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Vascular Abnormalities in Mice Lacking the Endothelial Gap Junction Proteins connexin37 and connexin40

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Abstract

Cells within the vascular wall are coupled by gap junctions, allowing for direct intercellular transfer of low molecular weight molecules. Although gap junctions are believed to be important for vascular development and function, their precise roles are not well understood. Mice lacking either connexin37 (Cx37) or connexin40 (Cx40), the predominant gap junction proteins present in vascular endothelium, are viable and exhibit phenotypes that are largely non-blood vessel related. Since Cx37 and Cx40 are coexpressed in endothelial cells and could overlap functionally, some roles of junctional communication may only be revealed by the elimination of both connexins. In this study, we interbreed Cx37 and Cx40 knockout mice to generate Cx37^{-/-}Cx40^{-/-} animals and show that they display severe vascular abnormalities and die perinatally. Cx37^{-/-}Cx40^{-/-} animals exhibit localized hemorrhages in skin, testis, gastrointestinal tissues, and lungs, with pronounced blood vessel dilatation and congestion occurring in some areas. Vascular anomalies were particularly striking in testis and intestine. In testis, abnormal vascular channels were present, with these channels coalescing into a cavernous, endothelium-lined blood pool resembling a hemangioma. These results provide evidence of a critical role for endothelial gap junction-mediated communication in the development and/or functional maintenance of segments of the mouse vasculature.

Keywords

connexin; gap junction; intercellular communication; endothelium; vascular abnormality; hemorrhage; hemangioma; vascular malformation

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References

REFERENCES

- 1 E.C. Beyer
Connexin43: A protein from rat heart homologous to a gap junction protein from liver
J. Cell Biol., 105 (1987), pp. 2621-2629

- 2 R. Bruzzone

Loading [Contrib]/a11y/accessibility-menu.js junctions in vascular endothelium, is restricted in its ability to interact with other connexins

- 3 W.J. Cai
Connexin37, not Cx40 and Cx43, is induced in vascular smooth muscle cells during coronary arteriogenesis
J. Mol. Cell. Cardiol., 33 (2001), pp. 957-967
- 4 A.T. Chaytor
Central role of heterocellular gap junctional communication in endothelium-dependent relaxations of rabbit arteries
J. Physiol., 508 (1998), pp. 561-573
- 5 G.J. Christ
Gap junctions in vascular tissues. Evaluating the role of intercellular communication in the modulation of vasomotor tone
Circ. Res., 79 (1996), pp. 631-646
- 6 C. de Wit
Impaired conduction of vasodilation along arterioles in connexin40-deficient mice
Circ. Res., 86 (2000), pp. 649-655
- 7 C.N. Dealy
Expression patterns of mRNAs for the gap junction proteins connexin43 and connexin42 suggest their involvement in chick limb morphogenesis and specification of the arterial vasculature
Dev. Dyn., 199 (1994), pp. 156-167
- 8 G.G. Emerson, S.S. Segal
Endothelial cell pathway for conduction of hyperpolarization and vasodilation along hamster feed artery
Circ. Res., 86 (2000), pp. 94-100
- 9 D. Feng
Reinterpretation of endothelial cell gaps induced by vasoactive mediators in guinea-pig, mouse and rat: Many are transcellular pores
J. Physiol., 504 (1997), pp. 747-761
- 10 J.E. Gabriels, D.L. Paul
Connexin43 is highly localized to sites of disturbed flow in rat aortic endothelium but connexin37 and connexin40 are more uniformly distributed
Circ. Res., 83 (1998), pp. 636-643
- 11 D.A. Goodenough
Connexins, connexons, and intercellular communication
Annu. Rev. Biochem., 65 (1996), pp. 475-502
- 12 J.A. Haefliger
Connexins 40 and 43 are differentially regulated within the kidneys of rats with renovascular hypertension
Kidney Int., 60 (2001), pp. 190-201
- 13 S. Kirchhoff
Reduced cardiac conduction velocity and predisposition to arrhythmias in connexin40-deficient mice
Curr. Biol., 8 (1998), pp. 299-302
- 14 Y.S. Ko
Connexin make-up of endothelial gap junctions in the rat pulmonary artery as revealed by immunofluorescence microscopy and triple-label immunogold electron microscopy
J. Histochem. Cytochem., 47 (1999), pp. 683-692
- 15 O. Krüger
Defective vascular development in connexin 45-deficient mice
Development, 127 (2000), pp. 4179-4193
- 16 M. Kumai
Loss of connexin45 causes a cushion defect in early cardiogenesis
Development, 127 (2000), pp. 3501-3512
- 17 N.M. Kumar, N.B. Gilula
The gap junction communication channel

- 18 D.T. Kurjiaka
Gap junction permeability is diminished in proliferating vascular smooth muscle cells
Am. J. Physiol., 275 (1998), pp. C1674-C1682
- 19 D.M. Larson, C.C. Haudenschild
Junctional transfer in wounded cultures of bovine aortic endothelial cells
Lab. Invest., 59 (1988), pp. 373-379
- 20 D.M. Larson
Gap junction messenger RNA expression by vascular wall cells
Circ. Res., 66 (1990), pp. 1074-1080
- 21 X Li, J.M. Simard
Multiple connexins form gap junction channels in rat basilar artery smooth muscle cells
Circ. Res., 84 (1999), pp. 1277-1284
- 22 Y. Liao
Endothelial cell-specific knockout of connexin 43 causes hypotension and bradycardia in mice
Proc. Natl. Acad. Sci. USA, 98 (2001), pp. 9989-9994
- 23 T.L. Little
Connexin 43 and connexin 40 gap junctional proteins are present in arteriolar smooth muscle and endothelium in vivo
Am. J. Physiol., 268 (1995), pp. H729-H739
- 24 C.W. Lo
Gap junction communication and the modulation of cardiac neural crest cells
Trends Cardiovasc. Med., 9 (1999), pp. 63-69
- 25 W.R. Loewenstein, B. Rose
The cell-cell channel in the control of growth
Semin. Cell Biol., 3 (1992), pp. 59-79
- 26 D.M. McDonald
Endothelial gaps and permeability of venules in rat tracheas exposed to inflammatory stimuli
Am. J. Physiol., 266 (1994), pp. L61-L83
- 27 K. Nakamura
Distribution of gap junction protein connexin 37 in smooth muscle cells of the rat trachea and pulmonary artery
Arch. Histol. Cytol., 62 (1999), pp. 27-37
- 28 M.S. Pepper
Junctional communication is induced in migrating capillary endothelial cells
J. Cell Biol., 109 (1989), pp. 3027-3038
- 29 A. Plum
Unique and shared functions of different connexins in mice
Curr. Biol., 10 (2000), pp. 1083-1091
- 30 A.G. Reaume
Cardiac malformation in neonatal mice lacking connexin43
Science, 267 (1995), pp. 1831-1834
- 31 K.E. Reed
Molecular cloning and functional expression of human connexin37, an endothelial cell gap junction protein
J. Clin. Invest., 91 (1993), pp. 997-1004
- 32 S.S. Segal, B.R. Duling
Conduction of vasomotor responses in arterioles: a role for cell-to-cell coupling?
Am. J. Physiol., 256 (1989), pp. H838-H845
- 33 A.M. Simon
Functional and molecular analysis of the gap junction protein connexin 37

Female infertility in mice lacking connexin 37

Nature, 385 (1997), pp. 525-529

- 34 A.M. Simon
Mice lacking connexin40 have cardiac conduction abnormalities characteristic of atrioventricular block and bundle branch block
Curr. Biol., 8 (1998), pp. 295-298
- 35 M. Theis
Endothelium-specific replacement of the connexin43 coding region by a lacZ reporter gene
Genesis, 29 (2001), pp. 1-13
- 36 O. Traub
Characterization of the gap junction protein connexin37 in murine endothelium, respiratory epithelium, and after transfection in human HeLa cells
Eur. J. Cell Biol., 77 (1998), pp. 313-322
- 37 M.J. van Kempen, H.J. Jongsma
Distribution of connexin37, connexin40 and connexin43 in the aorta and coronary artery of several mammals
Histochem. Cell Biol., 112 (1999), pp. 479-486
- 38 K. Willecke
Structural and functional diversity of connexin genes in the mouse and human genome
Biol. Chem., 383 (2002), pp. 725-737
- 39 J. Ya
Heart defects in connexin43-deficient mice
Circ. Res., 82 (1998), pp. 360-366
- 40 H. Yamasaki
Genetic and epigenetic changes of intercellular communication genes during multistage carcinogenesis
Cancer Detect. Prev., 23 (1999), pp. 273-279
- 41 H.I. Yeh
Gap junction localization and connexin expression in cytochemically identified endothelial cells of arterial tissue
J. Histochem. Cytochem., 45 (1997), pp. 539-550
- 42 H.I. Yeh
Individual gap junction plaques contain multiple connexins in arterial endothelium
Circ. Res., 83 (1998), pp. 1248-1263

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