The varied roles of nuclear receptors during vertebrate embryonic development

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Nuclear receptors comprise a superfamily of sequence-specific transcription factors whose members have diverse roles during development. This review will summarize the developmental roles of selected members of the nuclear receptor superfamily.

Introduction

During larval development in Drosophila, eight nuclear receptors are specifically expressed and perform specific functions [Thummel, 1995]. Seven of them are orphan receptors, for which ligands have not yet been identified. This phenomenon suggests nuclear receptors play an important role in insect embryonic development. At the end of the third instar larval and prepupal stages, pulses of ecdysone, the molting hormone of insects, directly induce a small set of early genes, such as the orphan nuclear receptor E75. These early genes later repress their own expression and also induce a large set of the late genes, including the orphan nuclear receptors E78B and DHR3. Then the mid-prepupal genes, such as βFTZ-F1, are induced. This cascade of expression of nuclear receptors during Drosophila metamorphosis not only suggests that nuclear receptors play crucial roles in regulating normal embryonic development, but also raises a possibility that nuclear receptors participate in regulating each others expression. Although this aspect of vertebrate orphan receptor regulation has not yet been examined in great depth, it may potentially provide another point of convergence in the regulation and function of nuclear receptor superfamily members [Thummel, 1995]. In vertebrate embryonic development, homologs of some Drosophila orphan nuclear receptors are found in embryos and loss of function of these receptors causes severe defects. Nuclear receptors clearly play an important role in regulating vertebrate embryonic development. The goal of this review is to summarize the major findings about the expression and function of nuclear receptors during vertebrate embryonic development (Table 1).

Hepatocyte Nuclear Factor 4α (HNF4α) (NR2A1)

In the adult, HNF4α is highly expressed at in liver, kidney, intestine, and pancreas and at low levels in the testis [Drewes et al., 1996; Miquerol et al., 1994; Sladek et al., 1990]. During embryonic development, HNF4α expression is found in the primary endoderm at embryonic day (E) 4.5 and in the visceral endoderm between E5.5 and 8.5 [Duncan et al., 1994]. Hepatic HNF4α expression is detected in the liver primordia by E8.5. At E10.5, HNF4α is expressed in the developing pancreas and the mesonephric tubules. HNF4α binds as homodimers to hormone responsive elements (HREs) configured as direct repeats with one base pair spacing (DR1) and regulates the expression of genes involved in the metabolism of carbohydrates, lipids, and cholesterol, as well as xenobiotics and amino acids. Targeted deletion of the HNF4α gene results in apoptosis of the embryonic ectoderm at E6.5, followed by abnormal mesoderm differentiation and embryonic death [Chen et al., 1994]. However, ablation of the HNF4α gene in either ES cells or E8.5 embryos is associated with significantly reduced expression of glycolytic enzymes, as well as glucose and fatty acid transport proteins [Stoffel and Duncan, 1997]. Embryoid bodies derived from HNF4α-/- ES cells differentiate into endoderm and express makers of the endoderm lineage, suggesting that it may control the differentiation of visceral endoderm [Duncan et al., 1997]. Its expression in visceral endoderm is regulated by the zinc finger transcription factor, GATA6 [Morrisey et al., 1998]. Recent studies show that HNF4α can directly regulate pregnane X receptor (PXR) expression during fetal liver development and thus regulate PXR responses to xenobiotics [Kamiya et al., 2003]. Liver-specific knockout of HNF4α in mice confirms its important role during differentiation of hepatocytes, hepatic storage of glycogen, and hepatic epithelium generation [Parviz et al., 2003]. These results suggest that HNF4α is crucial for early embryonic development. HNF4α is the earliest nuclear receptor to be expressed and functional in vertebrate embryos and HNF4α regulation of PXR is also a prime example of a cascade of nuclear receptor expression.

Estrogen related receptor β (ERRβ) (NR3B2)

Slightly later during embryogenesis, at E5.5, ERRβ transcripts are first detected in extraembryonic ectoderm [Luo et al., 1997; Pettersson et al., 1996]. At E8.5, ERRβ is specifically expressed in the chorion, suggesting that ERRβ may play a role in early placental development. The ERRβ knockout embryos have severely impaired
Table 1. A summary of nuclear receptors during early embryonic development

| Name         | Drosophila Homolog | Expression | Ligand | Lethality | Null mutant |
|--------------|--------------------|------------|--------|-----------|-------------|
| HNF4-alpha   | IFP-8             | E4.5 primary endoderm, E5.5 to HNF4B endoderm, E8.5 in liver and pancreas and posterior midgut | NA | Die at E5.5 | Asymmetric of embryonic endoderm at E5.5, abnormal mesoderm differentiation |
| ERR-beta     |                   | E5.5 to HNF4B endoderm, E8.5 in liver and pancreas and posterior midgut | NA | Die at E10.5 | Abnormal chorion development and over abundance of trophoblast giant cells. Anterior-posterior defects: Posterior truncation, open neural tube, prebafoid tail, hunch |
| GCNF         |                   | E5.5 to HNF4B endoderm, E8.5 in liver and pancreas and posterior midgut | NA | Die at E10.5 | Absence of mesoderm, overgrowth of mesoderm, abnormal mesodermal differentiation |
| PRN-gamma    |                   | E8.5 to HNF4B endoderm, E8.5 in liver and pancreas and posterior midgut | NA | Die at E10.5 | Severo myogenic defects, overgrowth of mesoderm, abnormal mesodermal differentiation |
| RAR-alpha    |                   | E8.5 in endoderm, posterior mesoderm | AF trans RA | - | Decreased viability, decreased growth, decreased growth |
| RAR-beta     |                   | E8.5 in endoderm, posterior mesoderm | AF trans RA | - | Decreased viability, decreased growth, decreased growth |
| RAR-gamma    |                   | E8.5 in endoderm, posterior mesoderm | AF trans RA | - | Decreased viability, decreased growth |
| ERR-alpha    | USP               | E8.5 in endoderm, posterior mesoderm | 0.5-0.4 RA | E12.5-16.5 | Vitamin A deficiency syndrome |
| ERR-beta     | USP               | Pectoral region | 0.5-0.4 RA | - | - |
| ERR-gamma    | USP               | Pectoral region | 0.5-0.4 RA | E12.5-16.5 | - |
| CORD-TIE     | USP               | Early mesoderm, E8.5 in endoderm, E8.5 in endoderm | 0.5-0.4 RA | - | Heart and vascular defects |
| CORD-TIE     | USP               | Early mesoderm, E8.5 in endoderm, E8.5 in endoderm | 0.5-0.4 RA | - | Heart and vascular defects |
| SF2          | F12               | E8.5 in endoderm, E10.5 in endoderm | 0.5-0.4 RA | E10 | Complete adrenogenital agenesis |
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Germ Cell Nuclear Factor (GCNF) (NR6A1)

In the adult, GCNF is highly expressed in germ cells. GCNF binds to DRO HREs as a homodimer and acts as a transcriptional repressor in the absence of ligand [Hummelke and Cooney, 2001]. GCNF expression is also found in both frog and mouse embryos [Chung et al., 2001; David et al., 1998; Joos et al., 1998]. In Xenopus, levels of GCNF expression increase from the gastrula stage to the mid-neural stage [David et al., 1998]. An anteroposterior gradient of GCNF expression then develops at the late neurula stage [David et al., 1998]. In the mouse, GCNF expression is turned on as early as the egg cylinder stage (Figure 1A). After gastrulation, GCNF expression is detected in the head-fold and throughout the primitive streak [Chung et al., 2001]. Unlike Xenopus, a posterior-anterior gradient of GCNF expression develops by the neural stage with the highest levels at presomitic mesoderm in the posterior (Figure 1B). Slightly later, it is expressed at its highest levels throughout the neuroectoderm (Figure 1C). By the late neurula stage (Figure 1D), GCNF expression is markedly reduced and GCNF expression turns off subsequently. Changes in GCNF expression in embryos affect normal embryonic development in both frog and mouse. Injection of the full-length or dominant negative (dn) GCNF transcripts into frog embryos disrupts normal embryonic development [David et al., 1998; Joos et al., 1998]. In the mouse, loss of GCNF function by gene targeting results in embryonic lethality, due to cardiovascular complications [Chung et al., 2001]. As GCNF has been shown to repress the in vitro expression of Oct4, which is essential for the maintenance of the mammalian germ line, ablation of GCNF in the mouse also shows a failure to repress Oct4 expression in somatic cells [Fuhrmann et al., 2001]. Thus, GCNF is critical for repressing Oct4 gene activity as pluripotent stem cells differentiate and thus play role in...
expressed in the lateral neural epithelium of both forebrain E8, RAR\(^{-7.5}\) [Ang and Duester, 1997; Ruberte et al., 1991]. At mouse embryos, RAR\(^{-}\) has been demonstrated in embryos of various animals. In embryonic development, RARs and RXRs have been reviewed in detail elsewhere [Begemann and Meyer, 2001; Kastner et al., 1995; Morriss-Kay and Ward, 1999; Mendelsohn et al., 1994]. Double knockouts, however, show more severe phenotypes [Kastner et al., 1997a; Lohnes et al., 1994; Mendelsohn et al., 1994]. The RAR\(^{\alpha/\gamma}\) double mutants display rhombencephalic defects [Lohnes et al., 1994]. The developmental defects generated include axial transformations. Some of the RAR knockout mice have phenotypes resembling those generated by inactivation of the Hox genes, which are targets of RA signaling [Durston et al., 1989]. Other defects belong to the fetal vitamin A deficiency syndrome [Lohnes et al., 1994].

Most of the single RAR gene knockouts are viable and have less significant phenotypes [Lohnes et al., 1994; Mendelsohn et al., 1994]. Double knockouts, however, show more severe phenotypes [Kastner et al., 1997a; Lohnes et al., 1994; Mendelsohn et al., 1994]. The RAR\(^{\alpha/\gamma}\) double mutants display rhombencephalic defects [Lohnes et al., 1994]. The developmental defects generated include axial transformations. Some of the RAR knockout mice have phenotypes resembling those generated by inactivation of the Hox genes, which are targets of RA signaling [Durston et al., 1989]. Other defects belong to the fetal vitamin A deficiency syndrome [Lohnes et al., 1994].

Single knockouts of RXR\(^{\beta}\) and RXR\(^{\gamma}\) are viable and do not show defects related to the vitamin A deficiency syndrome [Durston et al., 1989]. RXR\(^{\beta}\) was shown to be necessary for spermatogenesis [Kastner et al., 1994; Sucov et al., 1994]. In RXR\(^{\beta-}\) mice, the expression of choline acetyltransferase in the cholinergic interneurons has recently been shown to be down-regulated [Saga et al., 1999]. These results suggest that RXR\(^{\gamma}\) may play an important role in the proper functioning of neurons.

RXR\(^{\alpha}\) has been shown to be involved in cardiac and liver organogenesis and homozygous mutant fetuses die from embryonic days 12.5 to 16.5 [Kastner et al., 1994; Sucov et al., 1994]. The defects of these fetuses resemble those with the fetal vitamin A deficiency syndromes, including a myocardial hypoplasia, conotruncal and ocular defects. In addition, the lethality of RXR\(^{\alpha}\) fetuses may be due to cardiac, hepatic, and placental defects [Kastner et al., 1997b; Tran and Sucov, 1998]. In addition, a synergistic effect was observed in RXR\(^{\alpha/\beta}\)RARE mutants, however, no synergy was observed between the effects of mutations of either RXR\(^{\beta}\) or RXR\(^{\gamma}\) and those of the RAR mutations [Kastner et al., 1997a]. These results suggest that RXR\(^{\alpha/\beta}\) heterodimers are the most common functional unit in the RA signaling pathway during embryogenesis.

Peroxisome Proliferator-Activated Receptor \(\gamma\) (PPAR\(^{\gamma}\) ) (NR1C3)

PPARs mediate the effects of fatty acids and their derivatives at the transcriptional level by forming a heterodimer with RXR [Hihi et al., 2002]. PPAR\(^{\gamma}\) is expressed in syncytiotrophoblasts and cytотrophoblasts in human placental villi [Schaiff et al., 2000]. PPAR\(^{\gamma}\) deficiency causes embryonic lethality at E10 because of severe myocardial thinning [Barak et al., 1999]. In addition, PPAR\(^{\gamma}\) is required for epithelial differentiation of trophoblast tissue, which is important for proper placental vascularization. Unlike PPAR\(^{\beta/\delta}\) mutants [Barak et al., 2002], defects in PPAR\(^{\gamma/-}\) placentaffect differentiation of the labyrinthine trophoblast but do not disrupt the placental-decidual interface clearly distinguishing between the placental functions of either PPAR. PPAR\(^{\gamma/\alpha}\) heterodimers have been recently shown to play this crucial role in human trophoblast differentiation [Fournier et al., 2002; Tarrade et al., 2001a; Tarrade et al., 2001b]. Although the loss of PPAR\(^{\beta/\delta}\) function causes embryonic lethality at E10.5, this result is contributed by a maternal effect of PPAR\(^{\beta/\delta}\) in the uterus and placenta [Barak et al., 2002].

Retinoid receptors (RARs and RXRs) (NR1B1, 2 & 3 and NR2B1, 2 & 3)

The function and regulation of RA signaling during embryonic development is extremely complex and detailed discussion is beyond the scope of this review. It has been reviewed in detailed elsewhere [Begemann and Meyer, 2001; Kastner et al., 1995; Morriss-Kay and Ward, 1999; Ross et al., 2000; Zile, 2001]. In this minireview we will briefly highlight some important aspects of retinoid receptor function during embryonic development. Expression of different subtypes of RARs and RXRs has been demonstrated in embryos of various animals. In mouse embryos, RAR\(^{\alpha}\) is ubiquitously expressed at E6.5 -7.5 [Ang and Duester, 1997; Ruberte et al., 1991]. At E8, RAR\(^{\alpha}\) transcript appears in the neural epithelium of the brain and then at E8.5 it is widely and abundantly expressed in the lateral neural epithelium of both forebrain and hindbrain. At gastrulation stages, RAR\(^{\beta}\) is primarily expressed in the presumptive hindbrain ectoderm and the adjacent mesenchyme [Ang and Duester, 1997; Ruberte et al., 1991]. At E8.25, RAR\(^{\beta}\) expression is found in the caudal hindbrain region and hindgut [Ruberte et al., 1991; Ruberte et al., 1990]. RAR\(^{\gamma}\) is expressed after E8.5 in the open portion of the neural epithelium of the posterior neuropore [Ang and Duester, 1997; Ruberte et al., 1991]. After the neural tube closes, RAR\(^{\gamma}\) neural expression disappears. At E13.5, RAR\(^{\gamma}\) expression reappears and is strongly expressed in the developing limbs and skin [Dolè et al., 1990].

There is no close relationship between the expression of RARs and RXRs [Mangelsdorf et al., 1992; Mangelsdorf et al., 1990]. In rodent embryos, RXR\(^{\alpha}\) is expressed abundantly in liver, kidney, spleen, visceral tissues and skin [Mangelsdorf et al., 1992]. The expression of RXR\(^{\beta}\) is mainly in the central nervous system, while RXR\(^{\gamma}\) is found in the peripheral nervous system and in muscle.
With availability of various agonists, antagonists and double knockouts, more specific roles of retinoid receptors in embryonic development have been demonstrated, such as the development of branchial arch, hindbrain, inner ear, and pulmonary alveolus [Massaro et al., 2003; Matt et al., 2003; Romand et al., 2002; Wendling et al., 2001].

In early studies, ectopic addition of RA has been shown to have a teratogenic effect on normal embryonic development [Durston et al., 1989]. A RA gradient has been shown to exist along the anterior-posterior axis of the embryo [Maden et al., 1998]. The findings from knockouts of the key enzymes, retinaldehyde dehydrogenase 2 (Raldh2) and cyp26A1, involved in RA metabolism have demonstrated that these enzymes are essential for mouse embryonic development and early morphogenesis [Niederreither et al., 1999]. Raldh2 is responsible for embryonic RA synthesis while cyp26A1 metabolizes the active RA to hydroxylated retinoids [Marill et al., 2003]. Raldh2 and cyp26A1 are mutually exclusively expressed in vertebrate embryos to generate RA sensitive and RA free regions in the embryos [Abu-Abed et al., 2001; Swindell et al., 1999]. Raldh2 deficiency cause embryonic lethality at E10 and the null mutant embryos suffer severe defects, such as failure in axial rotation and dilated heart [Niederreither et al., 1999]. Ablation of cyp26A1 also causes embryonic lethality at E11.5 and the cyp26A1-/- embryos suffer severe posterior truncation [Abu-Abed et al., 2001]. Taken together, RARs and RXRs transduce the RA signaling, which is important for normal embryonic development.

**Chicken Ovalbumin Upstream Promoter Transcription Factors (COUP-TFs) (NR2F1 and NR2F2)**

COUP-TF binds to HREs as a homodimer and acts as transcriptional repressor [Pereira et al., 2000]. Similar to its Drosophila homologs, SVP, two members of mouse COUP-TFs are expressed in embryos. COUP-TF is first expressed in the neural ectoderm at E7.5 [Qiu et al., 1994; Qiu et al., 1997]. At E8.5 it is expressed in premigratory and migratory neural crest cells. In Xenopus laevis, misexpression of COUP-TFI leads to anterior truncations and malformations within the embryonic brain [Schuh and Kimelman, 1995]. Targeted disruption of mouse COUP-TFI results in perinatal death because of multiple defects in central and peripheral nervous system development [Qiu et al., 1997]. Most of COUP-TFI-/- embryos have fusions of the glossopharyngeal (IX) and vagus (X) cranial nerves. These defects impair both sensory and motor functions of the pharynx and the tongue, and lead to malnutrition, dehydration and usually death. Moreover, axonal projection and arborization are significantly reduced in the cervical plexus region and in the ophthalmic branch of the trigeminal nerve. Taken together, these results strongly suggest that COUP-TFI is a crucial component in the regulation of axon guidance, neurogenesis and cellular differentiation during embryonic development [Zhou et al., 2001]. A different pattern of expression for COUP-TFII offers clues about its distinct functions during mouse embryogenesis. At early stages of development, COUP-TFII is expressed in the sinus venosus, the elongating umbilical veins and the neuroepithelium [Pereira et al., 1999]. Later it is expressed in the common atrium. In addition, COUP-TFII is expressed most highly in the mesenchymal compartments of developing organs such as the salivary gland, prostate, lung, kidney, pancreas primordium and stomach. COUP-TFII knockout mice die at around E10, showing a variety of heart and vascular defects [Pereira et al., 1999]. Atrial development is halted at E9.0 in COUP-TFII-/- embryos. These results suggest that COUP-TFII may play a role in the regulation of mesenchymal-epithelial interactions during organogenesis, and in development of the cardiovascular system.

**Steroidogenic factor (SF1) (NR5A1)**

During mouse embryonic development, SF1 expression is first detected at E9.0 in the urogenital ridge, and subsequently in adrenal steroidogenic primordium (E11) and gonadal steroid-producing cells (E13) [Ikeda et al., 1994]. SF1 expression is also detected in the ventromedial hypothalamic nucleus (VMH) after E11.5 and in the pituitary gland after E13.5. Pituitary SF1 expression precedes the onset of FSH expression in gonadotropes, suggesting that SF1 might either directly regulate FSH gene transcription or regulate gonadotrope differentiation [Ingraham et al., 1994]. Using both in vitro and in vivo assays, SF1 can directly regulate expression another orphan receptor, DAX1, which is also important in mammalian gonad development and sex determination. [Hoyle et al., 2002]. The Wilms tumor suppressor (WT1) and the Lim homeobox protein, Lhx9m, have been recently shown to directly activate SF1 expression and thus mediate early gonadogenesis, [Wilhelm and Englert, 2002]. SF1-/- embryos have complete adrenal and gonadal agenesis, male-to-female sex-reversal, and persistence of Mullerian structures in males [Luo et al., 1994; Luo et al., 1995; Sadovsky et al., 1995]. SF1 null mutants are viable at birth, but die during the first 8 days of life due to adrenocortical insufficiency. These gene knockout experiments have provided strong evidence for a direct role for SF1 in regulating mammalian sexual development as well as the differentiation of steroidogenic tissues.

**Conclusion**

In summary, knockout mouse models currently offer great opportunities to understand the functions of individual nuclear receptors during embryonic development. Recent results from in vitro and in vivo studies show possible functional relationships between nuclear receptors. For instance, RA is capable of inducing expression of COUP-TFs and GCNF [Fuhrmann et al., 2001]. HNF4α regulates PXR expression [Kamiya et al., 2003], SF1 controls DAX1 expression [Hoyle et al., 2002]. Oct4 expression is sequentially regulated by SF1, GCNF and COUP-TF [Fuhrmann et al., 2001]. Xenopus GCNF is able to regulate RA signaling by controlling the expression of its catabolic enzyme, cyp26A1 [Barreto et al., 2003b]. These results come closer to the Thummel's speculation...
about the convergent regulation of nuclear receptors in invertebrates and vertebrates [Thummel, 1995]. Do nuclear receptors expressed in the early embryonic stages induce the expression of nuclear receptors in later stages? Although there is, as yet, no clear answer to this question, new technologies, such as, transgenic mouse techniques, RNAi, and gene array technology, as well as genomic information and bioinformatic resources should be capable of enhancing our opportunity to explore this area. An area that is ripe to be explored is the degree of cross-talk between different NR pathways in vertebrate development.

References

Abu-Abed, S., Dolle, P., Metzger, D., Beckett, B., Chambon, P. and Petkovich, M. (2001) The retinoid acid-metabolizing enzyme, Cyp26a1, is essential for normal hindbrain patterning, vertebral identity, and development of posterior structures Genes Dev 15, 226-40.

Ang, H. L. and Duester, G. (1997) Initiation of retinoid signaling in primitive streak mouse embryos: spatiotemporal expression patterns of receptors and metabolic enzymes for ligand synthesis Dev Dyn 208, 536-43.

Barak, Y., Liao, D., He, W., Ong, E. S., Nelson, M. C., Olefsky, J. M., Boland, R. and Evans, R. M. (2002) Effects of peroxisome proliferator-activated receptor γ on placentaion, adiposity, and colorectal cancer Proc Natl Acad Sci U S A 99, 303-8.

Barak, Y., Nelson, M. C., Ong, E. S., Jones, Y. Z., Ruiz-Lozano, P., Chien, K. R., Koder, A. and Evans, R. M. (1999) PPARγ is required for placental, cardiac, and adipose tissue development Mol Cell 4, 585-95.

Barreto, G., Reintsch, W., Kaufmann, C. and Dreyer, C. (2003a) The function of Xenopus germ cell nuclear factor (XgCNF) in morphogenetic movements during neurulation Dev Biol 257, 329-42.

Barreto, G., Borgmeyer, U. and Dreyer, C. (2003b) The germ cell nuclear factor is required for retinoic acid signaling during Xenopus development Mech Dev 120, 415-28.

Begemann, G. and Meyer, A. (2001) Hindbrain patterning revisited: timing and effects of retinoic acid signalling Bioessays 23, 981-6.

Chen, W. S., Manova, K., Weinstein, D. C., Duncan, S. A., Plump, A. S., Prezioso, V. R., Bachvarova, R. F. and Darnell, J. E., Jr. (1994) Disruption of the HNF-4 gene, expressed in visceral endoderm, leads to cell death in embryonic endoderm and impaired gastrulation of mouse embryos Genes Dev 8, 2466-77.

Chung, A. C., Katz, D., Pereira, F. A., Jackson, K. J., DeMayo, F. J., Cooney, A. J. and O'Malley, B. W. (2001) Loss of orphan receptor germ cell nuclear factor function results in ectopic development of the tail bud and a novel posterior truncation Mol Cell Biol 21, 663-77.

David, R., Joos, T. O. and Dreyer, C. (1998) Anteroposterior patterning and organogenesis of Xenopus laevis require a correct dose of germ cell nuclear factor (XgCNF) Mech Dev 79, 137-52.

Dolle, P., Ruberte, E., Leroi, P., Morrisey-Kay, G. and Chambon, P. (1990) Retinoid acid receptors and cellular retinoid binding proteins. I. A systematic study of their differential pattern of transcription during mouse organogenesis Development 110, 1133-51.

Drewes, T., Senkel, S., Holewa, B. and Ryffel, G. U. (1996) Human hepatocyte nuclear factor 4 isoforms are encoded by distinct and differentially expressed genes Mol Cell Biol 16, 925-31.

Duncan, S. A., Manova, K., Chen, W. S., Hoodless, P., Weinstein, D. C., Bachvarova, R. F. and Darnell, J. E., Jr. (1994) Expression of transcription factor HNF-4 in the extraembryonic endoderm, gut, and nephrogenic tissue of the developing mouse embryo: HNF-4 is a marker for primary endoderm in the implanting blastocyst Proc Natl Acad Sci U S A 91, 7598-602.

Duncan, S. A., Nagy, A. and Chan, W. (1997) Murine gastrulation requires HNF-4 regulated gene expression in the visceral endoderm: tetraploid rescue of Hnf4(-/-) embryos Development 124, 279-87.

Durston, A. J., Timmermans, J. P., Hage, W. J., Hendriks, H. F., de Vries, N. J., Heideveld, M. and Nieuwkoop, P. D. (1989) Retinoic acid causes an anteroposterior transformation in the developing central nervous system Nature 340, 140-4.

Fournier, T., Pavan, L., Tarrade, A., Schoonjans, K., Auwerx, J., Rochette-Egly, C. and Evain-Brion, D. (2002) The role of PPARγ/RXRα heterodimers in the regulation of human trophoblast invasion Ann NY Acad Sci 973, 26-30.

Fuhrmann, G., Chuang, A. C., Jackson, K. J., Hummelke, G., Bariahmad, A., Sutter, J., Sylvester, I., Scholer, H. R. and Cooney, A. J. (2001) Mouse germ line restriction of Otx4 expression by germ cell nuclear factor Dev Cell 1, 377-87.

Hilf, A. K., Michalik, L. and Wahli, W. (2002) PPARα: transcriptional effectors of fatty acids and their derivatives Cell Mol Life Sci 59, 790-8.

Hoyle, C., Narvaez, V., Alldus, G., Lovell-Badge, R. and Swain, A. (2001) Dax1 expression is dependent on steroidogenic factor 1 in the developing gonad Mol Endocrinol 16, 747-56.

Hummelke, G. C. and Cooney, A. J. (2001) Germ cell nuclear factor is a transcriptional repressor essential for embryonic development Front Biosci 6, D1186-91.

Ikeda, Y., Shen, W. H., Ingraham, H. A. and Parker, K. L. (1994) Developmental expression of mouse steroidogenic factor-1, an essential regulator of the steroid hydroxylases Mol Endocrinol 8, 654-62.

Ingraham, H. A., Lala, D. S., Ikeda, Y., Luo, X., Shen, W. H., Nachtigal, M. W., Abbud, R., Nilson, J. H. and Parker, K. L. (1994) The nuclear receptor steroidogenic factor 1 acts at multiple levels of the reproductive axis Genes Dev 8, 2302-12.

Joos, T. O., David, R. and Dreyer, C. (1996) XgCNF, a nuclear orphan receptor is expressed during neurulation in Xenopus laevis Mech Dev 60, 45-57.

Kamiya, A., Inoue, Y. and Gonzalez, F. J. (2003) Role of the hepatocyte nuclear factor 4alpha in control of the pregnane X receptor during fetal liver development Hepatology 37, 1375-84.

Kastner, P., Grondona, J. M., Mark, M., Gansmuller, A., LeMeur, M., Decimo, D., Vonesch, J. L., Dolle, P. and Chambon, P. (1994) Genetic analysis of RXRα developmental function: convergence of RXR and RAR signaling pathways in heart and eye morphogenesis Cell 78, 987-1003.

Kastner, P., Mark, M. and Chambon, P. (1995) Nonsteroid nuclear receptors: what are genetic studies telling us about their role in real life? Cell 83, 859-69.

Kastner, P., Mark, M., Ghyselfinck, N., Krezel, W., Dupe, V., Grondona, J. M. and Chambon, P. (1997a) Genetic evidence that the retinoid signal is transduced by heterodimeric RXR/RAR functional units during mouse development Development 124, 313-26.

Kastner, P., Messaddeq, N., Mark, M., Wendling, O., Grondona, J. M., Ward, S., Ghyselfinck, N. and Chambon, P. (1997b) Vitamin A deficiency and mutations of RXRalpha, RXRbeta and RARalpha lead to early differentiation of embryonic ventricular cardiomyocytes Development 124, 4749-58.

Lohnes, D., Mark, M., Mendelsohn, C., Dolle, P., Dierich, A., Gorry, P., Gansmuller, A. and Chambon, P. (1994) Function of the retinoid acid receptors (RARs) during development (I). Craniofacial and skeletal abnormalities in RAR double mutants Development 120, 2723-48.

Luo, J., Sladek, R., Bader, J. A., Matthysen, A., Rossant, J. and Giguere, V. (1997) Placental abnormalities in mouse embryos lacking the orphan nuclear receptor ERR-β Nature 388, 778-82.
Review

Luo, X., Iida, Y. and Parker, K. L. (1994) A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation Cell 77, 481-90.

Luo, X., Iida, Y. and Parker, K. L. (1995) The cell-specific nuclear receptor steroidogenic factor 1 plays multiple roles in reproductive function Philos Trans R Soc Lond B Biol Sci 350, 279-83.

Maden, M., Sonneveld, E., van der Saag, P. T. and Gale, E. (1998) The distribution of endogenous retinoid in the chick embryo: implications for developmental mechanisms Development 125, 4133-44.

Mangelsdorf, D. J., Borgmeyer, U., Heyman, R. A., Zhou, J. Y., Ong, E. S., Omo, A. E., Kakizuka, A. and Evans, R. M. (1992) Characterization of three RXR genes that mediate the action of 9-cis retinoic acid Genes Dev 6, 329-44.

Mangelsdorf, D. J., Ong, E. S., Dyck, J. A. and Evans, R. M. (1990) Nuclear receptor that identifies a novel retinoid acid response pathway Nature 345, 224-9.

Marill, J., Idres, N., Capron, C. C., Nguyen, E. and Chabot, G. G. (2003) Retinoic acid metabolism and mechanism of action: a review Curr Drug Metab 4, 1-10.

Massaro, G. D., Massardo, D. and Chambon, P. (2003) Retinoid acid receptor-α regulates pulmonary alveolus formation in mouse infants, but not during perinatal period Am J Physiol Lung Cell Mol Physiol 284, L631-3.

Matt, N., Ghyselinck, N. B., Wendling, O., Chambon, P. and Mark, M. (2003) Retinoic acid-induced developmental defects are mediated by RARbeta/RXR heterodimers in the pharyngeal endoderm Development 129, 2085-93.

Mendelsohn, C., Lohnes, D., Decimo, D., Luwkin, T., LeMeur, M., Chambon, P. and Mark, M. (1994) Function of the retinoic acid receptors (RARs) during development (II). Multiple abnormalities at various stages of organogenesis in RAR double mutants Development 120, 7249-71.

Miquerol, L., Lopez, S., Cartier, N., Tulliez, M., Raymondjean, M. and Kahn, A. (1994) Expression of the L-type pyruvate kinase gene and the hepatocyte nuclear factor 4 transcription factor in exocrine and endocrine pancreas J Biol Chem 269, 8944-51.

Morrissey, E. E., Tang, Z., Sigrist, K., Lu, M. M., Jiang, F., Ip, H. S. and Parmacek, M. S. (1998) GATA6 regulates HNF4 and is required for differentiation of visceral endoderm in the mouse embryo Genes Dev 12, 3579-90.

Morris-Kay, G. M. and Ward, S. J. (1999) Retinoids and mammalian development Int Rev Cytol 188, 73-131.

Niederreither, K., Subbarayan, V., Dolle, P. and Chambon, P. (1999) Embryonic retinoid acid synthesis is essential for early mouse post-implantation development Nat Genet 21, 444-8.

Parviz, F., Matullo, C., Garrison, W. D., Savatski, L., Adamson, J. W., Ning, G., Kaestner, K. H., Rossi, J. M., Zaret, K. S. and Duncan, S. A. (2003) Hepatocyte nuclear factor 4alpha controls the development of a hepatic epithelium and liver morphogenesis Nat Genet 34, 292-6.

Pereira, F. A., Qiu, Y., Zhou, G., Tsai, M. J. and Tsai, S. Y. (1999) The orphan nuclear receptor COUP-TFI is required for angiogenesis and heart development Genes Dev 13, 1037-49.

Pereira, F. A., Tsai, M. J. and Tsai, S. Y. (2000) COUP-TF orphan nuclear receptors in development and differentiation Cell Mol Life Sci 57, 1388-98.

Pettersson, K., Svensson, K., Mattson, R., Carlsson, B., Ohlsson, R. and M. A. (1996) Expression of a novel member of estrogen response element-binding nuclear receptors is restricted to the early stages of chorioanion formation during mouse embryogenesis Mech Dev 54, 211-23.

Qiu, Y., Cooney, A. J., Kuratani, S., DeMayo, F. J., Tsai, S. Y. and Tsai, M. J. (1994) Spatiotemporal expression patterns of chicken ovalbumin upstream promoter-transcription factors in the developing mouse central nervous system: evidence for a role in segmental patterning of the diencephalon Proc Natl Acad Sci U S A 91, 4451-5.

Qi, Y., Pereira, F. A., DeMayo, F. J., Lydon, J. P., Tsai, S. Y. and Tsai, M. J. (1997) Null mutation of mCOUP-TFI results in defects in morphogenesis of the glossohypopharyngeal ganglion, axonal projection, and arborization Genes Dev 11, 1925-37.

Romand, R., Hashino, E., Dolle, P., Vonesch, J. L., Chambon, P. and Ghyselinck, N. B. (2002) The retinoic acid receptors RARalpha and RARgamma are required for inner ear development Mech Dev 119, 213-23.

Ross, S. A., McCaffery, P. J., Drager, U. C. and De Luca, L. M. (2000) Retinoids in embryonal development Physiol Rev 80, 1021-54.

Ruberte, E., Dolle, P., Chambon, P. and Morrisey-Kay, G. (1991) Retinoic acid receptors and cellular retinoid binding proteins. II. Their differential pattern of transcription during early morphogenesis in mouse embryos Development 111, 45-60.

Ruberte, E., Dolle, P., Krust, A., Zelant, A., Morrisey-Kay, G. and Chambon, P. (1990) Specific spatial and temporal distribution of retinoic acid receptor γ transcripts during mouse embryogenesis Development 108, 213-22.

Sadovsky, Y., Crawford, P. A., Woodson, K. G., Polish, J. A., Clements, M. A., Tournelotte, L. M., Simburger, K. and Milbrandt, J. (1995) Mice deficient in the orphan receptor steroidogenic factor 1 lack adrenal glands and gonads but express P450 side-chain-cleavage enzyme in the placenta and have normal embryonic serum levels of corticosteroids Proc Natl Acad Sci U S A 92, 10939-43.

Sage, Y., Kobayashi, M., Ohta, H., Murai, N., Nakai, N., Oshima, M. and Taketo, M. M. (1999) Impaired extrapyramidal function caused by the targeted disruption of retinoid X receptor RXRgamma1 isoform Genes Cells 4, 219-28.

Schaff, W. T., Carlson, M. G., Smith, S. D., Levy, R., Nelson, D. M. and Sadovsky, Y. (2000) Peroxisome proliferator-activated receptor-γ modulates differentiation of human trophoblast in a ligand-specific manner J Clin Endocrinol Metab 85, 3874-81.

Schuh, T. J. and Kimelman, D. (1995) COUP-TFI is a potent regulator of retinoic acid-modulated development in Xenopus embryos Dev Biol 151, 39-49.

Sladek, F. M., Zhong, W. M., Lai, E. and Darnell, J. E., Jr. (1990) Liver-enriched transcription factor HNF-4 is a novel member of the steroid hormone receptor superfamily Genes Dev 4, 2353-65.

Stoffel, M. and Duncan, S. A. (1997) The maturity-onset diabetes of the young (MODY1) transcription factor HNF4alpha regulates expression of genes required for glucose transport and metabolism Proc Natl Acad Sci U S A 94, 13209-14.

Sucov, H. M., Dyson, E., Gumringer, C. L., Price, J., Chien, K. R. and Evans, R. M. (1994) RXR α mutant mice establish a genetic basis for vitamin A signaling in heart morphogenesis Genes Dev 8, 1007-18.

Swindell, E. C., Thaller, C., Sockanathan, S., Petkovich, M., Jessell, T. M. and Eichele, G. (1999) Complementary domains of retinoid acid production and degradation in the early chick embryo Dev Biol 216, 282-96.

Tarrade, A., Schoonjans, K., Guibourdenche, J., Bidart, J. M., Vidaud, M., Auwerx, J., Rottier-Egly, C. and Enav-Brion, D. (2001a) PPAR γ/RXR α heterodimers are involved in human β cell synthesis and human trophoblast differentiation Endocrinology 142, 4504-14.

Tarrade, A., Schoonjans, K., Pavan, L., Auwerx, J., Rottier-Egly, C., Enav-Brion, D. and Fournier, T. (2001b) PPARgamma/RXRalpha heterodimers control human trophoblast invasion J Clin Endocrinol Metab 86, 5017-24.

Thummel, C. S. (1995) From embryogenesis to metamorphosis: the regulation and function of Drosophila nuclear receptor superfamily members Cell 83, 871-7.
Tran, C. M. and Sucov, H. M. (1998) The RXRalpha gene functions in a non-cell-autonomous manner during mouse cardiac morphogenesis Development 125, 1951-6.

Tremblay, G. B., Kunath, T., Bergeron, D., Lapointe, L., Champigny, C., Bader, J. A., Rossant, J. and Giguere, V. (2001) Diethylstilbestrol regulates trophoblast stem cell differentiation as a ligand of orphan nuclear receptor ERR β Genes Dev 15, 833-8.

Wendling, O., Ghyselinck, N. B., Chambon, P. and Mark, M. (2001) Roles of retinoic acid receptors in early embryonic morphogenesis and hindbrain patterning Development 128, 2031-8.

Wilhelm, D. and Englert, C. (2002) The Wilms tumor suppressor WT1 regulates early gonad development by activation of Sf1 Genes Dev 16, 1839-51.

Zhou, C., Tsai, S. Y. and Tsai, M. J. (2001) COUP-TFI: an intrinsic factor for early regionalization of the neocortex Genes Dev 15, 2054-9.

Zile, M. H. (2001) Function of vitamin A in vertebrate embryonic development J Nutr 131, 705-8.