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Retinoid signaling in control of progenitor cell differentiation during mouse development

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Abstract

The vitamin A metabolite retinoic acid (RA) serves as a ligand for nuclear RA receptors that control differentiation of progenitor cells important for vertebrate development. Genetic studies in mouse embryos deficient for RA-generating enzymes have been invaluable for deciphering RA function. RA first begins to act during early organogenesis when RA generated in trunk mesoderm begins to function as a diffusible signal controlling progenitor cell differentiation. In neuroectoderm, RA functions as an instructive signal to stimulate neuronal differentiation of progenitor cells in the hindbrain and spinal cord. RA is not required for early neuronal differentiation of the forebrain, but at later stages RA stimulates neuronal differentiation in forebrain basal ganglia. RA also acts as a permissive signal for differentiation by repressing fibroblast growth factor (FGF) signaling in differentiated cells as they emerge from progenitor populations in the caudal progenitor zone and second heart field. In addition, RA signaling stimulates differentiation of spermatogonial germ cells and induces meiosis in male but not female gonads. A more complete understanding of the normal functions of RA signaling during development will guide efforts to use RA as a differentiation agent for therapeutic purposes.

Keywords

Retinoic acid signaling; FGF signaling; Embryogenesis; Progenitor cells

1. Retinoic Acid Signaling Pathway

Among the various diffusible cell-cell signaling factors that naturally direct developmental processes, retinoic acid (RA) is unique in that it is a small lipophilic molecule (M.W. 300) derived from vitamin A (retinol) (Fig. 1). Genetic studies have demonstrated that RA synthesis in mouse embryos is controlled mostly by retinol dehydrogenase-10 (RDH10) that produces retinaldehyde [1] plus three retinaldehyde dehydrogenases that generate RA (RALDH1, RALDH2, and RALDH3; also known as ALDH1A1, ALDH1A2, and ALDH1A3) [2, 3]. As *Rdh10* mutants still maintain a low amount of RA synthesis [1], there must exist at least one additional retinol dehydrogenase required for RA synthesis in embryos, but this has not yet been identified. Alcohol dehydrogenases have been found to participate in adult but not embryonic RA synthesis [4], but one candidate for an additional embryonic retinol dehydrogenase is RDHE2 (SDR16C5) expressed in the neural tube [5].

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Raldh1, *Raldh2*, and *Raldh3* single or compound null mutants suggest that no other enzyme is necessary for the second step of RA synthesis prior to stage E10.5 of mouse development, but after this stage it is less clear if these three RALDHs are the only enzymes required [2, 3].

RA directly regulates gene transcription by entering the nucleus of target cells where it functions as a ligand for nuclear RA receptors (RARα, RARβ, RARγ) that bind target genes at a DNA sequence known as a RA response element (RARE) [6-8]. This is in contrast to other common diffusible cell-cell signaling factors such as fibroblast growth factor (FGF) [9, 10], WNT [11, 12], transforming growth factor-beta (TGF β) superfamily [13, 14], and sonic hedgehog (SHH) [15, 16] which bind cell-surface receptors and initiate intracellular signaling pathways that ultimately impact transcription in the nucleus. Also, whereas these other pathways all existed before the evolution of chordate organisms, RA signaling is unique in that it appears to be a chordate invention [17]. All chordates (including amphioxus and tunicates - primitive invertebrate chordates) possess at least one RAR that can bind and respond to the major form of RA (all-*trans*-RA), as well as at least one retinaldehyde dehydrogenase (RALDH) that can synthesize RA from vitamin A (Table 1). Homology searches have identified genes in non-chordate animals that encode proteins distantly related to chordate RALDHs (aldehyde dehydrogenase family) and RARs (nuclear receptor family), but there has been no demonstration of non-chordate genes that function in the synthesis of all-*trans*-RA or transduction of an RA signal [18]. Thus, it appears that the ability to synthesize and use RA was invented late in evolution after other cell-cell signaling pathways had evolved. In addition to RAR, PPARdelta has been identified as a non-canonical RA receptor [19] that is required for RA-induced neuronal differentiation in vitro [20].

Over the years many lessons have been learned about the developmental roles of RA signaling from studies on vitamin A deficiency and RAR null mice [21-23]. Recent studies using model organisms lacking the ability to convert vitamin A to RA (either in the whole embryo or in specific tissues) have provided tremendous insight into the mechanism of RA signaling during development [24, 25]. The functions of RA during development and in the adult are still being deciphered, but it is clear that RA synthesized and secreted by certain differentiated cells plays a role in differentiation of nearby progenitor cells as further examined here (Table 2).

2. Retinoic acid control of neural progenitor cell differentiation

A role for RA in neural development has been firmly established, reviewed in [26], but there has been some disagreement as to where along the central nervous system RA is required. Treatment of embryonic stem cells with supraphysiological levels of RA (1-10 μM) can induce neuronal differentiation [27, 28], suggesting to some that all neural cells require RA for differentiation. However, this is not the case as shown by several studies. First of all, the concentration of endogenous RA ranges from 1-100 nM in mouse embryonic neural tissues [29, 30], suggesting that treatment of cells or embryos with much higher levels of RA may force neuronal differentiation unnaturally. In addition, RA is not synthesized in mouse embryos until E7.5 after formation of the headfold neuroectoderm comprising the forebrain and midbrain, and although RA activity is initially detected posteriorly, RA is not detected in the head until E8.5; thus, the role of RA in early embryonic neural differentiation may be limited to the hindbrain and spinal cord that develop in posterior neuroectoderm where RA is abundant [31-33]. Loss of RA activity in the forebrain/eye region of *Raldh2*-/-;*Raldh3*-/- double mutants resulted in no defect in forebrain development up to E8.75 when these mutants were still healthy enough to compare to wild-type [34]. Also, examination of *Rdh10*-/- embryos that lack physiological forebrain/eye RA activity (verified using a validated RA-reporter assay), demonstrated no defects in early forebrain development [35].

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In contrast, RA activity in the forebrain/eye (which is generated by enzymes in the eye) is required for normal optic cup formation [36, 37]. Thus, RA activity in the early forebrain may simply represent unnecessary spill-over from RA activity needed in the adjacent optic cups that develop as outgrowths from the forebrain neuroepithelium. However, a later role for RA in differentiation of forebrain basal ganglia has been discovered as discussed below.

Hindbrain

Raldh2 expression in mouse embryos initiates at E7.5 in presomitic mesoderm which secretes RA that can diffuse anteriorly into the developing hindbrain as far as rhombomere 3 (r3) [32]. One of the earliest targets of RA signaling during neural development are the 3'-*Hox* genes essential for rhombomere formation and identity that are expressed differentially along the anteroposterior axis of the posterior hindbrain beginning at E7.75 in mouse [38, 39]. *Hoxb1* is required for facial motor neuron differentiation in r4 [40, 41]. Studies in chick, mouse, and zebrafish have shown that RA generated by *Raldh2* is required for induction of *Hoxb1* and other *Hox* genes in the posterior hindbrain [21, 31, 32, 42-44]. During early hindbrain development, *Hoxb1* is transiently expressed throughout the entire posterior hindbrain up to the presumptive r3/r4 border, but later *Hoxb1* expression is limited to r4 [45]. Transgenic mouse embryos studies have elegantly shown that *Hoxb1* is directly regulated by RA through the actions of two RAREs, one located 3' to the promoter that stimulates early widespread expression in the posterior hindbrain up to the presumptive r3/r4 boundary [46], plus another RARE positioned 5' to the promoter that is required for repression of *Hoxb1* in r3 and r5, thus helping to limit expression to r4 [47]. Although induction of *Hoxb1* by RA is consistent with RA stimulating transcription by acting as a RAR ligand to recruit coactivators [48], the mechanism through which RA directly represses *Hoxb1* transcription has not been established. Genetic studies in mouse and zebrafish have shown that repression of *Hoxb1* posterior to r4 also requires *Hnf1b* (*vHnf1*) induced by RA signaling in neuroectoderm posterior to the r4/r5 boundary [32, 49, 50]. *Hnf1b* has been demonstrated to possess a functional RARE [51].

Spinal Cord

Neuroectoderm fated to become spinal cord emerges from the epiblast during body axis extension and is exposed to RA generated by *Raldh2* expressed in the adjacent presomitic mesoderm or somites [33]. In the spinal cord, several studies have concluded that RA produced in mesoderm and SHH produced in notochord and floor plate both act on ventral spinal cord progenitors to stimulate a motor neuron fate [33, 52-56]. Several transcription factors are required for dorsoventral patterning of the spinal cord leading to motor neuron differentiation including *Pax6* and *Nkx6.1* expressed dorsally and ventrally, respectively, as well as *Olig2* expressed in a region overlapping *Pax6* and *Nkx6.1* that marks the location where motor neurons form [57-59]. Loss of RA synthesis in mouse *Raldh2*-/- embryos results in loss of *Pax6* and *Olig2* expression in the spinal cord [33]. During motor neuron specification, RA is needed to induce *Pax6* which functions with *Nkx6.1* to induce *Olig2* that stimulates undifferentiated ventral spinal cord neuroectoderm to acquire a motor neuron fate [55]. As neurogenin-2 (NGN2) is known to induce *Pax6* in the spinal cord [60] RA may function by directly upregulating *Ngn2* (which has a RARE) that then induces *Pax6* [61].

Our present understanding of the spinal cord RA signaling mechanism in vertebrate embryos has been translated into successes in learning how to differentiate embryonic stem (ES) cells in vitro. Both mouse and human ES cells can be stimulated to form motor neurons at high efficiency when RA and SHH are used together as differentiation agents [62-64]. These findings provide hope that knowledge of normal RA function during early organogenesis can be used to generate replacement cells for spinal cord injuries or motor neuron diseases.

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Forebrain

RA has not been shown to be required for midbrain development, but a role in the forebrain has been established during late embryonic stages. At E12.5 in the mouse forebrain, *Raldh3* expression initiates in the subventricular zone of the lateral ganglionic eminence (LGE) located in ventral forebrain tissue that is fated to become basal ganglia [34, 65]. *Raldh3*–/– embryos fail to generate RA activity in the ventral forebrain and exhibit a defect in differentiation within the striatum that includes loss of *Drd2* expression (encoding dopamine receptor D2) in the nucleus accumbens [34]. A RARE located close to the *Drd2* promoter suggests that RA directly induces *Drd2* transcription [66]. Consistent with these observations, *RARb*-/- mice exhibit defects in striatal dopaminergic neurogenesis resulting in motor behavior impairment [67, 68].

RA generated by *Raldh3* in the LGE has also been shown to be required for expression of the enzyme that produces the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), i.e. glutamic acid decarboxylase-67 (GAD67). Thus, RA is required for GABAergic differentiation in the striatum which is adjacent to the LGE. *Raldh3*-/- embryos fail to generate both GABAergic striatal projection neurons and GABAergic interneurons migrating from the striatum to the olfactory bulb and cortex [69]. In addition, LGE-derived neurospheres from wild-type but not *Raldh3*-/- embryos produce RA needed for GABAergic differentiation in vitro. As no evidence exists for a RARE near the *Gad67* gene, it is unclear whether *Gad67* is a direct or indirect target of RA signaling in the striatum during GABAergic differentiation. RA treatment protocols have been described for mouse and human ES cells that result in differentiation to GABAergic neurons [69-72], thus providing a potential source of cells for therapeutic purposes.

Raldh genes are not expressed in the embryonic forebrain cortex and RA activity is not observed in this tissue using techniques that easily detect RA activity in the LGE where *Raldh3* is expressed [69, 73]. However, *Raldh2* is expressed in the meninges by E12.5 [74], a neural crest-derived tissue which provides an outer cover for the brain separating it from the cranial bones. Meningeal RA is likely the source of RA required to control RARs needed for proper cranial bone formation [75]. *Rdh10*, controlling the metabolism of retinol to retinaldehyde, is also expressed in the meninges by E12.5 [76]. Studies on E14.5 ethylnitrosourea-induced *Rdh10* mutants that exhibit a reduction in radial expansion of the forebrain cortex suggested that RA produced in the meninges may be a neurogenic factor inducing the switch from symmetric to asymmetric divisions in the ventricular zone needed for cortical expansion [76]. However, studies on E14.5 *Raldh2*-/- embryos do not support this conclusion [69]. As *Rdh10* mutants exhibit severe neural crest-derived craniofacial defects that distort the cranium [1], whereas *Raldh2*-/- embryos do not [69], thinning of the cortex in *Rdh10* mutants is unlikely to be a specific effect of RA on corticogenesis, but rather a defect in cranial neural crest migration and differentiation which leads to the altered cortical morphology. This conclusion is also supported by studies on E14.5 *Rdh10*-/- embryos treated early with retinaldehyde (E7.5-E9.5) to rescue the craniofacial defect, but that still lack RA activity later in the meninges at E14.5 and maintain normal cortical morphology [35]. The conclusion that RA is unnecessary for cortical differentiation is also supported by studies showing that mouse ES cells can be differentiated into forebrain cortical neurons without addition of RA [77].

3. Retinoic acid control of axial progenitor cells in the caudal progenitor zone

Tissue-specific induction of 3’-*Hox* genes, *Hnf1b*, *Ngn2*, *Drd2*, *Gad67* and other genes by RA signaling constitutes an instructive mechanism of RA action that is certainly an

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important function for RA during development. However, RA can also control development in a permissive fashion through its ability to repress gene expression as discussed below.

The development of vertebrate embryos occurs in a head-to-tail fashion through the process of body axis extension in which progenitor cells in the caudal progenitor zone generate new tissue [78]. Bipotential axial (neuromesodermal) progenitor cells present in the caudal progenitor zone differentiate into either neuroectoderm to generate the neural tube or presomitic mesoderm to form somites that are precursors of vertebrae and skeletal muscle [79]. *Fgf8* expressed in the caudal progenitor zone is essential for maintaining axial progenitor cell function needed to extend the body axis and for the process of somitogenesis [80]. RA generated in the presomitic mesoderm functions as a diffusible signal that represses *Fgf8* expression at the anterior end of the caudal progenitor zone, thus allowing cells exiting the progenitor zone to undergo neural differentiation or somitogenesis during body axis extension [54, 81-85]. As RA secreted by presomitic mesoderm was found to act at the neuroectoderm/epiblast junction in order to control somitogenesis [82], the target of RA signaling during body axis extension may be the axial progenitor cells where *Fgf8* is most highly expressed. *Fgf8* expression initiates in the caudal progenitor zone during early gastrulation with *Raldh2* expression following later in the presomitic mesoderm [32], Thus, RA signaling is introduced into the picture during late gastrulation and begins to restrict caudal FGF8 signaling at that time. RA-FGF8 antagonism allows cells at the border of these two signaling pathways to transition away from FGF8 signaling and begin responding to other signals that stimulate differentiation. RA repression of *Fgf8* is thus a fundamental permissive function of RA that occurs simultaneous to its instructive function during differentiation of neuroectoderm in the hindbrain and spinal cord.

4. Retinoic acid control of second heart field progenitor cells

The ability of RA signaling to repress gene expression is also important for heart development. The vertebrate heart initially develops as a ventral tube along the anteroposterior axis of the upper trunk from a population of ventral cardiac progenitor cells in the splanchnic lateral plate mesoderm called the first heart field [86]. As the heart tube lengthens, additional cardiac splanchnic mesodermal progenitor cells located dorsally in the second heart field are added to the anterior and posterior poles of the growing heart [86-90]. The LIM homeodomain transcription factor encoded by *Isl1* is expressed in cardiac progenitors of the second heart field, and as these cells are recruited to the heart tube *Isl1* is down-regulated, although *Isl1* expression remains dorsal to the heart and continues to contribute progenitors to the outflow tract at later stages [91]. Genetic studies in mouse embryos indicate that *Isl1*-/- embryos are missing the outflow tract, right ventricle, and much of the atria which all require a major contribution from second heart field progenitors [91]. In contrast, loss of the T-box transcription factor *Tbx5* results in sinoatrial defects and hypoplastic left ventricle, regions associated with a major contribution from the first heart field [92]. Thus, *Isl1* is important for maintaining cardiac progenitors along most of the heart anteroposterior axis with the exception of the left ventricle. Recent studies demonstrating the existence of a second heart field expressing an ancestral *Isl1* gene in *Ciona* have revealed an early chordate origin for the second heart field [93].

Raldh2 is first expressed in presomitic mesoderm and lateral plate mesoderm posterior to the heart just after the heart has begun to develop, and secreted RA travels into posterior cardiac mesoderm [94]. Studies in mouse have demonstrated that loss of RA synthesis in *Raldh2* mutants results in an enlarged heart tube lacking looping and chamber formation [95]. Zebrafish *raldh2* mutants exhibit an expansion in the number of cardiac progenitor cells [96] and vitamin A deficiency studies in avian embryos have shown that RA limits the size of the cardiac field [94, 97]. There are no clear examples of genes induced by RA that control the

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number of cardiac progenitors, but it appears that RA may function by limiting cardiac FGF signaling. A potential role for FGF signaling in zebrafish heart development was found in studies showing that expression of a constitutive-active FGF receptor resulted in an expanded heart [98]. Genetic studies in mice indicate that *Fgf8* expressed in dorsal splanchnic mesoderm is required to drive cardiac progenitors toward an Isl1$^+$ second heart field fate, thus demonstrating that *Fgf8* is an important cardiac signaling factor [99, 100]. In E8.5 *Raldh2*-/- mouse embryos, cardiac expression of *Fgf8* and *Isl1* was found to expand posteriorly, possibly accounting for the increase in heart size [101, 102]; similar results were observed in E8.5 *Rdh10* mutant hearts that lack physiological RA activity [103]. Also, *Raldh2*-/- and *Rdh10* mutant embryos exhibit ectopic FGF signaling posterior to the heart marked by *Sprouty2* expression [101, 103]. Thus, RA may limit the expansion of second heart field progenitors by repression of cardiac *Fgf8* expression, similar to how RA repression of *Fgf8* in the caudal progenitor zone is proposed to restrict expansion of caudal progenitors.

5. Retinoic acid regulation of male germ cell differentiation

Germ cells are specified in mouse embryos at about E6.5, then at E8.5 they begin to migrate through the posterior region of the embryo and the mesonephros until arriving in the developing gonad at E10.5. When they enter the gonad in the genital ridge, germ cells are bipotential but over the next 2-3 days they commit to either the male or female fate [104]. Bipotential germ cells divide mitotically until about E12.5-E13.5 when germ cells in the ovary terminate mitosis and enter prophase of the first meiotic division, a female-specific trait. In contrast, during this time germ cells of the testis fail to enter meiotic prophase, a male-specific trait, and arrest in the Go/G1 phase of the mitotic cycle until about postnatal day 5 when they enter meiosis [105].

RA has long been known to be required postnatally for spermatogenesis [106, 107], but a role for RA in oogenesis was not originally observed. More recent studies suggested that RA controls sex-specific onset of meiosis in germ cells. In those studies, which employed treatment of gonads with high levels of RA or RA receptor antagonists, RA generated by *Raldh2* in the embryonic mesonephros was proposed to function as a secreted factor that induces *Stra8* (required for meiotic initiation) in the adjacent embryonic ovary but not the embryonic testis due to testis-specific expression of *Cyp26b1* encoding a P450 enzyme that stimulates RA degradation [108, 109]. Premature onset of meiosis in the male germ cells was observed in testis organ cultures treated with a P450 inhibitor [108] or in *Cyp26b1*$^{-/-}$ mice [109]. However, investigation of *Raldh2*-/- mouse embryos revealed that *Stra8* is still expressed at a normal level in ovary despite a complete absence of RA activity in mesonephros and ovary [110]. In addition, treatment of *Raldh2*-/- testis organ cultures with a P450 inhibitor still allowed *Stra8* induction in the absence of RA activity [110]. These findings demonstrate that the critical role *Cyp26b1* plays in preventing meiosis in fetal testis does not involve degradation of RA, suggesting an RA-independent function for *Cyp26b1* during prevention of premature meiotic initiation in testis. Meanwhile other mechanisms for female-specific initiation of meiosis are suggested by genetic studies on *Dmrt1* [111] and *Msx1/2* [112].

In contrast, recent genetic studies on the role of RA in spermatogenesis have provided conclusive evidence for specific RA-regulated functions. Studies on compound *Raldh* conditional knockout mice have shown that RA generated at postnatal day 5 in Sertoli cells by *Raldh1* and *Raldh2* functions as a paracrine signal for initiation of spermatogonial germ cell differentiation to generate pre-meiotic spermatocytes [113]. Importantly, those studies also demonstrated that *Raldh2* subsequently expressed in pre-meiotic spermatocytes synthesizes RA needed to locally drive expression of *Stra8* (which has a nearby RARE) and

initiate meiosis [113]. Thus, genetic studies provide strong evidence that RA is required for male but not female germ cell differentiation.

6. Conclusions and Future Directions

Studies focused on how RA controls nuclear receptor function during development have provided deep insight into how RA controls differentiation of progenitor cells. Instrumental in this investigation has been the discovery of key enzymes encoded by *Rdh10*, *Raldh1*, *Raldh2*, and *Raldh3* that generate RA in specific differentiated cell types designed to control differentiation of nearby progenitor cells in a paracrine fashion, or perhaps in some cases change the differentiation status of the RA-generating cell in an autocrine fashion. The defects observed in mouse embryos carrying *Raldh* mutations have identified differentiation events controlled by RA signaling during embryogenesis, a process which is very similar in mice and humans. From such studies, we know that RA is required to induce specific genes for differentiation of neural progenitor cells in the posterior hindbrain, spinal cord, and forebrain basal ganglia. These studies have also demonstrated that RA antagonizes FGF signaling emanating from axial progenitor cells in the embryonic caudal progenitor zone, thus controlling differentiation as the body axis extends in a head-to-tail fashion. RA signaling also antagonizes FGF signaling in progenitor cells of the second heart field, suggesting that RA antagonism of FGF signaling may be a common mode of RA action. Regulation of male germ cell differentiation in the testis provides a glimpse into how RA continues to control progenitor cell differentiation postnatally.

Several open questions remain that can direct future studies. In addition to RDH10, what other enzyme(s) are required for metabolism of retinol to retinaldehyde in the first step of RA synthesis? Are RALDH1, RALDH2, and RALDH3 sufficient for the second step of RA synthesis or do additional enzymes play a role in the embryo or postnatally? During motor neuron differentiation, is the *Ngn2* RARE required for RA regulation, and are other genes direct targets of RA action? What is the mechanism of *Gad67* induction in the forebrain basal ganglia by RA? During body axis extension and second heart field development, does RA repress *Fgf8* expression directly or does repression occur indirectly through RA induction of a repressor? If RA does not function as a diffusible signal controlling female meiosis, what is the nature of this signal?

Discovery of how RA normally controls progenitor cells during organogenesis will provide information essential for the field of regenerative medicine. This knowledge will help establish regenerative treatments for damaged or aged human tissues based upon therapies designed to stimulate endogenous progenitor cells to produce differentiated cells in vivo or therapies that rely on introduction of differentiated cells produced in vitro from embryonic stem cells or induced pluripotent stem cells.

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Highlights

- Retinoic acid stimulates neuronal differentiation of progenitor cells in the posterior CNS and forebrain basal ganglia.
- Differentiation of progenitor cells in the caudal progenitor zone is controlled by retinoic acid antagonism of FGF signaling.
- FGF signaling in progenitor cells of the second heart field is limited by retinoic acid signaling.
- Retinoic acid is required for spermatogonial differentiation plus meiotic initiation in male but not female germ cells.

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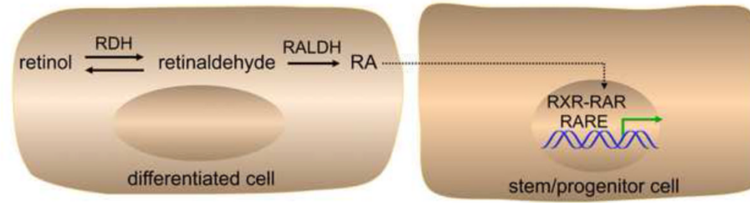

Fig. 1.
Retinoic acid signaling pathway. Some differentiated cells have the ability to metabolize retinol (vitamin A) to retinoic acid (RA). This is a two-step reaction in which retinol is first metabolized to retinaldehyde by retinol dehydrogenase (RDH) followed by metabolism of retinaldehyde to RA by retinaldehyde dehydrogenase (RALDH). RA can be secreted and taken up by other cells (including progenitor cells) to activate a paracrine signaling response. Inside the nucleus of target cells, RA functions as a ligand for the RA receptor (RAR) that binds as a heterodimer with retinoid-X receptor (RXR) to an RA response element (RARE) near a target gene. In response to binding of RA, RAR undergoes a conformational shift that alters the binding of coregulators that control transcription of RA target genes.

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Table 1

Retinaldehyde dehydrogenase genes.

common name	nomenclature	organisms with orthologs
Raldh1	*Aldh1a1*	mouse, rat, human, chick, frog
Raldh2	*Aldh1a2*	mouse, rat, human, chick, frog, zebrafish, tunicate, amphioxus
Raldh3	*Aldh1a3*	mouse, rat, human, chick, frog, zebrafish

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Table 2

RA-mediated differentiation of progenitor cells in mouse embryos.

RA-generating cell	***Raldh* gene**	**RA-responding progenitor cell**
presomitic mesoderm	*Raldh2*	posterior hindbrain neural progenitors
presomitic mesoderm or somite	*Raldh2*	ventral spinal cord neural progenitors
lateral ganglionic eminence	*Raldh3*	forebrain basal ganglia progenitors
presomitic mesoderm	*Raldh2*	axial (neuromesodermal) progenitors
presomitic & lateral plate mesoderm	*Raldh2*	second heart field progenitors
Sertoli cells	*Raldh1* & *Raldh2*	spermatogonia germ cells
premeiotic spermatocytes	*Raldh2*	premeiotic spermatocytes (autocrine)