

## Supplementary Note

1. Carmeliet, P. et al. Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. *Nature* **380**, 435-9 (1996).
2. Ferrara, N. et al. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature* **380**, 439-42 (1996).
3. Aase, K. et al. Vascular endothelial growth factor-B-deficient mice display an atrial conduction defect. *Circulation* **104**, 358-64 (2001).
4. Bellomo, D. et al. Mice lacking the vascular endothelial growth factor-B gene (*Vegfb*) have smaller hearts, dysfunctional coronary vasculature, and impaired recovery from cardiac ischemia. *Circ Res* **86**, E29-35 (2000).
5. Stalmans, I. et al. Arteriolar and venular patterning in retinas of mice selectively expressing VEGF isoforms. *J Clin Invest* **109**, 327-36 (2002).
6. Carmeliet, P. et al. Impaired myocardial angiogenesis and ischemic cardiomyopathy in mice lacking the vascular endothelial growth factor isoforms VEGF164 and VEGF188. *Nat Med* **5**, 495-502 (1999).
7. Luttmann, A. et al. Loss of placental growth factor protects mice against vascular permeability in pathological conditions. *Biochem Biophys Res Commun* **295**, 428-34 (2002).
8. Fong, G.H., Rossant, J., Gertsenstein, M. & Breitman, M.L. Role of the Flt-1 receptor tyrosine kinase in regulating the assembly of vascular endothelium. *Nature* **376**, 66-70 (1995).
9. Shalaby, F. et al. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. *Nature* **376**, 62-6 (1995).
10. Dumont, D.J. et al. Cardiovascular failure in mouse embryos deficient in VEGF receptor-3. *Science* **282**, 946-9 (1998).
11. Kawasaki, T. et al. A requirement for neuropilin-1 in embryonic vessel formation. *Development* **126**, 4895-902 (1999).
12. Yamada, Y. et al. Neuropilin-1 on hematopoietic cells as a source of vascular development. *Blood* **101**, 1801-9 (2003).
13. Takashima, S. et al. Targeting of both mouse neuropilin-1 and neuropilin-2 genes severely impairs developmental yolk sac and embryonic angiogenesis. *Proc Natl Acad Sci U S A* **99**, 3657-62 (2002).

14. Yuan, L. et al. Abnormal lymphatic vessel development in neuropilin 2 mutant mice. *Development* **129**, 4797-806 (2002).
15. Xue, Y. et al. Embryonic lethality and vascular defects in mice lacking the Notch ligand Jagged1. *Hum Mol Genet* **8**, 723-30 (1999).
16. Krebs, L.T. et al. Notch signaling is essential for vascular morphogenesis in mice. *Genes Dev* **14**, 1343-52 (2000).
17. Adams, R.H. et al. Roles of ephrinB ligands and EphB receptors in cardiovascular development: demarcation of arterial/venous domains, vascular morphogenesis, and sprouting angiogenesis. *Genes Dev* **13**, 295-306 (1999).
18. Wang, H.U., Chen, Z.F. & Anderson, D.J. Molecular distinction and angiogenic interaction between embryonic arteries and veins revealed by ephrin-B2 and its receptor Eph-B4. *Cell* **93**, 741-53 (1998).
19. Gerety, S.S. & Anderson, D.J. Cardiovascular ephrinB2 function is essential for embryonic angiogenesis. *Development* **129**, 1397-410 (2002).
20. Bostrom, H. et al. PDGF-A signaling is a critical event in lung alveolar myofibroblast development and alveogenesis. *Cell* **85**, 863-73 (1996).
21. Fruttiger, M. et al. Defective oligodendrocyte development and severe hypomyelination in PDGF-A knockout mice. *Development* **126**, 457-67 (1999).
22. Leveen, P. et al. Mice deficient for PDGF B show renal, cardiovascular, and hematological abnormalities. *Genes Dev* **8**, 1875-87 (1994).
23. Lindahl, P., Johansson, B.R., Leveen, P. & Betsholtz, C. Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. *Science* **277**, 242-5 (1997).
24. Soriano, P. The PDGF alpha receptor is required for neural crest cell development and for normal patterning of the somites. *Development* **124**, 2691-700 (1997).
25. Soriano, P. Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice. *Genes Dev* **8**, 1888-96 (1994).
26. Liu, Y. et al. Edg-1, the G protein-coupled receptor for sphingosine-1-phosphate, is essential for vascular maturation. *J Clin Invest* **106**, 951-61 (2000).
27. Ishii, I. et al. Selective loss of sphingosine 1-phosphate signaling with no obvious phenotypic abnormality in mice lacking its G protein-coupled receptor, LP(B3)/EDG-3. *J Biol Chem* **276**, 33697-704 (2001).

28. Offermanns, S., Mancino, V., Revel, J.P. & Simon, M.I. Vascular system defects and impaired cell chemokinesis as a result of Galpha13 deficiency. *Science* **275**, 533-6 (1997).
29. Suri, C. et al. Requisite role of angiopoietin-1, a ligand for the TIE2 receptor, during embryonic angiogenesis. *Cell* **87**, 1171-80 (1996).
30. Hackett, S.F., Wiegand, S., Yancopoulos, G. & Campochiaro, P.A. Angiopoietin-2 plays an important role in retinal angiogenesis. *J Cell Physiol* **192**, 182-7 (2002).
31. Gale, N.W. et al. Angiopoietin-2 is required for postnatal angiogenesis and lymphatic patterning, and only the latter role is rescued by Angiopoietin-1. *Dev Cell* **3**, 411-23. (2002).
32. Puri, M.C., Rossant, J., Alitalo, K., Bernstein, A. & Partanen, J. The receptor tyrosine kinase TIE is required for integrity and survival of vascular endothelial cells. *Embo J* **14**, 5884-91 (1995).
33. Sato, T.N. et al. Distinct roles of the receptor tyrosine kinases Tie-1 and Tie-2 in blood vessel formation. *Nature* **376**, 70-4 (1995).
34. Dickson, M.C. et al. Defective haematopoiesis and vasculogenesis in transforming growth factor-beta 1 knock out mice. *Development* **121**, 1845-54 (1995).
35. Oshima, M., Oshima, H. & Taketo, M.M. TGF-beta receptor type II deficiency results in defects of yolk sac hematopoiesis and vasculogenesis. *Dev Biol* **179**, 297-302 (1996).
36. Urness, L.D., Sorensen, L.K. & Li, D.Y. Arteriovenous malformations in mice lacking activin receptor-like kinase-1. *Nat Genet* **26**, 328-31 (2000).
37. Oh, S.P. et al. Activin receptor-like kinase 1 modulates transforming growth factor-beta 1 signaling in the regulation of angiogenesis. *Proc Natl Acad Sci U S A* **97**, 2626-31 (2000).
38. Larsson, J. et al. Abnormal angiogenesis but intact hematopoietic potential in TGF-beta type I receptor-deficient mice. *Embo J* **20**, 1663-73 (2001).
39. Li, D.Y. et al. Defective angiogenesis in mice lacking endoglin. *Science* **284**, 1534-7 (1999).
40. Weinstein, M. et al. Failure of egg cylinder elongation and mesoderm induction in mouse embryos lacking the tumor suppressor smad2. *Proc Natl Acad Sci U S A* **95**, 9378-83 (1998).
41. Nomura, M. & Li, E. Smad2 role in mesoderm formation, left-right patterning and craniofacial development. *Nature* **393**, 786-90 (1998).
42. Waldrip, W.R., Bikoff, E.K., Hoodless, P.A., Wrana, J.L. & Robertson, E.J. Smad2 signaling in extraembryonic tissues determines anterior-posterior polarity of the early mouse embryo. *Cell* **92**, 797-808 (1998).
43. Datto, M.B. et al. Targeted disruption of Smad3 reveals an essential role in transforming growth factor beta-mediated signal transduction. *Mol Cell Biol* **19**, 2495-504 (1999).

44. Yang, X. et al. Targeted disruption of SMAD3 results in impaired mucosal immunity and diminished T cell responsiveness to TGF-beta. *Embo J* **18**, 1280-91 (1999).
45. Ashcroft, G.S. et al. Mice lacking Smad3 show accelerated wound healing and an impaired local inflammatory response. *Nat Cell Biol* **1**, 260-6 (1999).
46. Chang, H. et al. Smad5 knockout mice die at mid-gestation due to multiple embryonic and extraembryonic defects. *Development* **126**, 1631-42 (1999).
47. Yang, X. et al. Angiogenesis defects and mesenchymal apoptosis in mice lacking SMAD5. *Development* **126**, 1571-80 (1999).
48. Ozaki, H. et al. Basic fibroblast growth factor is neither necessary nor sufficient for the development of retinal neovascularization. *Am J Pathol* **153**, 757-65 (1998).
49. Ortega, S., Ittmann, M., Tsang, S.H., Ehrlich, M. & Basilico, C. Neuronal defects and delayed wound healing in mice lacking fibroblast growth factor 2. *Proc Natl Acad Sci U S A* **95**, 5672-7 (1998).
50. Abtahian, F. et al. Regulation of blood and lymphatic vascular separation by signaling proteins SLP-76 and Syk. *Science* **299**, 247-51 (2003).
51. Carmeliet, P. et al. Targeted deficiency or cytosolic truncation of the VE-cadherin gene in mice impairs VEGF-mediated endothelial survival and angiogenesis. *Cell* **98**, 147-57 (1999).
52. Gory-Faure, S. et al. Role of vascular endothelial-cadherin in vascular morphogenesis. *Development* **126**, 2093-102 (1999).
53. Simon, A.M. & McWhorter, A.R. Vascular abnormalities in mice lacking the endothelial gap junction proteins connexin37 and connexin40. *Dev Biol* **251**, 206-20 (2002).
54. Kirchhoff, S. et al. Reduced cardiac conduction velocity and predisposition to arrhythmias in connexin40-deficient mice. *Curr Biol* **8**, 299-302 (1998).
55. Reaume, A.G. et al. Cardiac malformation in neonatal mice lacking connexin43. *Science* **267**, 1831-4 (1995).
56. Duncan, G.S. et al. Genetic evidence for functional redundancy of Platelet/Endothelial cell adhesion molecule-1 (PECAM-1): CD31-deficient mice reveal PECAM-1-dependent and PECAM-1-independent functions. *J Immunol* **162**, 3022-30 (1999).
57. Takahashi, T. et al. A mutant receptor tyrosine phosphatase, CD148, causes defects in vascular development. *Mol Cell Biol* **23**, 1817-31. (2003).
58. Hodivala-Dilke, K.M. et al. Beta3-integrin-deficient mice are a model for Glanzmann thrombasthenia showing placental defects and reduced survival. *J Clin Invest* **103**, 229-38 (1999).

59. Huang, X., Griffiths, M., Wu, J., Farese, R.V., Jr. & Sheppard, D. Normal development, wound healing, and adenovirus susceptibility in beta5-deficient mice. *Mol Cell Biol* **20**, 755-9 (2000).
60. Zhu, J. et al.  $\beta$ 8 integrins are required for vascular morphogenesis in mouse embryos. *Development* **129**, 2891-2903 (2002).
61. Itoh, T. et al. Unaltered secretion of beta-amyloid precursor protein in gelatinase A (matrix metalloproteinase 2)-deficient mice. *J Biol Chem* **272**, 22389-92 (1997).
62. Rudolph-Owen, L.A., Hulboy, D.L., Wilson, C.L., Mudgett, J. & Matrisian, L.M. Coordinate expression of matrix metalloproteinase family members in the uterus of normal, matrilysin-deficient, and stromelysin-1-deficient mice. *Endocrinology* **138**, 4902-11 (1997).
63. Carmeliet, P. et al. Plasminogen activator inhibitor-1 gene-deficient mice. I. Generation by homologous recombination and characterization. *J Clin Invest* **92**, 2746-55 (1993).
64. Carmeliet, P. et al. Plasminogen activator inhibitor-1 gene-deficient mice. II. Effects on hemostasis, thrombosis, and thrombolysis. *J Clin Invest* **92**, 2756-60 (1993).
65. Lawler, J. et al. Thrombospondin-1 is required for normal murine pulmonary homeostasis and its absence causes pneumonia. *J Clin Invest* **101**, 982-92 (1998).
66. Kyriakides, T.R. et al. Mice that lack thrombospondin 2 display connective tissue abnormalities that are associated with disordered collagen fibrillogenesis, an increased vascular density, and a bleeding diathesis. *J Cell Biol* **140**, 419-30 (1998).
67. Carmeliet, P. et al. Biological effects of disruption of the tissue-type plasminogen activator, urokinase-type plasminogen activator, and plasminogen activator inhibitor-1 genes in mice. *Ann N Y Acad Sci* **748**, 367-81; discussion 381-2 (1995).
68. Fukai, N. et al. Lack of collagen XVIII/endostatin results in eye abnormalities. *Embo J* **21**, 1535-44 (2002).
69. Gessler, M. et al. Mouse gridlock: no aortic coarctation or deficiency, but fatal cardiac defects in *Hey2*  $-/-$  mice. *Curr Biol* **12**, 1601-4 (2002).
70. Rajantie, I. et al. Bmx tyrosine kinase has a redundant function downstream of angiopoietin and vascular endothelial growth factor receptors in arterial endothelium. *Mol Cell Biol* **21**, 4647-55 (2001).
71. Iyer, N.V. et al. Cellular and developmental control of O<sub>2</sub> homeostasis by hypoxia-inducible factor $\dagger$ 1 $\alpha$ . *Genes Dev.* **12**, 149-162 (1998).
72. Ryan, H.E., Lo, J. & Johnson, R.S. HIF-1 $\alpha$  is required for solid tumor formation and embryonic vascularization. *EMBO J.* **17**, 3005-3015 (1998).

73. Lyden, D. et al. Id1 and Id3 are required for neurogenesis, angiogenesis and vascularization of tumour xenografts. *Nature* **401**, 670-7 (1999).
74. Baudino, T.A. et al. c-Myc is essential for vasculogenesis and angiogenesis during development and tumor progression. *Genes Dev* **16**, 2530-43 (2002).
75. Wigle, J.T. & Oliver, G. Prox1 function is required for the development of the murine lymphatic system. *Cell* **98**, 769-78 (1999).