures, requiring vascularization from the periphery. VEGFR2 blockade has been employed as an antiangiogenic strategy, but is associated with only partial efficacy and severe side effects, including hypertension.[9] Resistance occurs through compensatory increases in other angiogenic growth factors. Nearly every growth factor activates both rac and rho signaling in a chronological sequence. It is likely that ECSCR plays the role of a molecular switch, with a bias toward rac activation, given its influence on both actin and VEGFR2 (see figure). ECSCR blockade could be a strategy for overcoming these issues by decreasing endothelial chemotaxis to the adult human equivalent of a midline structure, a neoplasm. Finally, the set of lesions known as vascular malformations resemble the phenotype seen with ECSCR blockade, namely persistence (lack of apoptosis) and lack of migration. Studies should be performed to determine whether ECSCR is mutated or lost in vascular malformations, accounting for the defective remodeling and resistance to apoptosis.[10,11] If this is the case, adenoviral introduction of ECSCR could lead to regression of vascular malformations through remodeling.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Verma A, Bhattacharya R, Remadevi I, et al. Endothelial cell–specific chemotaxis receptor (ecscr) promotes angioblast migration during vasculogenesis and enhances VEGF receptor sensitivity. *Blood*. 2010;115(22):4614-4622.

2. Hainaud P, Contrerès JO, Villemain A, et al. The role of the vascular endothelial growth factor-Delta-like 4 ligand/

Notch4-ephrin B2 cascade in tumor vessel remodeling and endothelial cell functions. *Cancer Res.* 2006;66(17): 8501-8510.

3. Ridgway J, Zhang G, Wu Y, et al. Inhibition of Dll4 signalling inhibits tumour growth by deregulating angiogenesis. *Nature*. 2006;444(7122):1083-1087.

4. Perry BN, Govindarajan B, Bhandarkar SS, et al. Pharmacologic blockade of angiopoietin-2 is efficacious against model hemangiomas in mice. *J Invest Dermatol*. 2006; 126(10):2316-2322

5. Lapidoth M, Ben-Amitai D, Bhandarkar S, Fried L, Arbiser JL. Efficacy of topical application of eosin for ulcerated hemangiomas. *J Am Acad Dermatol*. 2009;60(2): 350-351.

6. Fried L, Arbiser JL. The reactive oxygen-driven tumor: relevance to melanoma. *Pigment Cell Melanoma Res.* 2008; 21(2):117-122.

7. Bhandarkar SS, Jaconi M, Fried LE, et al. Fulvene-5 potently inhibits NADPH oxidase 4 and blocks the growth of endothelial tumors in mice. *J Clin Invest*. 2009;119(8): 2359-2365.

8. Cai D, Netzer WJ, Zhong M, et al. Presenilin-1 uses phospholipase D1 as a negative regulator of beta-amyloid formation. *Proc Natl Acad Sci U S A*. 2006;103(6): 1941-1946.

9. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350(23): 2335-2342.

10. Chun CZ, Kaur S, Samant GV, et al. Snrk-1 is involved in multiple steps of angioblast development and acts via notch signaling pathway in artery-vein specification in vertebrates. *Blood*. 2009;113(5):1192-1199.

11. Arbiser JL, Bonner MY, Berrios RL. Hemangiomas, angiosarcomas, and vascular malformations represent the signaling abnormalities of pathogenic angiogenesis. *Curr Mol Med*. 2009;9(8):929-934.