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Experimental Studies on the Spatiotemporal Expression of WT1 and RALDH2 in the Embryonic Avian Heart: A Model for the Regulation of Myocardial and Valvuloseptal Development by Epicardially Derived Cells (EPDCs)

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Abstract

Epicardially derived cells (EPDCs) delaminate from the primitive epicardium through an epithelial-to-mesenchymal transformation (EMT). After this transformation, a subpopulation of cells progressively invades myocardial and valvuloseptal tissues. The first aim of the study was to determine the tissue-specific distribution of two molecules that are thought to play a crucial function in the interaction between EPDCs and other cardiac tissues, namely the Wilms' Tumor transcription factor (WT1) and retinaldehyde-dehydrogenase2 (RALDH2). This study was performed in normal avian and in quail-to-chick chimeric embryos. It was found that EPDCs that maintain the expression of WT1 and RALDH2 initially populate the subepicardial space and subsequently invade the ventricular myocardium. As EPDCs differentiate into the smooth muscle and endothelial cell lineage of the coronary vessels, the expression of WT1 and RALDH2 becomes downregulated. This process is accompanied by the upregulation of lineage-specific markers. We also observed EPDCs that continued to express WT1 (but very little RALDH2) which did not contribute to the formation of the coronary system. A subset of these cells eventually migrates into the atrioventricular (AV) cushions, at which point they no longer express WT1. The WT1/RALDH2-negative EPDCs in the AV cushions do, however, express the smooth muscle cell marker caldesmon. The second aim of this study was to determine the impact of abnormal epicardial growth on cardiac development. Experimental delay of epicardial growth distorted normal epicardial development, reduced the number of invasive WT1/RALDH2-positive EPDCs, and provoked anomalies in the coronary vessels, the ventricular myocardium, and the AV cushions. We suggest that the proper development of ventricular myocardium is dependent on the invasion of undifferentiated, WT1-positive, retinoic acid-synthesizing EPDCs. Furthermore, we propose that an interaction between EPDCs and endocardial (derived) cells is imperative for correct development of the AV cushions.

Keywords

cardiac development; EPDCs; epicardium; RALDH2; WT1

References

REFERENCES

1 J.F. Armstrong, K. Pritchard-Jones, W.A. Bickmore, N.D. Hastie, J.B. Bard
The expression of the Wilms' tumour gene, WT1, in the developing mammalian embryo
Mech. Dev., 40 (1993), pp. 85-97
Article PDF (4MB)

2 K. Berggren, E.B. Ezerman, P. McCaffery, C.J. Forehand
Expression and regulation of the retinoic acid synthetic enzyme RALDH-2 in the embryonic chicken wing
Dev. Dyn., 222 (2001), pp. 1-16

3 K.M. Call, T. Glaser, C.Y. Ito, A.J. Buckler, J. Pelletier, D.A. Haber, E.A. Rose, A. Kral, H. Yeger, W.H. Lewis, C. Jones, D.E. Housman
Isolation and characterization of a zinc finger polypeptide gene at the human chromosome 11 Wilms' tumor locus
Cell, 60 (1990), pp. 509-520
Article PDF (2MB)

4 P. Carmeliet
Cardiovascular biology. Creating unique blood vessels
Nature, 412 (2001), pp. 868-869

5 R. Carmona, M. González-Iriarte, J.M. Pérez-Pomares, R. Muñoz-Chápuli
Localization of the Wilms' tumour protein WT1 in avian embryos
Cell Tissue Res., 303 (2001), pp. 173-186

6 R.W. Dettman, W. Denetclaw Jr., C.P. Ordahl, J. Bristow
Common origin of coronary vascular smooth muscle, perivascular fibroblasts, and intermyocardial fibroblasts in the avian heart
Dev. Biol., 193 (1998), pp. 169-181
Article PDF (1MB)

7 E. Dyson, H.M. Sucov, S.W. Kubalak, G.W. Schmid-Schönbeim, F.A. DeLano, R.M. Evans, J. Ross Jr., K. Chien
Atrial-like phenotype is associated with embryonic ventricular failure in retinoid X receptor $\alpha^{-/-}$ mice
Proc. Natl. Acad. Sci. USA, 92 (1995), pp. 7386-7390

8 H. Eid, D.M. Larson, J.P. Springhorn, M.A. Attawia, R.C. Nayak, T.W. Smith, R.A. Kelly
Role of epicardial mesothelial cells in the modification of phenotype and function of adult rat ventricular myocytes in primary coculture
Circ. Res., 71 (1992), pp. 40-50

9 D.A. Filip, A. Radu, M. Simionescu
Interstitial cells of the heart valves possess characteristics similar to smooth muscle cells
Circ. Res., 59 (1986), pp. 310-320

10 M. Gessler, A. Poutska, W. Cavenee, R.L. Neve, S.H. Orkin, G.A. Bruns
Homozygous deletion in Wilms' tumours of a zinc-finger gene identified by chromosome jumping
Nature, 343 (1990), pp. 774-778

11 A.C. Gittenberger-de Groot, M.P. Vrancken Peeters, M.M. Mentink, R.G. Gourdie, R.E. Poelmann
Epicardium-derived cells contribute a novel population to the myocardial wall and the atrioventricular cushions
Circ. Res., 82 (1998), pp. 1043-1052

12 A.C. Gittenberger-de Groot, M.P. Vrancken Peeters, M. Bergwerff, M.M. Mentink, R.E. Poelmann
Epicardial outgrowth inhibition leads to compensatory mesothelial outflow tract collar and abnormal cardiac septation and coronary formation
Circ. Res., 87 (2000), pp. 969-971

13 P. Goodyer, M. Dehbi, E. Torban, W. Bruening, J. Pelletier
Repression of the retinoic acid receptor-alpha gene by the Wilms' tumor suppressor gene product, WT1
Oncogene, 10 (1995), pp. 1125-1129

14 P.J. Gruber, S.W. Kubalak, T. Pexieder, H.M. Sucov, R.M. Evans, K.R. Chien
RXR alpha deficiency confers genetic susceptibility for aortic sac, conotruncal, atrioventricular cushion, and ventricular muscle defects in mice
J. Clin. Invest., 98 (1996), pp. 1332-1343

15 V. Hamburger, H.L. Hamilton
A series of normal stages in the development of the chick embryo
J. Morphol., 88 (1951), pp. 49-92

16 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)

17 R. Hirakow
Epicardial formation in staged human embryos
Kaibogaku Zasshi, 67 (1992), pp. 616-622

18 T. Hiruma, R. Hirakow
Epicardial formation in embryonic chick heart. Computer aided reconstruction, scanning and transmission electron microscopic studies
Am. J. Anat., 184 (1989), pp. 129-138

19 E. Ho, Y. Shimada
Formation of the epicardium studied with the electron microscope
Dev. Biol., 66 (1978), pp. 579-585
Article PDF (7MB)

20 J.E. Hungerford, C.D. Little
Developmental biology of the vascular smooth muscle cell: Building a multilayered vessel wall
J. Vasc. Res., 36 (1999), pp. 2-27

21 P. Kastner, J.M. Grondona, M. Mark, A. Gansmuller, M. LeMeur, D. Decimo, J.L. Vonesch, P. Dolle, P. Chambon
Genetic analysis of RXRalpha developmental function: Convergence of RXR and RAR signalling pathways in heart and eye morphogenesis
Cell, 78 (1994), pp. 987-1003
Article PDF (22MB)

22 P. Kastner, N. Messaddeq, M. Mark, O. Wendling, J.M. Grondona, S. Ward, N. Ghyselinck, P. Chambon
Vitamin A deficiency and mutations of RXRalpha, RXRbeta and RARalpha lead to early differentiation of embryonic ventricular cardiomyocytes
Development, 124 (1997), pp. 4749-4758

23 M. Komiyama, K. Ito, Y. Shimada
Origin and development of the epicardium in the mouse embryo
Anat. Embryol., 176 (1987), pp. 183-189

24 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)

25 L. Kwee, H.S. Baldwin, H.M. Shen, C.L. Stewart, C. Buck, C.A. Buck, M.A. Labow
Defective development of the embryonic and extraembryonic circulatory systems in vascular cell adhesion molecule (VCAM-1) deficient mice
Development, 121 (1995), pp. 489-503

26 M.M. Lakkis, J.A. Epstein
Neurofibromin modulation of ras activity is required for normal endocardial–mesenchymal transformation in the developing heart
Development, 125 (1998), pp. 4359-4367

27 T.E. Landerholm, X.R. Dong, J. Lu, N.S. Belaguli, R.J. Schwartz, M.W. Majesky
A role for serum response factor in coronary smooth muscle differentiation from proepicardial cells
Development, 126 (1999), pp. 2053-2062

28 W.E.I. Li, K. Waldo, K.L. Linask, T. Chen, A. Wessels, M.S. Parmacek, M.L. Kirby, C.W. Lo
An essential role for connexin43 gap junctions in mouse coronary artery development

Development, 129 (2002), pp. 2031-2042

29 M. Little, G. Holmes, P. Walsh
WT1: What has the last decade told us?
BioEssays, 21 (1999), pp. 191-202

30 Q. Liu, H. Yan, N.J. Dawes, G.A. Mottino, J.S. Frank, H. Zhu
Insulin-like growth factor II induces DNA synthesis in fetal ventricular myocytes in vitro
Circ. Res., 79 (1996), pp. 716-726

31 C.W. Lo
Genes, gene knockouts, and mutations in the analysis of gap junctions
Dev. Genet., 24 (1999), pp. 1-4

32 J Lough, Y. Sugi
Endoderm and heart development
Dev. Dyn., 217 (2000), pp. 327-342

33 J. Lu, T.E. Landerholm, J.S. Wei, X.R. Dong, S.P. Wu, X. Liu, K. Nagata, M. Inagaki, M.W. Majesky
Coronary smooth muscle differentiation from proepicardial cells requires rhoA-mediated actin reorganization and p160 rho-kinase activity
Dev. Biol., 240 (2001), pp. 404-418
Article PDF (2MB)

34 P.C. Maisonpierre, C. Suri, P.F. Jones, S. Bartunkova, S.J. Wiegand, C. Radziejewski, D. Compton, J. McClain, T.H. Aldrich, N. Papadopoulos, T.J. Daly, S. Davis, T.N. Sato, G.D. Yancopoulos
Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis
Science, 277 (1997), pp. 55-60

35 J. Männer
Experimental study on the formation of the epicardium in chick embryos
Anat. Embryol., 187 (1993), pp. 281-289

36 J. Männer
Does the subepicardial mesenchyme contribute myocardioblasts to the myocardium of the chick embryo heart? A quail-chick chimera study tracing the fate of the epicardial primordium
Anat. Rec., 255 (1999), pp. 212-226

37 J. Männer, J.M. Pérez-Pomares, D. Macías, R. Muñoz-Chápuli
The origin, formation, and developmental significance of the epicardium: A review
Cell Tissues Organs, 169 (2001), pp. 89-103

38 P. McCaffery, U. Dräger
Retinoic acid synthesizing enzymes in the embryonic and adult vertebrate
Adv. Exp. Med. Biol., 372 (1995), pp. 173-183

39 T. Mikawa, D.A. Fischman
Retroviral analysis of cardiac morphogenesis: Discontinuous formation of coronary vessels
Proc. Natl. Acad. Sci. USA, 89 (1992), pp. 9504-9508

40 T. Mikawa, R.G. Gourdie
Pericardial mesoderm generates a population of coronary smooth muscle cells migrating into the heart along with ingrowth of the epicardial organ
Dev. Biol., 174 (1996), pp. 221-232
Article PDF (461KB)

41 A.W. Moore, L. McInnes, J. Kreidberg, N.D. Hastie, A. Schedl
YAC complementation shows a requirement for WT1 in the development of epicardium, adrenal gland and throughout nephrogenesis
Development, 126 (1999), pp. 1845-1857

42 A.W. Moore, A. Schedl, L. McInnes, M. Doyle, J. Hecksher-Sorensen, N.D. Hastie
YAC transgenic analysis reveals Wilms' tumour 1 gene activity in the proliferating coelomic epithelium, developing diaphragm

and limb
Mech. Dev., 79 (1998), pp. 169-184
Article PDF (1MB)

43 C.J. Morabito, R.W. Dettman, J. Kattan, J.M. Collier, J. Bristow
Positive and negative regulation of epicardial–mesenchymal transformation during avian heart development
Dev. Biol., 234 (2001), pp. 204-215
Article PDF (1MB)

44 J.B. Moss, J. Xavier-Neto, M.D. Shapiro, S.M. Nayeem, P. McCaffery, U. Dräger, N. Rosenthal
Dynamic patterns of retinoic acid synthesis and response in the developing mammalian heart
Dev. Biol., 199 (1998), pp. 55-71
Article PDF (7MB)

45 Y. Nakajima, V. Mironov, T. Yamagishi, H. Nakamura, R.R. Markwald
Expression of smooth muscle alpha-actin in mesenchymal cells during formation of avian endocardial cushion tissue: A role for transforming growth factor beta3
Dev. Dyn., 209 (1997), pp. 296-309

46 Y. Nakajima, T. Yamagishi, K. Yoshimura, M. Nomura, H. Nakamura
Antisense oligodeoxynucleotide complementary to smooth muscle alpha-actin inhibits endothelial-mesenchymal transformation during chick cardiogenesis
Dev. Dyn., 216 (1998), pp. 489-498

47 L. Pardanaud, C. Altmann, P. Kitos, F. Dieterlen-Lievre, C.A. Buck
Vasculogenesis in the early quail blastodisc as studied with a monoclonal antibody recognizing endothelial cells
Development, 100 (1987), pp. 339-349

48 J.M. Pérez-Pomares, D. Macías, L. García-Garrido, R. Muñoz-Chápuli
Contribution of the primitive epicardium to the subepicardial mesenchyme in hamster and chick embryos
Dev. Dyn., 210 (1997), pp. 96-105

49 J.M. Pérez-Pomares, D. Macías, L. García-Garrido, R. Muñoz-Chápuli
The origin of the subepicardial mesenchyme in the avian embryo: An immunohistochemical and quail-chimera study
Dev. Biol., 200 (1998), pp. 57-68
Article PDF (928KB)

50 J.M. Pérez-Pomares, D. Macías, L. García-Garrido, R. Muñoz-Chápuli
Immunohistochemical evidence of a mesothelial contribution to the ventral wall of the aorta in avian embryos
Histochem. J., 31 (1999), pp. 771-779

51 J.M. Pérez-Pomares, A. Phelps, R. Muñoz-Chápuli, A. Wessels
The contribution of the proepicardium to avian cardiovascular development
Int. J. Dev. Biol., 45 (2001), pp. 155-156

52 K.A. Pinco, S. Liu, J.T. Yang
alpha4 integrin is expressed in a subset of cranial neural crest cells and in epicardial progenitor cells during early mouse development
Mech. Dev., 100 (2001), pp. 99-103
Article PDF (761KB)

53 A.F. Ramsdell, R.R. Markwald
Induction of endocardial tissue in the avian heart is regulated, in part, by TGFbeta-3-mediated autocrine signaling
Dev. Biol., 188 (1997), pp. 64-74
Article PDF (1MB)

54 A.G. Reaume, P.A. de Sousa, S. Kulkarni, B.L. Langille, D. Zhu, T.C. Davies, S.C. Juneja, G.M. Kidder, J. Rossant
Cardiac malformation in neonatal mice lacking connexin43
Science, 267 (1995), pp. 1831-1834

55 D.E. Reese, D.M. Bader
Cloning and expression of hbves, a novel and highly conserved mRNA expressed in the developing and adult heart and skeletal muscle in the human

Mamm. Genome, 10 (1999), pp. 913-915

56 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

57 H.M. Sucov, E. Dyson, C.L. Gumeringer, J. Price, K.R. Chien, R.M. Evans
RXRa mutant mice establish a genetic basis for vitamin A signaling in heart morphogenesis
Genes Dev., 8 (1994), pp. 1007-1018

58 C. Suri, P.F. Jones, S. Patan, S. Bartunkova, P.C. Maisonpierre, S. Davis, T.N. Sato, G.D. Yancopoulos
Requisite role of angiopoietin-1, a ligand for the TIE2 receptor, during embryonic angiogenesis
Cell, 87 (1996), pp. 1171-1180
Article PDF (1MB)

59 P.P.L. Tam, G.C. Schoenwolf
Cardiac fate maps: Lineage allocation, morphogenetic movement, and cell commitment
R.P. Harvey, N. Rosenthal (Eds.), Heart Development, Academic Press, San Diego (1999), pp. 3-18
Article PDF (13MB)

60 S.G. Tevosian, A.E. Deconinck, M. Tanaka, M. Schinke, S.H. Litovsky, S. Izumo, Y. Fujiwara, S.H. Orkin
FOG-2, a cofactor for GATA transcription factors, is essential for heart morphogenesis and development of coronary vessels from epicardium
Cell, 101 (2000), pp. 729-739
Article PDF (592KB)

61 T.S. Vincent, G.G. Re, D.J. Hazen-Martin, B.I. Tarnowski, M.C. Willingham, A.J. Garvin
All-trans-retinoic acid-induced growth suppression of blastemal Wilms' tumor
Pediatr. Pathol. Lab. Med., 16 (1996), pp. 777-789

62 S. Viragh, C.E. Challice
Origin and differentiation of cardiac muscle cells in the mouse
J. Ultrastruct. Res., 42 (1973), pp. 1-24
Article PDF (20MB)

63 S. Viragh, C.E. Challice
The origin of the epicardium and the embryonic myocardial circulation in the mouse
Anat. Rec., 201 (1981), pp. 157-168

64 S. Viragh, A.C. Gittenberger-de Groot, R.E. Poelmann, F. Kalman
Early development of quail heart epicardium and associated vascular and glandular structures
Anat. Embryol., 188 (1993), pp. 381-393

65 M.-P.F.M. Vrancken Peeters, A.C. Gittenberger-de Groot, M.M.T. Mentink, R.E. Poelmann
Smooth muscle cells and fibroblasts of the coronary arteries derive from epithelial-mesenchymal transformation of the epicardium
Anat. Embryol., 199 (1999), pp. 367-378

66 M.-P.F.M. Vrancken Peeters, M.M.T. Mentink, R.E. Poelmann, A.C. Gittenberger-de Groot
Cytokeratins as a marker for epicardial formation in the quail embryo
Anat. Embryol., 191 (1995), pp. 503-508

67 A.M. Wada, D.E. Reese, D.M. Bader
Bves. prototype of a new class of cell adhesion molecules expressed during coronary artery development
Development, 128 (2001), pp. 2085-2093

68 A. Wessels, R.R. Markwald
Cardiac morphogenesis and dysmorphogenesis. I. Normal development
Methods Mol. Biol., 136 (2000), pp. 239-259

69 J.G. Wilson, C.B. Roth, J. Warkany
An analysis of the syndrome malformations induced by maternal vitamin A deficiency. Effects of restoration of vitamin A at various times during gestation

various times during gestation
Am. J. Anat., 92 (1953), pp. 189-217

70 H. Wu, S.H. Lee, X. Liu, M.L. Iruela-Arispe
Inactivation of erythropoietin leads to defects in cardiac morphogenesis
Development, 126 (1999), pp. 3597-3605

71 J.T. Yang, H. Rayburn, R.O. Hynes
Cell adhesion events mediated by alpha 4 integrins are essential in placental and cardiac development
Development, 121 (1995), pp. 549-560

72 J. Xavier-Neto, M.D. Shapiro, L. Houghton, N. Rosenthal
Sequential programs of retinoic acid synthesis in the myocardial and epicardial layers of the developing avian heart
Dev. Biol., 219 (2000), pp. 129-141
Article PDF (674KB)

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