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Zygotic Wnt Activity Is Required for *Brachyury* Expression in the Early *Xenopus laevis* Embryo

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Abstract

The canonical, β -catenin-dependent Wnt pathway is a crucial player in the early events of *Xenopus* development. Dorsal axis formation and mesoderm patterning are accepted effects of this pathway, but the regulation of expression of genes involved in mesoderm specification is not. This conclusion is based largely on the inability of the Wnt pathway to induce mesoderm in animal cap explants. Using injections of inhibitors of canonical Wnt signaling, we demonstrate that expression of the general mesodermal marker *Brachyury* (*Xbra*) requires a zygotic, ligand-dependent Wnt activity throughout the marginal zone. Analysis of the *Xbra* promoter reveals that putative TCF-binding sites mediate Wnt activation, the first sites in this well-studied promoter to which an activation role can be ascribed. However, established mesoderm inducers like eFGF and activin can bypass the Wnt requirement for *Xbra* expression. Another mesoderm promoting factor, *VegT*, activates *Xbra* in a *Wnt*-dependent manner. We also show that the activin/nodal signaling is necessary for ectopic *Xbra* induction by the Wnt pathway, but not by *VegT*. Our data significantly change the understanding of *Brachyury* regulation in *Xenopus*, implying the existence of an unknown zygotic Wnt ligand in Spemann's organizer. Since *Brachyury* is considered to have a major role in mesoderm formation, it is possible that Wnts might play a role in mesoderm specification, in addition to patterning.

Keywords

Wnt; *Xbra*; Tcf; mesoderm; induction; repression; eFGF; activin; zygotic; *VegT*

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References

REFERENCES

- 1 E. Agius, M. Oelgeschlager, O. Wessely, C. Kemp, E.M. De Robertis
Endodermal Nodal-related signals and mesoderm induction in Xenopus
Development, 127 (2000), pp. 1173-1183
- 2 E. Amaya, T.J. Musci, M.W. Kirschner
Expression of a dominant negative mutant of the FGF receptor disrupts mesoderm formation in Xenopus embryos
Cell, 66 (1991), pp. 257-270

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- 3 L.M. Angerer, R.C. Angerer
Animal–vegetal axis patterning mechanisms in the early sea urchin embryo
Dev. Biol., 218 (2000), pp. 1-12
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- 4 S.J. Arnold, J. Stappert, A. Bauer, A. Kispert, B.G. Hermann, R. Kemler
Brachyury is a target gene of the Wnt/beta-catenin signaling pathway
Mech. Dev., 91 (2000), pp. 249-258
Article  PDF (470KB)
- 5 J. Behrens, J.P. von Kries, M. Kuhl, L. Bruhn, D. Wedlich, R. Grosschedl, W. Birchmeier
Functional interaction of beta-catenin with the transcription factor LEF-1
Nature, 382 (1996), pp. 638-642
- 6 M. Brannon, M. Gomperts, L. Sumoy, R.T. Moon, D. Kimelman
A beta-catenin/XTcf-3 complex binds to the siamois promoter to regulate dorsal axis specification in Xenopus
Genes Dev., 11 (1997), pp. 2359-2370
- 7 M. Brannon, D. Kimelman
Activation of Siamois by the Wnt pathway
Dev. Biol., 180 (1996), pp. 344-347
Article  PDF (494KB)
- 8 W.M. Brieher, B.M. Gumbiner
Regulation of C-cadherin function during activin induced morphogenesis of Xenopus animal caps
J. Cell Biol., 126 (1994), pp. 519-527
- 9 G. Camac, L. Kodjabachian, J.B. Gurdon, P. Lemaire
The homeobox gene Siamois is a target of the Wnt dorsalisierung pathway and triggers organizer activity in the absence of mesoderm
Development, 122 (1996), pp. 3055-3065
- 10 E.S. Casey, M.A. O'Reilly, F.L. Conlon, J.C. Smith
The T-box transcription factor Brachyury regulates expression of eFGF through binding to a non-palindromic response element
Development, 125 (1998), pp. 3887-3894
- 11 A. Chakrabarti, G. Matthews, A. Colman, L. Dale
Secretary and inductive properties of Drosophila wingless protein in Xenopus oocytes and embryos
Development, 115 (1992), pp. 355-369
- 12 C. Chang, P.A. Wilson, L.S. Mathews, A. Hemmati-Brivanlou
A Xenopus type I activin receptor mediates mesodermal but not neural specification during embryogenesis
Development, 124 (1997), pp. 827-837
- 13 J.L. Christian, J.A. McMahon, A.P. McMahon, R.T. Moon
Xwnt-8, a Xenopus Wnt-1/int-1-related gene responsive to mesoderm- inducing growth factors, may play a role in ventral mesodermal patterning during embryogenesis
Development, 111 (1991), pp. 1045-1055
- 14 J.L. Christian, R.T. Moon
Interactions between Xwnt-8 and Spemann organizer signaling pathways generate dorsoventral pattern in the embryonic mesoderm of Xenopus
Genes Dev., 7 (1993), pp. 13-28
- 15 J.L. Christian, D.J. Olson, R.T. Moon
Xwnt-8 modifies the character of mesoderm induced by bFGF in isolated Xenopus ectoderm
EMBO J., 11 (1992), pp. 33-41
- 16 D. Clements, R.V. Friday, H.R. Woodland
Mode of action of VegT in mesoderm and endoderm formation
Development, 126 (1999), pp. 4903-4911
- 17 F.L. Conlon, S.G. Sedgwick, K.M. Weston, J.C. Smith

Inhibition of Xbra transcription activation causes defects in mesodermal patterning and reveals autoregulation of Xbra in dorsal mesoderm

Development, 122 (1996), pp. 2427-2435

- 18 F.L. Conlon, J.C. Smith
Interference with brachyury function inhibits convergent extension, causes apoptosis, and reveals separate requirements in the FGF and activin signalling pathways
Dev. Biol., 213 (1999), pp. 85-100
Article  PDF (1MB)
- 19 Y. Cui, J.D. Brown, R.T. Moon, J.L. Christian
Xwnt-8b: a maternally expressed Xenopus Wnt gene with a potential role in establishing the dorsoventral axis
Development, 121 (1995), pp. 2177-2186
- 20 V. Cunliffe, J.C. Smith
Ectopic mesoderm formation in Xenopus embryos caused by widespread expression of a Brachyury homologue
Nature, 358 (1992), pp. 427-430
- 21 R.S. Darken, P.A. Wilson
Axis induction by wnt signaling: Target promoter responsiveness regulates competence
Dev. Biol., 234 (2001), pp. 42-54
Article  PDF (362KB)
- 22 M.A. Deardorff, C. Tan, L.J. Conrad, P.S. Klein
Frizzled-8 is expressed in the Spemann organizer and plays a role in early morphogenesis
Development, 125 (1998), pp. 2687-2700
- 23 A. Djiane, J. Riou, M. Umbhauer, J. Boucaut, D. Shi
Role of frizzled 7 in the regulation of convergent extension movements during gastrulation in *Xenopus laevis*
Development, 127 (2000), pp. 3091-3100
- 24 P.M. Domingos, N. Itasaki, C.M. Jones, S. Mercurio, M.C. Sargent, R. Krumlauf
The Wnt/beta-catenin pathway posteriorizes neural tissue in *Xenopus* by an indirect mechanism requiring FGF signaling
Dev. Biol., 239 (2001), pp. 148-160
Article  PDF (3MB)
- 25 F. Fagotto, N. Funayama, U. Gluck, B.M. Gumbiner
Binding to cadherins antagonizes the signaling activity of beta-catenin during axis formation in *Xenopus*
J. Cell Biol., 132 (1996), pp. 1105-1114
- 26 F. Fagotto, K. Guger, B.M. Gumbiner
Induction of the primary dorsalizing center in *Xenopus* by the Wnt/GSK/beta-catenin signaling pathway, but not by Vg1, Activin or Noggin
Development, 124 (1997), pp. 453-460
- 27 M.J. Fan, W. Gruning, G. Walz, S.Y. Sokol
Wnt signaling and transcriptional control of Siamois in *Xenopus* embryos
Proc. Natl. Acad. Sci. USA, 95 (1998), pp. 5626-5631
- 28 N. Funayama, F. Fagotto, P. McCrea, B.M. Gumbiner
Embryonic axis induction by the armadillo repeat domain of beta-catenin: Evidence for intracellular signaling
J. Cell Biol., 128 (1995), pp. 959-968
- 29 J. Galceran, S.C. Hsu, R. Grosschedl
Rescue of a Wnt mutation by an activated form of LEF-1: Regulation of maintenance but not initiation of Brachyury expression
Proc. Natl. Acad. Sci. USA, 98 (2001), pp. 8668-8673
- 30 J. Gerhart
Pieter Nieuwkoop's contributions to the understanding of meso-endoderm induction and neural induction in chordate development
Int. J. Dev. Biol., 43 (1999), pp. 605-613
- 31 H. Haegel, L. Lanue, M. Ohsugi, L. Fedorov, K. Herrenknecht, R. Kemler
Loss of brachyury affects dorsal-ventral development of *Xenopus*

Lack of beta-catenin affects mouse development at gastrulation

Development, 121 (1995), pp. 3529-3537

- 32 F.S. Hamilton, G.N. Wheeler, S. Hoppler
Difference in XTcf-3 dependency accounts for change in response to beta-catenin-mediated Wnt signalling in Xenopus blastula
Development, 128 (2001), pp. 2063-2073
- 33 R. Harland, J. Gerhart
Formation and function of Spemann's organizer
Annu. Rev. Cell Dev. Biol., 13 (1997), pp. 611-667
- 34 J. Heasman
Patterning the Xenopus blastula
Development, 124 (1997), pp. 4179-4191
- 35 J. Heasman, A. Crawford, K. Goldstone, P. Garner-Hamrick, B. Gumbiner, P. McCrea, C. Kintner, C.Y. Noro, C. Wylie
Overexpression of cadherins and underexpression of beta-catenin inhibit dorsal mesoderm induction in early Xenopus embryos
Cell, 79 (1994), pp. 791-803
Article  PDF (18MB)
- 36 J. Heasman, M. Kofron, C. Wylie
Beta-catenin signaling activity dissected in the early Xenopus embryo: A novel antisense approach
Dev. Biol., 222 (2000), pp. 124-134
Article  PDF (4MB)
- 37 A. Hemmati-Brivanlou, D.A. Melton
A truncated activin receptor inhibits mesoderm induction and formation of axial structures in Xenopus embryos
Nature, 359 (1992), pp. 609-614
- 38 D. Henrique, J. Adam, A. Myat, A. Chitnis, J. Lewis, D. Ish-Horowicz
Expression of a Delta homologue in prospective neurons in the chick
Nature, 375 (1995), pp. 787-790
- 39 B. Hobmayer, F. Rentzsch, K. Kuhn, C.M. Happel, C.C. von Laue, P. Snyder, U. Rothbacher, T.W. Holstein
WNT signalling molecules act in axis formation in the diploblastic metazoan Hydra
Nature, 407 (2000), pp. 186-189
- 40 S. Hoppler, J.D. Brown, R.T. Moon
Expression of a dominant-negative Wnt blocks induction of MyoD in Xenopus embryos
Genes Dev., 10 (1996), pp. 2805-2817
- 41 C. Hudson, D. Clements, R.V. Friday, D. Stott, H.R. Woodland
Xsox17alpha and -beta mediate endoderm formation in Xenopus
Cell, 91 (1997), pp. 397-405
Article  PDF (330KB)
- 42 J. Huelsken, R. Vogel, V. Brinkmann, B. Erdmann, C. Birchmeier, W. Birchmeier
Requirement for beta-catenin in anterior-posterior axis formation in mice
J. Cell Biol., 148 (2000), pp. 567-578
- 43 C.E. Hyde, R.W. Old
Regulation of the early expression of the Xenopus nodal-related 1 gene, Xnr1
Development, 127 (2000), pp. 1221-1229
- 44 H.V. Isaacs, D. Tannahill, J.M. Slack
Expression of a novel FGF in the Xenopus embryo. A new candidate inducing factor for mesoderm formation and anteroposterior specification
Development, 114 (1992), pp. 711-720
- 45 K. Itoh, V.E. Krupnik, S.Y. Sokol
Axis determination in Xenopus involves biochemical interactions of axin, glycogen synthase kinase 3 and beta-catenin
Curr. Biol., 8 (1998), pp. 591-594
Article  PDF (112KB)

- 46 C. Kelly, A.J. Chin, J.L. Leatherman, D.J. Kozlowski, E.S. Weinberg
Maternally controlled (beta)-catenin-mediated signaling is required for organizer formation in the zebrafish
Development, 127 (2000), pp. 3899-3911
- 47 D.S. Kessler
Siamois is required for formation of Spemann's organizer
Proc. Natl. Acad. Sci. USA, 94 (1997), pp. 13017-13022
- 48 C.H. Kim, T. Oda, M. Itoh, D. Jiang, K.B. Artinger, S.C. Chandrasekharappa, W. Driever, A.B. Chitnis
Repressor activity of Headless/Tcf3 is essential for vertebrate head formation
Nature, 407 (2000), pp. 913-916
- 49 M. Kofron, T. Demel, J. Xanthos, J. Lohr, B. Sun, H. Sive, S. Osada, C. Wright, C. Wylie, J. Heasman
Mesoderm induction in Xenopus is a zygotic event regulated by maternal VegT via TGFbeta growth factors
Development, 126 (1999), pp. 5759-5770
- 50 M. Kofron, A. Spagnuolo, M. Klymkowsky, C. Wylie, J. Heasman
The roles of maternal alpha-catenin and plakoglobin in the early Xenopus embryo
Development, 124 (1997), pp. 1553-1560
- 51 M. Ku, D.A. Melton
Xwnt-11: A maternally expressed Xenopus wnt gene
Development, 119 (1993), pp. 1161-1173
- 52 M. Kuhl, K. Geis, L.C. Sheldahl, T. Pukrop, R.T. Moon, D. Wedlich
Antagonistic regulation of convergent extension movements in Xenopus by Wnt/beta-catenin and Wnt/Ca signaling
Mech. Dev., 106 (2001), pp. 61-76
Article  PDF (2MB)
- 53 C.A. Larabell, M. Torres, B.A. Rowning, C. Yost, J.R. Miller, M. Wu, D. Kimelman, R.T. Moon
Establishment of the dorso-ventral axis in Xenopus embryos is presaged by early asymmetries in beta-catenin that are modulated by the Wnt signaling pathway
J. Cell Biol., 136 (1997), pp. 1123-1136
- 54 B.V. Latinkic, M. Umbhauer, K.A. Neal, W. Lerchner, J.C. Smith, V. Cunliffe
The Xenopus Brachyury promoter is activated by FGF and low concentrations of activin and suppressed by high concentrations of activin and by paired-type homeodomain proteins
Genes Dev., 11 (1997), pp. 3265-3276
- 55 M.N. Laurent, I.L. Blitz, C. Hashimoto, U. Rothbacher, K.W. Cho
The Xenopus homeobox gene twin mediates Wnt induction of goosecoid in establishment of Spemann's organizer
Development, 124 (1997), pp. 4905-4916
- 56 M.A. Lee, J. Heasman, M. Whitman
Timing of endogenous activin-like signals and regional specification of the Xenopus embryo
Development, 128 (2001), pp. 2939-2952
- 57 W. Lerchner, B.V. Latinkic, J.E. Remacle, D. Huylebroeck, J.C. Smith
Region-specific activation of the Xenopus brachyury promoter involves active repression in ectoderm and endoderm: a study using transgenic frog embryos
Development, 127 (2000), pp. 2729-2739
- 58 L. Leyns, T. Bouwmeester, S.-H. Kim, S. Piccolo, E.M. De Robertis
Frzb-1 is a secreted antagonist of Wnt signaling expressed in the Spemann organizer
Cell, 88 (1997), pp. 747-756
Article  PDF (2MB)
- 59 P. Liu, M. Wakamiya, M.J. Shea, U. Albrecht, R.R. Behringer, A. Bradley
Requirement for Wnt3 in vertebrate axis formation
Nat. Genet., 22 (1999), pp. 361-365
- 60 K.D. Lustig, K. Kroll, E. Sun, R. Ramos, H. Elmendorf, M.W. Kirschner
A Xenopus nodal-related gene that acts in synergy with noggin to induce complete secondary axis and notochord formation

Development, 122 (1996), pp. 3275-3282

- 61 K.D. Lustig, K.L. Kroll, E.E. Sun, M.W. Kirschner
Expression cloning of a Xenopus T-related gene (Xombi) involved in mesodermal patterning and blastopore lip formation
Development, 122 (1996), pp. 4001-4012
- 62 R. McKendry, S.C. Hsu, R.M. Harland, R. Grosschedl
LEF-1/TCF proteins mediate wnt-inducible transcription from the Xenopus nodal-related 3 promoter
Dev. Biol., 192 (1997), pp. 420-431
Article  PDF (704KB)
- 63 P.E. Mead, Y. Zhou, K.D. Lustig, T.L. Huber, M.W. Kirschner, L.I. Zon
Cloning of Mix-related homeodomain proteins using fast retrieval of gel shift activities, (FROGS), a technique for the isolation of DNA-binding proteins
Proc. Natl. Acad. Sci. USA, 95 (1998), pp. 11251-11256
- 64 M. Molenaar, M. van de Wetering, M. Oosterwegel, J. Peterson-Maduro, S. Godsake, V. Korinek, J. Roose, O. Destree, H. Clevers
XTcf-3 transcription factor mediates beta-catenin-induced axis formation in Xenopus embryos
Cell, 86 (1996), pp. 391-399
Article  PDF (2MB)
- 65 O. Nakamura, K. Kishiyama
Prospective fates of blastomeres at the 32-cell stage of *Xenopus laevis* embryos
Proc. Japan Acad., 47 (1971), pp. 407-412
- 66 J. Newport, M. Kirschner
A major developmental transition in early Xenopus embryos. II. Control of the onset of transcription
Cell, 30 (1982), pp. 687-696
Article  PDF (2MB)
- 67 P.D. Nieuwkoop, J. Faber
Normal Table of *Xenopus laevis*, North Holland Publishing Co, Amsterdam (1967)
- 68 E. Reissmann, H. Jomvall, A. Blokzijl, O. Andersson, C. Chang, G. Minchiotti, M.G. Persico, C.F. Ibanez, A.H. Brivanlou
The orphan receptor ALK7 and the Activin receptor ALK4 mediate signaling by Nodal proteins during vertebrate development
Genes Dev., 15 (2001), pp. 2010-2022
- 69 I. Sadowski, J. Ma, S. Triezenberg, M. Ptashne
Gal4-VP16 is an unusually potent transcription activator
Nature, 335 (1988), pp. 563-569
- 70 Y. Sasai, B. Lu, H. Steinbeisser, D. Geissert, L.K. Gont, E.M. De Robertis
Xenopus chordin: A novel dorsalizing factor activated by organizer-specific homeobox genes
Cell, 79 (1994), pp. 779-790
Article  PDF (18MB)
- 71 H.L. Sive, R.M. Grainger, R.M. Harland
Early Development of *Xenopus laevis*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor (1994)
- 72 J. Smith
T-box genes: What they do and how they do it
Trends Genet., 15 (1999), pp. 154-158
Article  PDF (465KB)
- 73 J.C. Smith
Making mesoderm: Upstream and downstream of Xbra
Int. J. Dev. Biol., 45 (2001), pp. 219-224
- 74 J.C. Smith, B.M. Price, J.B. Green, D. Weigel, B.G. Hermann
Expression of a Xenopus homolog of Brachyury (T) is an immediate-early response to mesoderm induction
Cell, 67 (1991), pp. 79-87
Article  PDF (4MB)
- 75 W.C. Smith, R.M. Harland

Injected Xwnt-8 RNA acts early in Xenopus embryos to promote formation of a vegetal dorsalizing center

Cell, 67 (1991), pp. 753-765

Article  PDF (8MB)

76 S.Y. Sokol

Mesoderm formation in Xenopus ectodermal explants overexpressing Xwnt8: Evidence for a cooperating signal reaching the animal pole by gastrulation

Development, 118 (1993), pp. 1335-1342

77 S.Y. Sokol

Analysis of Dishevelled signalling pathways during Xenopus development

Curr. Biol., 6 (1996), pp. 1456-1467

Article  PDF (782KB)

78 S.Y. Sokol, D.A. Melton

Interaction of Wnt and activin in dorsal mesoderm induction in Xenopus

Dev. Biol., 154 (1992), pp. 348-355

Article  PDF (3MB)

79 F. Stennard, G. Camac, J.B. Gurdon

The Xenopus T-box gene, Antipodean, encodes a vegetally localised maternal mRNA and can trigger mesoderm formation

Development, 122 (1996), pp. 4179-4188

80 S. Sumanas, P. Strege, J. Heasman, S.C. Ekker

The putative wnt receptor Xenopus frizzled-7 functions upstream of beta-catenin in vertebrate dorsoventral mesoderm patterning

Development, 127 (2000), pp. 1981-1990

81 M. Tada, J.C. Smith

Xwnt11 is a target of Xenopus Brachyury: Regulation of gastrulation movements via Dishevelled, but not through the canonical Wnt pathway

Development, 127 (2000), pp. 2227-2238

82 M. Tada, M.-A.J. O'Reilly, J.C. Smith

Analysis of competence and of Brachyury autoinduction by use of a hormone-inducible Xbra

Development, 124 (1997), pp. 2225-2234

83 S. Takahashi, C. Yokota, K. Takano, K. Tanegashima, Y. Onuma, J. Goto, M. Asashima

Two novel nodal-related genes initiate early inductive events in Xenopus Nieuwkoop center

Development, 127 (2000), pp. 5319-5329

84 M. van de Wetering, R. Cavallo, D. Dooijes, M. van Beest, J. van Es, J. Loureiro, A. Ypma, D. Hursh, T. Jones, A. Bejsovec, M. Peifer, M. Martini, H. Clevers

Armadillo coactivates transcription driven by the product of the Drosophila segment polarity gene dTCF

Cell, 88 (1997), pp. 789-799

Article  PDF (548KB)

85 A. Vonica, W. Weng, B.M. Gumbiner, J.M. Venuti

TCF is the nuclear effector of the beta-catenin signal that patterns the sea urchin animal-vegetal axis

Dev. Biol., 217 (2000), pp. 230-243

Article  PDF (526KB)

86 S. Wang, M. Kranks, K. Lin, F.P. Luyten, M. Moos Jr.

Frzb, a secreted protein expressed in the Spemann organizer, binds and inhibits Wnt-8

Cell, 88 (1997), pp. 757-766

Article  PDF (381KB)

87 C. Wylie, M. Kofron, C. Payne, R. Anderson, M. Hosobuchi, E. Joseph, J. Heasman

Maternal beta-catenin establishes a “dorsal signal” in early Xenopus embryos

Development, 122 (1996), pp. 2987-2996

88 T.P. Yamaguchi, S. Takada, Y. Yoshikawa, N. Wu, A.P. McMahon

T (Brachyury) is a direct target of Wnt3a during paraxial mesoderm specification

Genes Dev., 13 (1999), pp. 3185-3190

- 89 J. Zhang, M.L. King
Xenopus VegT RNA is localized to the vegetal cortex during oogenesis and encodes a novel T-box transcription factor involved in mesodermal patterning
Development, 122 (1996), pp. 4119-4129
- 90 A.M. Zorn, G.D. Barish, B.O. Williams, P. Lavender, M.W. Klymkowsky, H.E. Varmus
Regulation of Wnt signaling by Sox proteins: XSox17 alpha/beta and XSox3 physically interact with beta-catenin
Mol. Cell, 4 (1999), pp. 487-498
Article  PDF (570KB)
- 91 A.M. Zorn, K. Butler, J.B. Gurdon
Anterior endomesoderm specification in Xenopus by Wnt/beta-catenin and TGF-beta signaling pathways
Dev. Biol., 209 (1999), pp. 282-297
Article  PDF (662KB)

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