Zebrafish VEGF Receptors: A Guideline to Nomenclature

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Introduction

In placental mammals (eutherians), there exist three paralogous genes of the vascular endothelial growth factor (VEGF) receptor family, namely FLT1 (also named VEGFR1), KDR (also named FLK1 and VEGFR2), and FLT4 (also named VEGFR3). Recent analysis of the VEGF receptor repertoire in basally diverging vertebrates has identified a fourth representative of this gene family, which was secondarily lost within the eutherian lineage, but is still present in marsupials and platypus (monotremata). Because this fourth member was initially described as an orthologue of the human KDR gene in zebrafish, confusion has arisen regarding the evolutionary relationships of vertebrate VEGF receptors. Here, we revise the nomenclature of zebrafish VEGF receptors and name the fourth vertebrate VEGF receptor gene kdr-like.

The members of the VEGF family of ligands, among them VEGF-A, VEGF-B, and VEGF-C, mediate cellular responses by binding their cognate receptors. The receptors, which belong to the type III receptor tyrosine kinase family, are single-pass transmembrane proteins containing seven extracellular immunoglobulin domains and a split intracellular tyrosine kinase domain. In human, mouse, and other mammals, three VEGF receptors have been identified, namely FLT1 (also named VEGFR1), KDR (also named FLK1 and VEGFR2), and FLT4 (also named VEGFR3).

Since their initial identification in mammals, proteins homologous to VEGFRs have been identified in several basally diverging vertebrates, including birds [1,2], amphibians [3], and teleost fish. In the zebrafish, four genes encoding VEGF receptor proteins have been identified: the FLT1 orthologue [4,5], the FLT4 orthologue [6], and two genes with highest similarity to KDR/Flk1. The first of these to be cloned [6-9] and functionally characterized [10] has been used in more than 80 papers as a marker of endothelial...
cells in the zebrafish and was originally named as the zebrafish orthologue of KDR/FLK1. However, the recent identification of a second potential KDR/FLK1 orthologue [4,11,12], which in fact is more similar to the human gene, has caused confusion over the evolutionary relationships of zebrafish and mammalian VEGF receptors.

In many cases, the presence of two zebrafish orthologues of a single human gene can be attributed to a whole-genome duplication event that occurred within the teleost lineage. It was therefore hypothesized that zebrafish contains duplicated KDR genes, which were consequently called kdra (the gene originally called flk1) and kdrb (the gene that is most similar to human KDR). However, two lines of evidence have recently challenged this view [4,13–15] and rather suggest that this is a case of “ohnologs” [16,17]. First, experimental data revealed significant functional similarity of zebrafish flk1/kdra and kdrb. Both genes are expressed in all endothelial cells, whereas flt1 and flt4 have a more restricted expression. Furthermore, zebrafish VEGF can bind and activate both flk1/kdra and kdrb [11]. Finally, flk1/kdra and kdrb genetically interact: knock-down of kdrb in a flk1/kdra mutant background resulted in similar phenotypes as those observed in embryos in which vegfr2 was knocked down or in which a downstream signaling component, phospholipase-cy1, is mutated ([12] and N. Lawson, unpublished data).

Conclusion

Therefore, to reflect that flk1/kdra is a prominent receptor in VEGF-A signaling in zebrafish, while at the same time indicating that it represents a fourth class of vertebrate VEGF receptors (and is not the result of a teleost gene duplication), we propose to rename this gene kdr-like. As the zebrafish kdrb gene is clearly orthologous to mammalian KDR, we propose to rename this gene kdr.

Acknowledgments

We apologize to those authors whose work we were unable to cite for space reasons.

References

1. Marcelle C, Eichmann A (1992) Molecular cloning of a family of protein kinase genes expressed in the avian embryo. Oncogene 7:2479–2487.
2. Sugihiya T, Takahashi T, Shimizu T, Yao A, Kinugawa K, et al. (2000) Expression of genes encoding vascular endothelial growth factor and its Flk-1 receptor in the chick embryonic heart. Mol Cell Cardiol 32:1039–1051.
3. Cleaver O, Tonissen KF, Saha MS, Krieg PA (1997) Neovascularization of the Xenopus embryo. Dev Dyn 210:66–77.
4. Busonman J, Bakkers J, Schulte-Merker S (2007) Early endocardial morphogenesis requires Scl/Tall. PLoS Genet 3:e140. doi:10.1371/journal.pgen.0030140.
5. Rother H, Jost S, Wessels G, Tran N, Most P, et al. (2005) VEGF-PLCγ1amma1 pathway controls cardiac contractility in the embryonic heart. Genes Dev 19:1624–1634.
6. Thompson MA, Ransom DG, Pratt SJ, MacLennan H, Kieran MW, et al. (1998) The cloche and spadetail genes differentially affect hematopoiesis and vasculogenesis. Dev Biol 197:249–269.
7. Fouquet B, Weinstein BM, Sekura FC, Fishman MC (1997) Vessel patterning in the embryo of the zebrafish: guidance by notochord. Dev Biol 183:37–48.
8. Liu W, Bogove BW, Sawyer H, Hug B, Bell B, et al. (1997) The zebrafish gene cloche acts upstream of a flk-1 homologue to regulate endothelial cell differentiation. Development 124:381–389.
9. Sumoy L, Keasey JB, Dittrman TD, Kimelman D (1997) A role for notochord in axial vascular development revealed by analysis of phenotype and the expression of VEGFR-2 in zebrafish flk1 mutant embryos. Mech Dev 63:15–27.
10. Habecck HA, Oldenhal J, Walderich B, Maischein HM, Schulte-Merker S (2002) Analysis of a zebrafish VEGF receptor mutant reveals specific disruption of angiogenesis. Curr Biol 12:1405–1412.
11. Bahary N, Goishi K, Stuckenholz C, Weber G, MacLennan H, et al. (1998) The cloche and spadetail genes differentially affect hematopoiesis and vasculogenesis. Dev Biol 197:249–269.
12. Coreassin LD, Villefranc JA, Kacergis MC, Weinstein BM, Lawson ND (2006) Distinct genetic interactions between multiple Vegf receptors are required for development of different blood vessel types in zebrafish. Proc Natl Acad Sci U S A 103:6554–6559.
13. Mulley JF, Ciuff CH, Holland PW (2006) Breakup of a homeobox cluster after genome duplication in teleosts. Proc Natl Acad Sci U S A 103:10369–10372.
14. Prohaska SJ, Stadler PF (2006) Evolution of the vertebrate ParaHox clusters. J Exp Zoolog B Mol Dev Evol 306:481–487.
15. Siegel N, Hoegg S, Salburger W, Braasch I, Meyer A (2007) Comparative genomics of ParaHox clusters of teleost fishes: gene cluster breakup and the retention of gene sets following whole genome duplications. BMC Genomics 8:312.
16. Postlethwait JH (2006) The zebrafish genome in context: Ohnologs gone missing. J Exp Zool Mol Dev Evol 308:563–573.
17. Wolfe K (2000) Robustness: it’s not where you think it is. Nat Genet 25:3–4.