BMP and RA signaling cooperate to regulate Apolipoprotein C1 expression during embryonic development

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Apolipoproteins, the major components of lipoproteins, play physiological roles in lipoprotein metabolism. Contrary to the well-documented effects on plasma lipid, little is known about the function and regulation of Apolipoprotein C1 (apoc1) during embryonic development. Here we have shown that apoc1 gene is highly expressed in the yolk syncytial layer, a structure implicated in embryonic and larval nutrition. The apoc1 transcripts are also observed in the deep cell layer at the ventral and lateral region during gastrulation, and in the tail paraxial mesoderm during somitogenesis. By whole-mount in situ hybridization and quantified RT-qPCR, we further demonstrate that apoc1 expression is induced by bone morphogenetic proteins (BMPs) signaling, while retinoic acid (RA) signaling suppresses the expression of BMP ligands and inhibits the BMP effect in this process.

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1. Introduction

Lipids play many fundamental roles during animal lifetime. These include providing substrate fuel for metabolism, use as architectural components in membrane, protection for organ insulation, and acting as chemical messengers for signaling transduction (Ryan and van, 2000; Eaton, 2008; Fahy et al., 2009; Nohturfft and Zhang, 2009; Subramaniam et al., 2011). In lower vertebrates, such as fish and frog, lipids are also prominent components of egg yolk, which consists of mass lipoproteins, phosphoproteins and lipid inclusions (Mommsen and Walsh, 1988; Gui and Zhu, 2012). The embryonic development completely depends on endogenous nutrition and energy supplied by the yolk repository. Very-low-density lipoprotein (VLDL), the major lipoprotein in teleost yolk, is rich in neutral lipids (Endo et al., 2011). As one of the protein components in VLDL, Apoc1 is transferred between VLDL and high density lipoprotein (HDL), and serves as an important mediator of VLDL metabolism (Grundy, 1990; Jong et al., 1999; Westerterp et al., 2007). Recently, we observed that teleost embryos express considerable Apoc1 (Wang et al., 2008, 2012). However, little is known about its regulative mechanism and function in yolk development and embryo nutrition.

Retinoic acid (RA), a vitamin A derivative, plays critical roles in a number of physiological processes (Duester, 2008; Niederreither and Dolle, 2008; Vilhais-Neto and Pourquié, 2008). Evidence in mammalian has established that RA acts as a ligand of nuclear receptors (Giguere et al., 1987; Petkovich et al., 1987; Mangelsdorf and Evans, 1995; Shaw et al., 2003), which regulate transcription of a wide range of target lipoprotein genes. For example, RA status regulates expression of hepatic Apolipoprotein A-I and Apolipoprotein A-II genes, both of which are associated with HDL (Grenier et al., 2007). HDL and oxidized-LDL uptake is increased by RA through upregulation of expression of CD36, a type of scavenger receptor (Wuttge et al., 2001). RA induces expression of Apolipoprotein CIII that delays the catabolism of triglyceride-rich lipoprotein (VLDL and chylomicrons) (Vu-Dac et al., 1998). Furthermore, RA inhibits lipoprotein lipase activity, which hydrolyzes triglyceride from VLDL (Davies et al., 2001). Therefore, RA administration results in hypertriglycerideremia by increasing VLDL production and decreasing VLDL utilization (Vajreswari and Jeyakumar, 2008).

Bone morphogenetic proteins (BMPs) are important class of morphogens that regulate development and maintain normal tissue functions (Plouin et al., 2011; Guo and Wu, 2012). Recently, their roles in lipoprotein metabolism have begun to be revealed (Schulz and Tseng, 2009). Bmp2 up-regulates Apolipoprotein E, which associates with several lipoproteins and mediates their uptake, to inhibit smooth muscle cell growth (Bachner et al., 1999; Yao et al., 2008). Apolipoprotein B100 secretion increases in HepG2 cells treated with Bmp2, and Bmp signaling regulates LDL cholesterol metabolism (Derwall et al., 2012). Additionally, Bmp1 promotes HDL formation and following
reverse cholesterol transport through stimulating the maturation of newly secreted proapo A1 (Chau et al., 2007; Zhu et al., 2009). However, the function and underlined mechanism of BMPs involved in lipid metabolism is still largely unknown, and its value in the field of developmental biology is underappreciated. In this study, zebrafish was used to study the regulation of Apoc1, since this fish provides an opportunity to combine embryological, genetic and molecular analyses in vivo (Hong et al., 2014). We revealed a crosstalk between BMP and RA signaling to regulate the expression of apoc1 during zebrafish embryogenesis.

2. Materials and methods

2.1. Fish maintenance

Zebrafish (’AB strain) stocks and embryos were raised at 28.5 °C and stage-matched based on morphological criteria (Mei et al., 2009; Wang et al., 2011). The animal treatments were approved by the Institute of Hydrobiology Institutional Animal Care and Use Committee (Approval ID: keshuizhuan 0829).

2.2. Whole-mount in situ hybridization and immunofluorescence staining

In situ hybridization and immunofluorescence staining were carried out as previously described (Li et al., 2013; Xu et al., 2014). Riboprobes for bmp2b (GenBank: BC114256) (Nikaido et al., 1997), bmp4 (GenBank: BC078423) (Chin et al., 1997) and apoc1 (GenBank: CN326047) (Wang et al., 2013) were made by using DIG RNA labeling kit (Roche). Anti-phosphorylated Smad1/5/8 antibody (CST) was used at 1:200.

2.3. Morpholino oligonucleotides, constructs and mRNA injections

Morpholino oligonucleotides of bmp2b (Lele et al., 2001), bmp4 (Leung et al., 2005), bmp7 (GenBank: AF201379) (Lele et al., 2001), alk8 (GenBank: AF038425) (Bauer et al., 2001) were obtained from Gene Tools. smad1 and smad5 morpholinos were kindly provided by Yong-hua Sun (IHB). The mRNA was synthesized by using Message Machine-Kit (Ambion). The microinjections were performed as described previously (Liu et al., 2009; Zhong et al., 2014).

2.4. RA treatments

Embryos at 4 hpf (hours post fertilization) or 12 hpf were incubated in 0.5 μM ATRA (Sigma), 16 μM DEAB (sigma) or DMSO (control) in E3 embryo media. Early embryos were collected and fixed for in situ hybridization at 85% epiboly, while late embryos at 26 hpf.

3. Results

3.1. Expression pattern of apoc1 during embryogenesis in zebrafish

Zebrafish apoc1 is a maternal gene and the zygotic message is initially transcribed at the blastula stage as the previous report (Wang et al., 2013), in which we examined its expression in early embryogenesis. In this study, we first analyzed the expression pattern later than late gastrulation by using whole mount in situ hybridization (WISH). During gastrulation, apoc1 is expressed gradually in the blastoderm at the epiboly stage, showing the highest levels on the ventral side and progressively lowering levels toward the dorsal axis (Fig. 1A and B). The ventral apoc1 is mainly resided in the margin (Fig. 1B), where is presumptive ventral mesoderm. As embryo develops, it becomes more posterior and is restricted to the paraxial mesoderm at the somite stages (Fig. 1C–E). The caudal expression of apoc1 decreases gradually and disappears at the high-pec stage (Fig. 1F and G). At the pec-fin stage, apoc1 is expressed in the liver primordium (Fig. 1H), which will develop to be liver, an adult organ with the highest expression level of apoc1 (Lauer et al., 1988).

At the 85% epiboly stage, apoc1 message begins to be detectable in the entire yolk syncytial layer (YSL) (Fig. 1B, arrow), similar to other apolipoproteins that have been reported in fish (Babin et al., 1997; Poupard et al., 2000; Xia et al., 2008). YSL is a layer consisting of a membrane-enclosed group of nuclei on top of the yolk cells and beneath the blastoderm cells. The expression in YSL becomes stronger at the following developmental stages (Fig. 1C–H). In addition, apoc1 message is also detected in prechordal plate at the gastrulation (Fig. 1A and B, blank arrowheads). Therefore, apoc1 is expressed in several territories during zebrafish development. In this paper, we selected the late epiboly stage and the 26-somite stage to investigate the regulation of apoc1 gene expression, since the patterns at these stages are representative.

3.2. apoc1 is regulated by BMP signaling

The expression pattern of apoc1 at the gastrula stage is similar as that of BMP ligands, which appear higher expression levels on the ventral side and lower levels on the dorsal side (Kishimoto et al., 1997; Nikaido et al., 1997; Dick et al., 2000). This suggests that apoc1 expression would be involved with BMP signaling. In this study, two independent approaches, WISH and real-time quantitative PCR (qPCR), were used to evaluate gene expression level in response to the treatments. Activin receptor-like kinase 8 (Alk8) was identified in zebrafish as a

Fig. 1. Spatiotemporal expression pattern of apoc1 in zebrafish embryos. Dorsal to the right at early stages (A–C) and head to the left at late stages (D–H). Lateral view unless indicated; H: dorsal view; E: ventral view. prechordal plate is indicated by blank arrowheads. YSL is indicated by arrows. Liver region is indicated by black arrowhead.
type I receptor for BMP signaling (Mintzer et al., 2001), while Smad1 and Smad5 are the transcription factors that transduce extracellular signals from BMP ligands to nucleus (Graff et al., 1996; Suzuki et al., 1997). Therefore, knockdown of Alk8 or Smad1/5 would inhibit the activity of BMP signaling. At the 85% epiboly stage, apoc1 expression is largely reduced in Alk8 and Smad1/5 morphants (Fig. 2B and C), compared to wild type controls (Fig. 2A). Conversely, apoc1 is ectopically and enormously expressed on the whole blastoderm of the embryos with excess BMP signaling via injecting BMP ligands mRNA (Bmp2/4/7) at 1-cell stage (Fig. 2D–F). However, knockdown of Bmp4 almost does not affect apoc1 expression (Fig. 2H), while that of Bmp2b and Bmp7 does as that of Alk8 and Smads (Fig. 2F and I). It suggests that Bmp4 ligand would play a redundant role in this process. In addition, qPCR analysis presented the similar results as that of WISH (Fig. 2J).

We next examined apoc1 expression responding to BMP signaling at the 26 somite stage about 22 hpf. Knockdown of Bmp2b causes severe dorsalization and ventral tissues are almost missing (Fig. 3A and B). Compared to WT siblings, apoc1 expression in the paraxial mesoderm disappears while that in the YSL only moderately weaken in Bmp2b morphants (Fig. 3A and B, arrowheads, E), as well as in Smad1/5 double morphants (Fig. 3C). This suggests that there are some BMP-independent factors induce apoc1 expression in the YSL. Opposite to BMP-deficient embryos, excess BMP signaling by overexpressing Bmp2b results in severe ventralization (Fig. 3D). It increases the expression level of apoc1 both in the tail region and in the YSL (Fig. 3A, D and E). Taken together, BMP signaling is required for apoc1 transcription during embryogenesis in zebrafish.

3.3. apoc1 is regulated by RA signaling

To study the RA effects on apoc1 expression, we treated embryos with 4-diethylaminobenzaldehyde (DEAB), an inhibitor for de novo RA synthesis, and all-trans retinoic acid (ATRA), a ligand of RA signaling. Both reagents are effective because the expression of cyp26a1, a RA-metabolizing enzyme activated by RA signaling, is up-regulated by ATRA and is inhibited by DEAB (Fig. 4A), similar to the previous reports (Abu-Abed et al., 2001; Dobbs-McAuliffe et al., 2004). Compared with DMSO controls (Fig. 4B), apoc1 expression increases in DEAB group at the 75% epiboly stage, although the pattern is unchanged (Fig. 4C and E). When ATRA was applied, apoc1 expression is largely inhibited (Fig. 4D and E). This phenotype responding to exogenous RA appears identical to that observed in BMP-deficient embryos (Fig. 2). Interestingly, the apoc1 expression in prechordal plate is almost unaffected (Fig. 4, arrows), suggesting it is RA-independent.

At the 26-somite stage, compared with DMSO controls (Fig. 5A), RA inhibition via DEAB treatment increases apoc1 expression both in the tail region and in the YSL (Fig. 5B and D). Similar to that in the early stage (Fig. 4C), the expression pattern of apoc1 does not change. Furthermore, apoc1 expression is down-regulated by ATRA, and the expression in caudal paraxial mesoderm is undetectable (Fig. 5C and D), as the effects of BMP deficiency (Fig. 3). Therefore, RA signaling is a negative regulator for Apoc1, and suggests a possible interaction with BMP signaling.

3.4. RA inhibits BMP-mediated apoc1 expression during zebrafish gastrulation

To reveal the possible interaction between the BMP and RA pathway involved in Apoc1, we first tested the effects of RA on BMPs, which is still not clear in early zebrafish embryo. Compared with DMSO controls, both the expression of BMP ligands (bmp2, bmp4 and bmp7) and the activity of BMP signaling pathway by examining phosphorylated SMAD1/5/8 are inhibited in ATRA-treated embryos and are elevated in DEAB-treated embryos (Fig. 6). Therefore, RA negatively regulates BMP signaling activity.

![Fig. 2.](https://example.com/fig2.png) Effect of BMP signaling on apoc1 expression at gastrula stage. (A–I) One-cell stage embryos injected with indicated MOs or mRNAs were raised to gastrula and visualized by WISH using antisense probe of apoc1. smad1+5MO: the mixture of smad1MO (0.25 mM) and smad5MO (0.25 mM). Lower panels (dorsal to the right and anterior to the top) show the single embryo in upper panels. (J) apoc1 expression was examined by qPCR. Error bars represent mean ± s.d., *P < 0.001, **P < 0.05, one way ANOVA with Holm–Sidak method.
The RA effect on BMP activity is similar to that on apoc1 expression, suggesting that BMP signaling would be a downstream target of RA to mediate apoc1 expression. To test this hypothesis, we further examined the crosstalk between RA and BMP signaling in apoc1 expression at the gastrula stage. In Bmp2b morphants, both excess and deficient RA do not affect apoc1 expression (Fig. 7A–D), suggesting that BMP signaling is necessary for RA action in this process. As the downstream target, excessive BMP signaling would inactivate embryo response to RA treatments. However, when Bmp signaling is excessive, RA inhibition through DEAB treatment unexpectedly elevates apoc1 expression level (Fig. 7F and H) compared with DMSO controls (Fig. 7E). Furthermore, exogenous ATRA decreases apoc1 expression (Fig. 7G and H). These indicate that RA would inhibit some BMP-independent factors that amplify BMP-mediating apoc1 expression. Taken together, RA negatively regulates BMP-mediated apoc1 expression during gastrulation in zebrafish.

### 3.5. RA inhibits BMP-mediated apoc1 expression during somitogenesis

Since the expression pattern of apoc1 during somitogenesis is different from that during gastrulation, we finally explored the crosstalk between BMP and RA signaling at the 26-somite stage. In Bmp2b or SMADs morphants, apoc1 disappears in the tail region and remain expressed in the YSL (Figs. 8A and 3C). DEAB treatment does not affect the expression (Fig. 8B and D), which increases in WT embryos treated with DEAB (Fig. 5D). This means that RA regulates apoc1 expression through Bmp signaling during somitogenesis, similar to that at the gastrula stage. Thus, high level of RA should not affect apoc1 expression when BMP signaling has been removed. However, ATRA decreases apoc1 expression in Bmp2b morphants (Fig. 8C and D), implying that exogenous RA inhibits BMP-independent apoc1 expression in YSL.

As a downstream target of RA, overabundant BMP signaling would compromise the RA effects on apoc1 expression. Indeed, DEAB does not affect the expression in the embryos overexpressing bmp2b mRNA (Fig. 8E, F and H), different from the situation during gastrulation (Fig. 7H). In consistent with Bmp2b morphants (Fig. 8C), ATRA suppresses the apoc1 expression in Bmp2b-overexpressing embryos (Fig. 8G and H), also indicating that exogenous RA inhibits BMP-independent apoc1 expression in the YSL. Since RA deficient cannot affect apoc1 expression, this effect of ATRA is likely artificial. Taken together, RA signaling inhibits apoc1 expression in BMP-dependent and -independent manner during zebrafish somitogenesis.

### 4. Discussion

Apoc1, the smallest member of Apolipoprotein family, was originally identified in human VLDL, HDL and chylomicrons (McConathy et al.,
1972; Shulman et al., 1975). It has been shown to play some roles in lipid metabolism and inflammation (Olsson et al., 2010). However, with the exception of our previous studies in fish finding that Apoc1 highly exists in embryos, the regulative mechanisms and functions in embryonic development and nutrition remained unexplored.

Several apolipoproteins have been reported to be expressed during zebrafish embryogenesis. apoe (Babin et al., 1997), apoa1 (Babin et al., 1997), apoa2 (Zhang et al., 2011), apo-14 (Zhou et al., 2005; Xia et al., 2008) all reside in YSL and follows in liver, as well as apoc1 we report (Fig. 1). YSL is a transient syncytium at the surface of the yolk cell and beneath the bottom of the blastoderm cell. The YSL is required for the hydrolysis of yolk material and for the transfer of nutrients from the yolk to the blastoderm and larval tissues in many teleost species (Carvalho and Heisenberg, 2010). High expression of apolipoproteins in YSL would be helpful for transporting material, such as lipid. When the stock in yolk is exhausted, YSL finally disappears at the end of larval stage. As the major organ that regulates lipid metabolism, liver formed at the late embryonic stage shares enormous gene expression with YSL, and relays the functions of YSL (Cheng et al., 2006; Carvalho and Heisenberg, 2010). Therefore, the expression pattern of apolipoproteins is obviously correlated with their function in lipid metabolism during embryonic development.

However, the expression pattern of apoc1 is more complicated than that of other apolipoproteins. During gastrulation, apoc1 expression exhibits a gradient along the ventral–dorsal axis, with the highest expression level on the ventral side (Fig. 1). Furthermore, apoc1 message is even detected in the prechordal plate (Fig. 1), although the function is unknown. apoc1 expression pattern is very similar to BMP ligands, and our results further demonstrate that apoc1 expression during gastrulation depends on BMP signaling (Fig. 2). During somitogenesis, besides in the YSL, apoc1 expression occurs in tail paraxial mesoderm that derives from the blastoderm margin. Around the tail bud, BMP ligands, including bm2b and bm4 (Stickney et al., 2007; Reichert et al., 2013), are highly expressed, and then diffuse to regulate apoc1 expression (Fig. 3).

Although large is unknown about Apoc1 regulation, the close proximity of apoe and apoc1 in the same gene cluster on zebrafish chromosome 16 (Wang et al., 2013), as well as in mouse and human, suggests conservative coordinate regulation between them. Similar to apoe (Zechner et al., 1991), apoc1 mRNA is highly up-regulated during late stage of adipocyte differentiation (Wassef et al., 2004). Furthermore, the ligands of LXR/RXR, the nuclear transcription factors controlling the Apoe gene (Laffitte et al., 2001), also up-regulates apoc1 expression in murine macrophages (Mak et al., 2002). In zebrafish, apoe gene is highly expressed in the YSL and the tail bud during embryogenesis (Babin et al., 1997), very similar to that of Apoc1 (Fig. 1). The similar pattern between apoc1 and apoe thus suggests a functional link between them.

In mammalian, Apolipoprotein C1 typically associates with chylomycin remnant, VLDL, and HDL, similar to Apoe. Apoc1 has been shown to modulate Apoe-dependent lipoprotein uptake by inhibiting binding of VLDL, LDL and HDL to their receptors (Kowal et al., 1990; Weisgraber et al., 1990; Scheyek and Eisenberg, 1991). In addition, it regulates some important enzymes involved in lipoprotein metabolism.

Fig. 4. Effect of RA signaling on apoc1 expression at gastrula stage. (A) cyp26a1 expression was examined in ATRA and DEAB-treated embryos by qPCR. (B–D) embryos treated with ATRA and DEAB were visualized by WISH using antisense probe of apoc1. Lower panels (dorsal to the right and anterior to the top) show the single embryo in upper panels. Arrows indicate prechordal plate. (E) apoc1 expression was examined by qPCR. DMSO was used as control. Error bars represent mean ± s.d., *P < 0.001, one way AVOVA with Holm–Sidak method.
Therefore, high expression in YSL and liver suggests that \(apoc1\) and \(apoe\) would regulate liposome metabolism during embryonic and larval development in zebrafish. Since the spatio-temporal expression pattern of \(apoc1\) is not only in YSL and in liver, Apoc1 function should be more complicated than only regulating lipid metabolism. An example is that \(apoc1\) regulates epiboly movement through E-cadherin-mediated intercalation during gastrulation because of its gradient expression along radial axis (Wang et al., 2013).

The proper embryonic development and organ maintenance require communications among signaling pathways. The crosstalk between RA and BMP pathways varies depending on the context of different systems (Means and Gudas, 1995). For example, during the neural development in chicken, RA signaling inhibits BMP-regulated proliferation and differentiation of neural progenitor cells through suppressing BMP signaling (Sheng et al., 2010); during second heart field formation in mouse, RA up-regulated cardiac Bmp expression at the looping stage (Ryckebusch et al., 2008); RA and BMP signaling exhibited both antagonistic and synergistic effects on the osteogenesis of bone marrow stromal cells (Bi et al., 2013). In our case, \(apoc1\) expression is cooperated by BMP and RA signaling pathways during zebrafish development. BMP signaling is required for \(apoc1\) expression, although some other BMP-independent factors also induce \(apoc1\) in YSL. During these processes, RA signaling counterbalances BMP effects. In addition, during gastrulation, RA signaling inhibits other BMP-independent factor that is require for BMP-inducing \(apoc1\) expression.

5. Conclusions

In conclusion, our results reveal the crosstalk between BMP and RA signaling in regulating apolipoprotein \(C1\) in zebrafish embryos. Through

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**Fig. 5.** Effect of RA signaling on \(apoc1\) expression at 26-somite stage. (A–C) embryos treated with ATRA and DEAB were visualized by WISH using antisense probe of \(apoc1\). Lower panels (lateral view) show the single embryo in upper panels. Arrowheads indicate YSL and arrows indicate tail. (D) \(apoc1\) expression was examined by qPCR. DMSO was used as control. Error bars represent mean + s.d., \(^* P < 0.001\), one way AVOVA with Holm-Sidak method.
Fig. 6. Effect of RA signaling on BMP signaling. (A and B) embryos treated with ATRA and DEAB were visualized by WISH using antisense probes of bmp2b and bmp4. Lower panels (dorsal to the right and animal to the top) show the single embryo in upper panels. (C) bmps expression were examined by qPCR and normalized to DMSO (n = 3). β-actin was used as the internal control gene. (D) The transcript activation of BMP signaling was tested by immunofluorescence using anti-phosphorylated Smad1/5/8 antibody (dorsal to the right and animal to the top). (E) Fluorescence was quantified and normalized to DMSO (n = 9 for each sample). DMSO was used as control. Error bars represent mean ± s.d., *P < 0.001, **P < 0.05, one way AVOVA with Holm–Sidak method.

Fig. 7. Crosstalk between RA and BMP signaling during gastrulation. (A–C, E–G) Embryos injected with bmp2b morpholino (A–C) and bmp2b mRNA (E–G) treated with DMSO, DEAB and ATRA were visualized by WISH using antisense probes of apoc1. (D, H) apoc1 expression was examined by qPCR in Bmp2b morphants (D) and in bmp2b-overexpressing embryos (H), and normalized DMSO (n = 3). β-actin was used as the internal control gene. Error bars represent mean ± s.d., *P < 0.001, **P < 0.05, one way AVOVA with Holm–Sidak method.
modulating apolipoprotein, BMP and RA signaling would regulate the systemic and cellular nutrition and lipid metabolism during embryonic development.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

YW and JFG conceived the project and designed experiments. YW and WL performed microscopy and DATA culture of China within the special Fund for Agro-scientific Research Program (Grant No. 201103012), the Ministry of Agriculture and Rural Affairs of China (Grant No. 30971414). Both apolipoprotein, BMP and RA signaling would regulate the systemic and cellular nutrition and lipid metabolism during embryonic development.

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