

Fundamental Papers in Vascular Development

Vascular Endothelial Growth Factor/Vascular Permeability Factor (VEGF/VPFL)

Senger, D., Galli, S., Dvorak, A., Perruzzi, C., Harvey, V., Dvorak, H., 1983. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 219, 983–985. <https://pubmed.ncbi.nlm.nih.gov/6823562/>

Connolly, D.T., Heuvelman, D.M., Nelson, R., Olander, J.V., Eppley, B.L., Delfino, J.J., Siegel, N.R., Leimgruber, R.M., Feder, J., 1989. Tumor vascular permeability factor stimulates endothelial cell growth and angiogenesis. *Journal of Clinical Investigation* 84, 1470–1478. <https://pubmed.ncbi.nlm.nih.gov/2478587/>

Keck, P., Hauser, S., Krivi, G., Sanzo, K., Warren, T., Feder, J., Connolly, D., 1989. Vascular permeability factor, an endothelial cell mitogen related to PDGF. *Science*. 246, 1309–1312. <https://pubmed.ncbi.nlm.nih.gov/2479987/>

Leung, D., Cachianes, G., Kung, W., Goeddel, D., Ferrara, N., 1989. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science*. 246, 1306–1309. <https://pubmed.ncbi.nlm.nih.gov/2479986/>

Lee, S., Jilani, S. M., Nikolova, G. V., Carpizo, D. & Iruela-Arispe, M. L. Processing of VEGF-A by matrix metalloproteinases regulates bioavailability and vascular patterning in tumors. *J. Cell Biol.* 169, 681–691 (2005). <https://rupress.org/jcb/article/169/4/681/51663/Processing-of-VEGF-A-by-matrix-metalloproteinases>

Ruhrberg, C. et al. Spatially restricted patterning cues provided by heparin-binding VEGF-A control blood vessel branching morphogenesis. *Genes Dev.* 16, 2684–2698 (2002). <http://genesdev.cshlp.org/content/16/20/2684>

Knockouts of VEGF and VEGF receptors

Ferrara, N., Carver-Moore, K., Chen, H., Dowd, M., Lu, L., O'Shea, K.S., Powell-Braxton, L., Hillan, K.J., Moore, M.W., 1996. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature* 380, 439–442. <https://www.nature.com/articles/380439a0>

Carmeliet, P., Ferreira, V., Breier, G., Pollefeyt, S., Kieckens, L., Gertsenstein, M., Fahrig, M., Vandenhoeck, A., Harpal, K., Eberhardt, C., Declercq, C., Pawling, J., Moons, L., Collen, D., Risau, W., Nagy, A., 1996. Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. *Nature*. 380, 435–439. <https://pubmed.ncbi.nlm.nih.gov/8602241/>

Kappel, A., Schlaeger, T.M., Flamme, I., Orkin, S.H., Risau, W., Breier, G., 2000. Role of SCL/Tal-1, GATA, and ets transcription factor binding sites for the regulation of flk-1 expression during murine vascular development. *Blood*. 96, 3078–3085.

<https://pubmed.ncbi.nlm.nih.gov/11049987/>

Millauer, B., 1993. High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis. *Cell*. 72, 835–846.

<https://pubmed.ncbi.nlm.nih.gov/7681362/>

Shalaby, F., Rossant, J., Yamaguchi, T.P., Gertsenstein, M., Wu, X.-F., Breitman, M.L., Schuh, A.C., 1995. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. *Nature*. 376, 62–66.

<https://pubmed.ncbi.nlm.nih.gov/7596435/>

Yamaguchi, T.P., Dumont D. J., Conlon R.A., Breitman, M.L., Rossant J., 1993 Flk-1, an flt-related receptor tyrosine kinase is an early marker for endothelial cell precursors. *Development* 118, 489-98.

<https://pubmed.ncbi.nlm.nih.gov/8223275/>

Fong G.H., Rossant J., Gertsenstein M., Breitman, M.L. 1995. Role of the Flt-1 receptor tyrosine kinase in regulating the assembly of vascular endothelium. *Nature* 376, 66-70.

<https://pubmed.ncbi.nlm.nih.gov/7596436/>

Kearney, J.B., Ambler C.A., Monaco K.A., Johnson N., Rapoport R.G., Bautch V.L., 2002. Vascular endothelial growth factor receptor Flt-1 negatively regulates developmental blood vessel formation by modulating endothelial cell division. *Blood*. 99, 2397–2407.

<https://pubmed.ncbi.nlm.nih.gov/11895772/>

Dumont D.J., Jussila L., Taipale J., Lymboussaki A., Mustonen T., Pajusola K., Breitman M., Alitalo K. 1998. Cardiovascular failure in mouse embryos deficient in VEGF receptor-3. *Science* 282, 946–949.

<https://pubmed.ncbi.nlm.nih.gov/9794766/>

Roles of Tie1, Tie2, and angiopoietins1

Sato T.N., Tozawa Y., Deutsch U., Wolburg-Buchholz K., Fujiwara Y., Gendron-Maguire M., Gridley T., Wolburg H., Risau W., Qin Y. 1995 Distinct roles of the receptor tyrosine kinases Tie-1 and Tie-2 in blood vessel formation. *Nature*. 376:70-4.

<https://pubmed.ncbi.nlm.nih.gov/7596437/>

Suri C., Jones P.F., Patan S., Bartunkova S., Maisonpierre P.C., Davis S., Sato T.N., Yancopoulos G.D. 1996. Requisite role of angiopoietin-1, a ligand for the TIE2 receptor, during embryonic angiogenesis. *Cell* 87, 1171-80.

<https://pubmed.ncbi.nlm.nih.gov/8980224/>

Neuropilins

Shay Soker, Seiji Takashima, Hua Quan Mia, Gera Neufeld, Michael Klagsbrun. Neuropilin-1 Is Expressed by Endothelial and Tumor Cells as an Isoform-Specific Receptor for Vascular Endothelial Growth Factor. 1998. *Cell* 92, 735-745.

<https://pubmed.ncbi.nlm.nih.gov/9529250/>

Gu, C. et al. Neuropilin-1 conveys semaphorin and VEGF signaling during neural and cardiovascular development. *Dev. Cell* 5, 45–57 (2003).

<https://pubmed.ncbi.nlm.nih.gov/12852851/>

Role of hemodynamics in vascular development

Luo Y., Ferreira-Cornwell M., Baldwin H., Kostetskii I., Lenox J., Lieberman M., Radice G. 2001. Rescuing the N-cadherin knockout by cardiac-specific expression of N- or E-cadherin. *Development*. 128, 459-69. <https://pubmed.ncbi.nlm.nih.gov/11171330/>

Lucitti, J. L., Jones, E. A., Huang, C., Chen, J., Fraser, S. E., Dickinson, M. E. 2007. Vascular remodeling of the mouse yolk sac requires hemodynamic force. *Development*. 134, 3317-26. <https://pubmed.ncbi.nlm.nih.gov/17720695/>

Development of arteries and veins

Wang H.U., Chen Z-F., and Anderson D.J. 1998. Molecular Distinction and Angiogenic Interaction between Embryonic Arteries and Veins Revealed by ephrin-B2 and Its Receptor Eph-B4. *Cell*. 93, 741-753. [https://www.cell.com/cell/pdf/S0092-8674\(00\)81436-1.pdf](https://www.cell.com/cell/pdf/S0092-8674(00)81436-1.pdf)

Lawson ND, Vogel AM, Weinstein BM. 2002. sonic hedgehog and vascular endothelial growth factor act upstream of the Notch pathway during arterial endothelial differentiation. *Dev Cell* 3, 127-36. <https://pubmed.ncbi.nlm.nih.gov/12110173/>

You, L. R., Lin, F. J., Lee, C. T., DeMayo, F. J., Tsai, M. J., Tsai, S. Y. 2005. Suppression of Notch signaling by the COUP-TFII transcription factor regulates vein identity. *Nature*. 435, 98-104 <https://pubmed.ncbi.nlm.nih.gov/15875024/>

Meadows, S. M., Fletcher, P. J., Moran, C., Xu, K., Neufeld, G., Chauvet, S., Mann, F., Krieg, P. A., Cleaver, O. 2012 Integration of repulsive guidance cues generates avascular zones that shape mammalian blood vessels. *Circ Res* 110, 34-46. <https://www.ahajournals.org/doi/10.1161/circresaha.111.249847>

Reese, D. E., Hall, C. E., Mikawa, T. 2004. Negative regulation of midline vascular development by the notochord. *Dev Cell* 6, 699-708 <https://pubmed.ncbi.nlm.nih.gov/15130494/>

Bressan, M., Davis, P., Timmer, J., Herzlinger, D., 2009. Mikawa, T. Notochord-derived BMP antagonists inhibit endothelial cell generation and network formation. *Dev. Biol*. 326, 101-11. <https://pubmed.ncbi.nlm.nih.gov/19041859/>

Wythe, J. D., Dang, L. T., Devine, W. P., Boudreau, E., Artap, S. T., He, D., Schachterle, W., Stainier, D. Y., Oettgen, P., Black, B. L., Bruneau, B. G., Fish, J. E. 2013 ETS factors regulate Vegf-dependent arterial specification. *Dev. Cell* 26, 45-58. <https://pubmed.ncbi.nlm.nih.gov/23830865/>

Red-Horse K, Ueno H, Weissman IL, Krasnow MA. 2010. Coronary arteries form by developmental reprogramming of venous cells. *Nature* 464:549–553.

<https://www.nature.com/articles/nature08873>

Hong CC, Peterson QP, Hong JY, Peterson RT. 2006. Artery/vein specification is governed by opposing phosphatidylinositol-3 kinase and MAP kinase/ERK signaling. *Curr Biol* 16:1366–1372.

<https://pubmed.ncbi.nlm.nih.gov/16824925/>

Hong CC, Kume T, Peterson RT. 2008. Role of crosstalk between phosphatidylinositol 3-kinase and extracellular signal-regulated kinase/mitogen-activated protein kinase pathways in artery-vein specification. *Circ Res* 103:573–579.

<https://www.ahajournals.org/doi/10.1161/circresaha.108.180745>

Ren, B., Deng, Y., Mukhopadhyay, A., Lanahan, A. A., Zhuang, Z. W., Moodie, K. L., Mulligan-Kehoe, M. J., Byzova, T. V., Peterson, R. T., Simons, M. 2010. ERK1/2-Akt1 crosstalk regulates arteriogenesis in mice and zebrafish. *J. Clin. Invest.*, 120, 1217-28

<https://pubmed.ncbi.nlm.nih.gov/20237411/>

Deng, Y., Larrivee, B., Zhuang, Z. W., Atri, D., Moraes, F., Prahst, C., Eichmann, A., Simons, M. 2013. Blood. Endothelial RAF1/ERK activation regulates arterial morphogenesis 121, 3988-96.

<https://pubmed.ncbi.nlm.nih.gov/23529931/>

Pardanaud, L., Pibouin-Fragner, L., Dubrac, A., Mathivet, T., English, I., Brunet, I., Simons, M., Eichmann, A. 2016. Sympathetic Innervation Promotes Arterial Fate by Enhancing Endothelial ERK Activity. *Circ. Res.* 119, 607-20.

<https://www.ahajournals.org/doi/full/10.1161/CIRCRESAHA.116.308473>

Eichmann, A., Makinen, T., Alitalo, K. 2005. Neural guidance molecules regulate vascular remodeling and vessel navigation. *Genes and Development* 19, 1013-21

<https://pubmed.ncbi.nlm.nih.gov/15879551/>

Kohli V, Schumacher JA, Desai SP, Rehn K, Sumanas S. 2013 Arterial and venous progenitors of the major axial vessels originate at distinct locations. *Dev Cell* 25, 196-206.

<https://pubmed.ncbi.nlm.nih.gov/23639444/>

Corada, M., Orsenigo, F., Morini, M.F., Pitulescu, M.E., Bhat, G., Nyqvist, D., Breviario, F., Conti, V., Briot, A., Iruela-Arispe, M.L., Adams, R.H., Dejana, E. 2013. Sox17 is indispensable for acquisition and maintenance of arterial identity. *Nat Commun* 4, 2609.

<https://pubmed.ncbi.nlm.nih.gov/24153254/>

Vasculogenesis

Sakurai, Y., Ohgimoto, K., Kataoka, Y., Yoshida, N., Shibuya, M. 2005. Essential role of Flk-1 (VEGF receptor 2) tyrosine residue 1173 in vasculogenesis in mice. *Proc Natl Acad Sci U S A.* 102, 1076-81.

<https://pubmed.ncbi.nlm.nih.gov/15644447/>

Sumanas S, Lin S. Ets1-related protein is a key regulator of vasculogenesis in zebrafish. *PLoS Biol.* 2006 Jan;4(1):e10. doi: 10.1371/journal.pbio.0040010. <https://pubmed.ncbi.nlm.nih.gov/16336046/>

Vogeli KM, Jin SW, Martin GR, Stainier DY. 2006. A common progenitor for haematopoietic and endothelial lineages in the zebrafish gastrula. *Nature* 443, 337–339. <https://pubmed.ncbi.nlm.nih.gov/16988712/>

Koh W, Mahan RD, Davis GE. 2008. Cdc42- and Rac1-mediated endothelial lumen formation requires Pak2, Pak4 and Par3, and PKC-dependent signaling. *J Cell Sci* 121, 989-1001. <https://pubmed.ncbi.nlm.nih.gov/18319301/>

Lee, D., Park, C., Lee, H., Lugus, J.J., Kim, S.H., Arentson, E., Chung, Y.S., Gomez, G., Kyba, M., Lin, S., Janknecht, R., Lim, D.S., Choi K. 2008. ER71 acts downstream of BMP, Notch, and Wnt signaling in blood and vessel progenitor specification. *Cell Stem Cell* 2, 497-507. <https://pubmed.ncbi.nlm.nih.gov/18462699/>

De Val, S., Chi, N.C., Meadows, S.M., Minovitsky, S., Anderson, J.P., Harris, I.S., Ehlers, M.L., Agarwal, P., Visel, A., Xu, S.M., Pennacchio, L.A., Dubchak, I., Krieg, P.A., Stainier, D.Y.R., Black, B.L. 2008. Combinatorial regulation of endothelial gene expression by ets and forkhead transcription factors. *Cell* 135, 1053-64. <https://pubmed.ncbi.nlm.nih.gov/19070576/>

Chong, D. C., Koo, Y., Xu, K., Fu, S., Cleaver, O. 2011 Stepwise arteriovenous fate acquisition during mammalian vasculogenesis. *Dev Dyn* 240, 2153-65. <https://pubmed.ncbi.nlm.nih.gov/21793101/>

Helker, C. S., Schuermann, A., Pollmann, C., Chng, S. C., Kiefer, F., Reversade, B., Herzog, W. 2015 *eLife* 4, e06726. The hormonal peptide Elabela guides angioblasts to the midline during vasculogenesis. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4468421/>

Reischauer S, Stone OA, Villasenor A, Chi N, Jin SW, Martin M, Lee MT, Fukuda N, Marass M, Witty A, Fiddes I, Kuo T, Chung WS, Salek S, Lerrigo R, Alsiö J, Luo S, Tworus D, Augustine SM, Muceniaks S, Nystedt B, Giraldez AJ, Schroth GP, Andersson O, Stainier DY. 2016. Cloche is a bHLH-PAS transcription factor that drives haemato-vascular specification. *Nature*. 535, 294-8. <https://pubmed.ncbi.nlm.nih.gov/27411634/>

Angiogenesis

Lobov, I. B. et al. Delta-like ligand 4 (Dll4) is induced by VEGF as a negative regulator of angiogenic sprouting. *Proc. Natl Acad. Sci. USA* 104, 3219–3224 (2007). <https://pubmed.ncbi.nlm.nih.gov/17296940/>

Suchting, S. et al. The Notch ligand Delta-like 4 negatively regulates endothelial tip cell formation and vessel branching. *Proc. Natl Acad. Sci. USA* 104, 3225–3230 (2007). <https://pubmed.ncbi.nlm.nih.gov/17296941/>

Hellstrom, M. et al. Dll4 signaling through Notch1 regulates formation of tip cells during angiogenesis. *Nature* 445, 776–780 (2007). <https://pubmed.ncbi.nlm.nih.gov/17259973/>

Siekmann, A. F. & Lawson, N. D. Notch signalling limits angiogenic cell behaviour in developing zebrafish arteries. *Nature* 445, 781–784 (2007).
<https://www.nature.com/articles/nature05577>

Gerhardt, H. et al. VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J. Cell Biol.* 161, 1163–1177 (2003).
<https://rupress.org/jcb/article/161/6/1163/33446/VEGF-guides-angiogenic-sprouting-utilizing>

Lu, X. et al. The netrin receptor UNC5B mediates guidance events controlling morphogenesis of the vascular system. *Nature* 432, 179–186 (2004).
<https://pubmed.ncbi.nlm.nih.gov/15510105/>

Gerhardt, H. et al. Neuropilin-1 is required for endothelial tip cell guidance in the developing central nervous system. *Dev. Dyn.* 231, 503–509 (2004).
<https://pubmed.ncbi.nlm.nih.gov/15376331/>

Kamei, M. et al. Endothelial tubes assemble from intracellular vacuoles in vivo. *Nature*. 442, 453–456 (2006). <https://pubmed.ncbi.nlm.nih.gov/16799567/>

Torres-Vazquez, J. et al. Semaphorin–plexin signaling guides patterning of the developing vasculature. *Dev. Cell* 7, 117–123 (2004).
[https://www.cell.com/fulltext/S1534-5807\(04\)00201-1](https://www.cell.com/fulltext/S1534-5807(04)00201-1)

Bedell, V. M. et al. roundabout4 is essential for angiogenesis in vivo. *Proc. Natl Acad. Sci. USA* 102, 6373–6378 (2005). <https://pubmed.ncbi.nlm.nih.gov/15849270/>

Corada, M., Nyqvist, D., Orsenigo, F., Caprini, A., Giampietro, C., Taketo, M.M., Iruela-Arispe, M.L., Adams, R.H., Dejana, E., (2010). The Wnt/beta-catenin pathway modulates vascular remodeling and specification by upregulating Dll4/Notch signaling *Dev Cell* 18, 938-49. <https://pubmed.ncbi.nlm.nih.gov/20627076/>

Tumor angiogenesis

Folkman M.J., Long D.M., Becker F.F. (1963) Growth and metastasis of tumor in organ culture. *Cancer* 16:453–467 <https://pubmed.ncbi.nlm.nih.gov/13958548/>

Folkman J (1971) Tumor angiogenesis. Therapeutic implications. *N Engl J Med* 285:1182–1186. <https://pubmed.ncbi.nlm.nih.gov/4938153/>

O'Reilly MS, et al. (1994) Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell* 79:315–328.
[https://www.cell.com/fulltext/0092-8674\(94\)90200-3](https://www.cell.com/fulltext/0092-8674(94)90200-3)

O'Reilly MS, Boehm T, Shing Y, Fukai N, Vasios G, Lane WS, Flynn E, Birkhead JR, Olsen BR, Folkman J (1997) Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell* 88, 277–285.

<https://www.sciencedirect.com/science/article/pii/S0092867400818486>

D'Amato RJ, Loughnan MS, Flynn E, Folkman J (1994) Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 91, 4082–4085.

<https://pubmed.ncbi.nlm.nih.gov/7513432/>

**Lymphangiogenesis (also see Publications in Lymphatics,
<https://www.navbo.org/papers-in-vascular-biology/>)**

Wigle, J.T., Oliver, G. (1999). Prox1 function is required for the development of the murine lymphatic system. *Cell* 98, 769-78. <https://pubmed.ncbi.nlm.nih.gov/10499794/>

Karkkainen MJ, Haiko P, Sainio K, Partanen J, Taipale J, Petrova TV, Jeltsch M, Jackson DG, Talikka M, Rauvala H, Betsholtz C, Alitalo K. (2004). Vascular endothelial growth factor C is required for sprouting of the first lymphatic vessels from embryonic veins. *Nat Immunol* 5, 74-80. <https://pubmed.ncbi.nlm.nih.gov/14634646/>

Nicenboim, J., Malkinson, G., Lupo, T., Asaf, L., Sela, Y., Mayseless, O., Gibbs-Bar, L., Senderovich, N., Hashimshony, T., Shin, M., Jerafi-Vider, A., Avraham-Davidi, I., Krupalnik, V., Hofi, R., Almog, G., Astin, J.W., Golani, O., Ben-Dor, S., Crosier, P.S., Herzog, W., Lawson, N.D., Hanna, J.H., Yanai, I., Yaniv, K., 2015. Lymphatic vessels arise from specialized angioblasts within a venous niche. *Nature* 522, 56-61.

<https://pubmed.ncbi.nlm.nih.gov/25992545/>