Developmental Biology

Volume 249, Issue 1, 1 September 2002, Pages 16-29

Regular Article

The Mouse *Kreisler* (*Krml1*/*MafB*) Segmentation Gene Is Required for Differentiation of Glomerular Visceral Epithelial Cells

Virginia S. Sadl [a]1 … Sabine P. Cordes [a, c]2

Show more

https://doi.org/10.1006/dbio.2002.0751

Abstract

Molecular components of the glomerular filtration mechanism play critical roles in renal diseases. Many of these components are produced during the final stages of differentiation of glomerular visceral epithelial cells, also known as podocytes. While basic domain leucine zipper (bZip) transcription factors of the Maf subfamily have been implicated in cellular differentiation processes, *Kreisler (Krml1/MafB)*, the gene affected in the mouse *kreisler (kr)* mutation, is known for its role in hindbrain patterning. Here we show that mice homozygous for the kr^{enu} mutation develop renal disease and that *Kreisler* is essential for cellular differentiation of podocytes. Consistent with abnormal podocyte differentiation, kr^{enu} homozygotes show proteinuria, and fusion and effacement of podocyte foot processes, which are also observed in the nephrotic syndrome. Kreisler acts during the final stages of glomerular development—the transition between the capillary loop and mature stages—and downstream of the Pod1 basic domain helix–loop–helix transcription factor. The levels of Podocin, the gene mutated in autosomal recessive steroid-resistant nephrotic syndrome (NPHS2), and Nephrin, the gene mutated in congenital nephrotic syndrome of the Finnish type (NPHS1), are slightly reduced in kr^{enu}/kr^{enu} podocytes. However, these observations alone are unlikely to account for the aberrant podocyte foot process formation. Thus, Kreisler must regulate other unknown genes required for podocyte function and with possible roles in kidney disease.

Keywords

Kreisler (Krml1/MafB); *Pod1 (epicardin/capsulin)*; podocyte; kidney disease; cellular differentiation; proteinuria

Recommended articles Citing articles (79)

References

REFERENCES

1 S. Abdelhak, V. Kalatzis, R. Heilig, S. Compain, D. Samson, C. Vincent, D. Weil, C. Cruaud, I. Sahly, M. Leibovici, M. Bitner-Glindzicz, M. Francis, D. Lacombe, J. Vigneron, R. Charachon, K. Boven, P. Bedbeder, N. Van Regemorter, J. Weissenbach, C. Petit
A human homologue of the *Drosophila* eyes absent gene underlies branchio-oto-renal (BOR) syndrome and identifies a novel gene family
Nat. Genet., 15 (1997), pp. 157-164

2 D.R. Abrahamson
Glomerulogenesis in the developing kidney
Semin. Nephrol., 11 (1991), pp. 375-389

3 V. Blank, N.C. Andrews
The Maf transcription factors: Regulators of differentiation
Trends Biochem. Sci., 22 (1997), pp. 437-441
Article PDF (1MB)

4 H. Chen, Y. Lun, D. Ovchinnikov, H. Kokubo, K.C. Oberg, C.V. Pepicelli, L. Gan, B. Lee, R.L. Johnson
Limb and kidney defects in Lmx1b mutant mice suggest an involvement of LMX1B in human nail patella syndrome
Nat. Genet., 19 (1998), pp. 51-55

5 S.P. Cordes, G.S. Barsh
The mouse segmentation gene kr encodes a novel basic domain-leucine zipper transcription factor
Cell, 79 (1994), pp. 1025-1034
Article PDF (5MB)

6 D. Cosgrove, D.T. Meehan, J.A. Grunkemeyer, J.M. Kornak, R. Sayers, W.J. Hunter, G.C. Samuelson
Collagen COL4A3 knockout: A mouse model for autosomal Alport syndrome
Genes Dev., 10 (1996), pp. 2981-2992

7 M.S. Deol
The abnormalities of the inner ear in *kreisler* mice
J. Embryol. Exp. Morphol., 12 (1964), pp. 475-490

8 D.B. Donoviel, D.D. Freed, H. Vogel, D.G. Potter, E. Hawkins, J.P. Barrish, B.N. Mathur, C.A. Turner, R. Geske, C.A. Montgomery, M. Starbuck, M. Brandt, A. Gupta, R. Ramirez-Solis, B.P. Zambrowicz, D.R. Powell
Proteinuria and perinatal lethality in mice lacking NEPH1, a novel protein with homology to NEPHRIN
Mol. Cell. Biol., 21 (2001), pp. 4829-4836

9 G.R. Dressler, J.E. Wilkinson, U.W. Rothenpieler, L.T. Patterson, L. Williams-Simons, H. Westhpal
Deregulation of *Pax-2* expression in transgenic mice generates severe kidney abnormalities
Nature, 362 (1993), pp. 65-67

10 S.D. Dreyer, G. Zhou, A. Baldini, A. Winterpacht, B. Zabel, W. Cole, R.L. Johnson, B. Lee
Mutations in *LMX1B* cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome
Nat. Genet., 19 (1998), pp. 47-50

11 A. Eichmann, A. Grapin-Botton, L. Kelly, T. Graf, N.M. Le Douarin, M. Sieweke
The expression pattern of the *mafB/kr* gene in birds and mice reveals that the *kreisler* phenotype does not represent a null mutant
Mech. Dev., 65 (1997), pp. 111-122
Article PDF (12MB)

12 M.A. Frohman, G.R. Martin, S.P. Cordes, L.P. Halamek, G.S. Barsh
Altered rhombomere-specific gene expression and hyoid bone differentiation in the mouse segmentation mutant, *kreisler (kr)*
Development, 117 (1993), pp. 925-936

13 M. Hellstrom, M. Kalen, P. Lindahl, A. Abramsson, C. Betsholtz
Role of PDGF-B and PDGFR-beta in recruitment of vascular smooth muscle cells and pericytes during embryonic blood vessel formation in the mouse
Development, 126 (1999), pp. 3047-3055

14 H. Hidai, R. Bardales, R. Goodwin, T. Quertermous, E.E. Quertermous
Cloning of capsulin, a basic helix–loop–helix factor expressed in progenitor cells of the pericardium and the coronary arteries
Mech. Dev., 73 (1998), pp. 33-43
Article PDF (1MB)

15 L.B. Holzman, P.L. St John, I.A. Kovari, R. Verma, H. Holthofer, D.R. Abrahamson
Nephrin localizes to the slit pore of the glomerular epithelial cell
Kidney Int., 56 (1999), pp. 1481-1491
Article PDF (708KB)

16 J. Imaki, H. Onodera, K. Tsuchiya, T. Imaki, T. Mochizuki, T. Mishima, K. Yamashita, K. Yoshida, M. Sakai
Developmental expression of maf-1 messenger ribonucleic acids in rat kidney by in situ hybridization histochemistry
Biochem. Biophys. Res. Commun., 272 (2000), pp. 777-782
Article PDF (612KB)

17 N.M. Inamdar, Y.I. Ahn, J. Alam
The heme responsive element of the mouse heme oxygenase-1 gene is an extended AP-1 binding site that resembles the recognition sequences for MAF and NF-E2 transcription factors
Biochem. Biophys. Res. Commun., 221 (1996), pp. 570-576
Article PDF (70KB)

18 K.R. Johnson, S.A. Cook, L.C. Erway, A.N. Matthews, L.P. Sanford, N.E. Paradies, R.A. Friedman
Inner ear and kidney anomalies caused by IAP insertion in an intron of the Eya1 gene in a mouse model of BOR syndrome
Hum. Mol. Genet., 8 (1999), pp. 645-653

19 V. Kalatzis, I. Sahly, A. El-Amraoui, C. Petit
Eya1 expression in the developing ear and kidney: Towards the understanding of the pathogenesis of Branchio-Oto-Renal (BOR) syndrome
Dev. Dyn., 213 (1998), pp. 486-499

20 J.M. Kaplan, S.H. Kim, K.N. North, H. Rennke, L.A. Correia, H.Q. Tong, B.J. Mathis, J.C. Rodriguez-Perez, P.G. Allen, A.H. Beggs, M.R. Pollak
Mutations in ACTN4, encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis
Nat. Genet., 24 (2000), pp. 251-256

21 H. Kawachi, H. Koike, H. Kurihara, E. Yaoita, M. Orikasa, M.A. Shia, Sakai, T. Yamamoto, D.J. Salant, F. Shimizu
Cloning of rat nephrin: Expression in developing glomeruli and in proteinuric states
Kidney Int., 57 (2000), pp. 1949-1961
Article PDF (2MB)

22 M. Kestila, U. Lenkkeri, M. Mannikko, J. Lamerdin, P. McCready, H. Putaala, V. Ruotsalainen, T. Morita, M. Nissinen, R. Herva, C.E. Kashtan, L. Peltonen, C. Holmberg, A. Olsen, K. Tryggvason
Positionally cloned gene for a novel glomerular protein—nephrin—is mutated in congenital nephrotic syndrome
Mol. Cell, 1 (1998), pp. 575-582
Article PDF (1MB)

23 J.I. Kim, T. Li, I.C. Ho, M.J. Grusby, L.H. Glimcher
Requirement for the c-Maf transcription factor in crystallin gene regulation and lens development
Proc. Natl. Acad. Sci. USA, 96 (1999), pp. 3781-3785

24 J.A. Kreidberg, M.J. Donovan, S.L. Goldstein, H. Rennke, K. Shepherd, R.C. Jones, R. Jaenisch
Alpha 3 beta 1 integrin has a crucial role in kidney and lung organogenesis
Development, 122 (1996), pp. 3537-3547

25 J.A. Kreidberg, H. Sariola, J.M. Loring, M. Maeda, J. Pelletier, D. Housman, R. Jaenisch
WT-1 is required for early kidney development
Cell, 74 (1993), pp. 679-691
Article PDF (8MB)

26 W. Kriz, M. Elger, M. Nagata, M. Kretzler, S. Uiker, I. Koeppen-Hageman, S. Tenschert, K.V. Lemley
The role of podocytes in the development of glomerular sclerosis
Kidney Int., 45 (1994), pp. S-64-S-72

27 M.S. Lechner, G.R. Dressler
The molecular basis of embryonic kidney development
Mech. Dev., 62 (1997), pp. 105-120
Article PDF (5MB)

28 S. Lehtonen, A. Ora, V.M. Olkkonen, L. Geng, M. Zerial, S. Somlo, E. Lehtonen
In vivo interaction of the adapter protein CD2-associated protein with the type 2 polycystic kidney disease protein, polycystin-2 [In Process Citation]
J. Biol. Chem., 275 (2000), pp. 32888-32893

29 P. Leveen, M. Pekny, S. Gebre-Medhin, B. Swolin, E. Larsson, C. Betsholtz
Mice deficient for PDGF B show renal, cardiovascular, and hematological abnormalities
Genes Dev., 8 (1994), pp. 1875-1887

30 C. Li, V. Ruotsalainen, K. Tryggvason, A.S. Shaw, J.H. Miner
CD2AP is expressed with nephrin in developing podocytes and is found widely in mature kidney and elsewhere [In Process Citation]
Am. J. Physiol. Renal Physiol., 279 (2000), pp. F785-F792

31 J. Lu, J.A. Richardson, E.N. Olson
Capsulin: A novel bHLH transcription factor expressed in epicardial progenitors and mesenchyme of visceral organs
Mech. Dev., 73 (1998), pp. 23-32
Article PDF (2MB)

32 W. Lu, C.L. Phillips, P.D. Killen, T. Hlaing, W.R. Harrison, F.F. Elder, J.H. Miner, P.A. Overbeek, M.H. Meisler
Insertional mutation of the collagen genes Col4a3 and Col4a4 in a mouse model of Alport syndrome
Genomics, 61 (1999), pp. 113-124
Article PDF (672KB)

33 N.R. Manley, M.R. Capecchi
Hox group 3 paralogs regulate the development and migration of the thymus, thyroid, and parathyroid glands
Dev. Biol., 195 (1998), pp. 1-15
Article PDF (6MB)

34 S.L. Mansour, K.R. Thomas, M.R. Capecchi
Disruption of the proto-oncogene int-2 in mouse embryo-derived stem cells: A general strategy for targetting mutations to non-selectable genes
Nature, 336 (1988), pp. 348-352

35 M. Manzanares, S. Cordes, L. Ariza-McNaughton, V. Sadl, K. Maruthainar, G. Barsh, R. Krumlauf
Conserved and distinct roles of kreisler in regulation of the paralogous Hoxa3 and Hoxb3 genes
Development, 126 (1999), pp. 759-769

36 M. Manzanares, S.P. Cordes, C.-T. Kwan, M.-H. Sham, G.S. Barsh, R. Krumlauf
Segmental regulation of *Hoxb3* by Kreisler
Nature, 387 (1997), pp. 191-195

37 J.H. Millonig, K.J. Millen, M.E. Hatten
The mouse Dreher gene Lmx1a controls formation of the roof plate in the vertebrate CNS
Nature, 403 (2000), pp. 764-769

38 J.H. Miner, C. Li
Defective glomerulogenesis in the absence of laminin alpha5 demonstrates a developmental role for the kidney glomerular basement membrane
Dev. Biol., 217 (2000), pp. 278-289
Article PDF (1MB)

39 C. Moens, S.P. Cordes, G. Barsh, C. Kimmel
Equivalence in the genetic control of hindbrain segmentation in fish and mouse
Development, 125 (1998), pp. 381-391

40 P.G. Noakes, J.H. Miner, M. Gautam, J.M. Cunningham, J.R. Sanes, J.P. Merlie
The renal glomerulus of mice lacking s-laminin/laminin beta 2: nephrosis despite molecular compensation by laminin beta 1
Nat. Genet., 10 (1995), pp. 400-406

41 M.E. Pagtalunan, P.L. Miller, S. Jumping-Eagle, R.G. Nelson, B.D. Myers, H.G. Rennke, N.S. Coplon, L. Sun, T.W. Meyer
Podocyte loss and progressive glomerular injury in type II diabetes
J. Clin. Invest., 99 (1997), pp. 342-348

42 J. Pelletier, W. Bruening, C.E. Kashtan, S.M. Mauer, J.C. Manivel, J.E. Striegel, D.C. Houghton, C. Junien, R. Habib, L. Fouser
Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys–Drash syndrome

Cell, 67 (1991), pp. 437-447
Article PDF (1MB)

43 H. Putaala, K. Sainio, H. Sariola, K. Tryggvason
Primary structure of mouse and rat nephrin cDNA and structure and expression of the mouse gene
J. Am. Soc. Nephrol., 11 (2000), pp. 991-1001

44 S.E. Quaggin, L. Schwartz, S. Cui, P. Igarashi, J. Deimling, M. Post, J. Rossant
The basic-helix–loop–helix protein pod1 is critically important for kidney and lung organogenesis
Development, 126 (1999), pp. 5771-5783

45 S.E. Quaggin, G.B. Vanden Heuvel, P. Igarash
Pod-1, a mesoderm-specific basic-helix–loop–helix protein expressed in mesenchymal and glomerular epithelial cells in the developing kidney
Mech. Dev., 71 (1998), pp. 37-48
Article PDF (2MB)

46 B.Z. Ring, S.P. Cordes, P.A. Overbeek, G.S. Barsh
Regulation of mouse lens fiber cell development and differentiation by the Maf gene
Development, 127 (2000), pp. 307-317

47 L. Robb, L. Mifsud, L. Hartley, C. Biben, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, R.P. Harvey
epicardin: A novel basic helix–loop–helix transcription factor gene expressed in epicardium, branchial arch myoblasts, and mesenchyme of developing lung, gut, kidney, and gonads
Dev. Dyn., 213 (1998), pp. 105-113

48 T. Sasaki, K. Mann, J.H. Miner, N. Miosge, R. Timpl
Domain IV of mouse laminin beta1 and beta2 chains
Eur. J. Biochem., 269 (2002), pp. 431-442

49 K. Schwarz, M. Simons, J. Reiser, M.A. Saleem, C. Faul, W. Kriz, A.S. Shaw, L.B. Holzman, P. Mundel
Podocin, a raft-associated component of the glomerular slit diaphragm, interacts with CD2AP and nephrin
J. Clin. Invest., 108 (2001), pp. 1621-1629

50 J.A. Shavit, H. Motohashi, K. Onodera, J. Akasaka, M. Yamamoto, J.D. Engel
Impaired megakaryopoiesis and behavioral defects in mafG-null mutant mice
Genes Dev., 12 (1998), pp. 2164-2174

51 P. Soriano
Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice
Genes Dev., 8 (1994), pp. 1888-1896

52 E.E. Storm, D.M. Kingsley
Joint patterning defects caused by single and double mutations in members of the bone morphogenetic protein (BMP) family
Development, 122 (1996), pp. 3969-3979

53 M.A. Wong, S. Cui, S.E. Quaggin
Identification and characterization of a glomerular-specific promoter from the human nephrin gene
Am. J. Physiol. Renal Physiol., 279 (2000), pp. F1027-F1032

54 P.X Xu, J. Adams, H. Peters, M.C. Brown, S. Heaney, R. Maas
Eya1-deficient mice lack ears and kidneys and show abnormal apoptosis of organ primordia
Nat. Genet., 23 (1999), pp. 113-117

1 These authors contributed equally to this work.

2 To whom correspondence should be addressed. Fax: (416) 586-8588. E-mail: cordes@mshri.on.ca.