Research & Reviews

ISSN: 2319-9865

Research and Reviews: Journal of Medical and Health Sciences

Retinoids and Reproduction

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Review Article

Received: 27/03/2013
Revised: 08/05/2013
Accepted: 10/05/2013

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Keywords: Retinoids, testes, ovary, mitosis, meiosis

ABSTRACT

Retinoids are essential for reproduction. Rats maintained on a diet deficient in retinol but containing instead retinoic acid grow well and outwardly healthy. But they lose the vision and ability to reproduce. The rats with vitamin A deficiency have lowered testosterone levels which can be restored by retinoic acid. Again retinoic acid cannot restore germinal epithelium of the seminiferous tubules in Vitamin A deficient rats. The action of retinoic acid is required for the commitment of germ cells to enter meiosis in both mammalian males and females.

INTRODUCTION

Vitamin A, a fat soluble vitamin is commonly known as retinol. It is also available in the form of retinal (retinaldehyde), ester and retinoic acid (vitamin A acid). Together they are known as Retinoids though all can work in different places, eg- retinal in retina, retinol in skin and retinoic acid in different tissues including in gonads. Vitamin A deficiency itself manifests itself 1) scaliness of the skin, 2) failure of growth, 3) failure of reproduction associated with atrophy of the germinal epithelium of the testes and sometimes with interruption of the female sexual cycle and 4) keratinization of the cornea with resultant corneal opacity , destruction and blindness. Retinol can be converted to retinal or retinoic acid, again retinal can be reduced to retinol or oxidized to retinoic acid but retinoic acid cannot be reduced to aldehyde or alcohol. So ultimately retinoic acid is excreted after its functions in different places. Retinoids are only available in animals but not in plants. But perform of vitamin A or provitamin A is found in plants as several forms carotene which is converted to vitamin A in the intestine or liver. But carotene is not probably biologically active [1, 2, 3].

Scope of Review

Mitosis

Mitosis is a process of cell division where the daughter cells are produced with equal number of chromosomes and this phenomenon occurs in somatic cells. Mitosis consists of different phases like prophase, metaphase, anaphase and telophase. The first step is replication (duplication) of all DNA in the chromosomes. Both strands of the DNA in each chromosome are replicated. The principal enzymes for DNA replication are a complex multiple enzymes called DNA polymerase. It attaches and removes along the DNA template strand. Formations of each new DNA strand occur simultaneously in hundreds of segments .Afterwards the ends of the subunits are joined together by the DNA ligase. Lastly the two sets of daughter chromosomes are pulled completely apart. Then a new nuclear membrane develops around each set of chromosomes. One of the double helices thus formed goes to one daughter cell and one to the other, so the amount of DNA in each daughter cell is the same as that of the parent cells [4, 5].

Meiosis

Meiosis is the distribution of the genetic material of the chromosome into two then to four daughter cells, each of which receives half the no (haploid) of chromosome of the original cell which are diploid. It is also called meiotic division. This special type of cell division

ISSN: 2319-9865

occurs only in germ cells of the gonads. It shares certain features with mitosis but involves two distinct steps of cell division that reduce the chromosome to the haploid state.

The first meiotic division is a reduction division because the chromosome number is reduced from diploid to haploid by pairing of homologous chromosome in prophase and their segregation in anaphase. Homologous chromosomes one from each parent pair during prophase and separates during anaphase, with one representative from each pair going to each pole of the meiotic spindle. The X and Y chromosomes are not homologous but they have homologous segments at the tips of their short arms. They pair in these regions only. The secondary spermatocytes or secondary oocytes have the haploid chromosome number (double chromatid chromosome) that is half the number of chromosomes of the preceeding cells (primary spermatocytes or primary oocytes).

After the first meiotic division which results into daughter cells (2n), the two chromatids of each chromosome separate during second meiotic division to yield four gametes with haploid number (1n). When the egg is fertilized by the sperm the two haploid sets combine to restore the diploid state (2n) in the zygote [6, 7].

Major Conclusion

Retinoids are a group of substances of vitamin A family consisting of retinol, retinyl esters, retinal and retinoic acid. Vitamin A is an essential micronutrient throughout the life cycle. Both the deficiency and excess of vitamin A during embryonic development result in congenital malformations. But it is essential for growth, vision, reproduction, embryonic development and tissue maintenance [8,9,10].

Vitamin A is essential for reproduction. This was shown in experiments by Thompson et.al [11]. Similar to those in which Dowling and Wald [12] demonstrated the separation of the visual from systemic function of the vitamin. Rats maintained on a diet deficient in retinol but containing instead retinoic acid grew well and were outwardly healthy but became blind and also lost their ability to reproduce [11] as in males, spermatogenesis stopped [13]. Females became pregnant but the rate of cell division in both placenta and fetus was markedly reduced around the fourteenth day of pregnancy [11]; around the sixteenth day lesions were visible in the placenta and the fetuses were resorbed (Howell et.al.; 1964) and no offspring were born. But small amount of retinol restored reproduction to normal [8].

Similar experiments were done latter in guinea pigs [15] and in the male pig [13]. During early part of 60's it was not clear how vitamin A discharges this function in reproduction or why its failure results in the very different defects seen in the sexes. Although animals maintained on retinoic acid are not hormonally normal [17, 18], the basic inadequacy seems not to be endocrinological [19] and spermatogenesis can be restored by injection of retinol, but not retinoic acid, into the testis, indicating that it has a direct role in the organ [16, 20]. Following the fate of labeled retinol taken up by the testis has not thrown much light on how it works there [21, 22]. The effects of vitamin A deficiency on the male reproductive organs (that is atrophy of accessory sex organs; small, edematous testes; degeneration of the germinal epithelium; decrease in size of the seminiferous tubules and cessation of spermatogenesis) are well known. Earlier work [23] utilizing free labeled retinyl acetate led to the conclusion that the sertoli cells of the seminiferous tubules were the site of uptake of vitamin A by the testis. The interstitial cells in testis consist of fibroblasts, macrophages and Leydig cells [21]. If retinol performs its testicular function within the Leydig cells one could suppose that it is required for the synthesis and secretion of male steroid hormones i.e., testosterone.

A recent report by Appling and Chytil [18] gave strong support to this suggestion. These authors showed that vitamin A deficient rats had low serum testosterone (that is 92±17 ng /dl serum, in deficient rats compared to 244±52ng/dl in retinol-fed controls i.e. $p<0.05$). Most interesting was the finding that continuous feeding of retinoic acid (2 µg/gm diet) to vitamin A deficient rats could completely restore serum testosterone level. This is the first reported finding of a function for retinoic acid in the mammalian testis. From earlier work by any authors [11] it was assumed that though retinoic acid could performed all functions of retinol such as effect on growth and maintenance of epithelia, it was without function in the testis and the visual cycle of the eye. Particularly a puzzling was the well known existing of an intracellular retinoic acid binding protein in testis [24]. If it had no function, why was it there? The results of Appling and Chytil now suggested that retinoic acid either derived directly from the blood stream or from the oxidation of retinol, acts on the Leydig cells to maintain serum testosterone. There can be no doubt that the degeneration of the germinal epithelium, seminiferous tubules and the cessation of spermatogenesis in vitamin A deficient rats is not prevented by retinoic acid. According to Appling and Chytil vitamin A has a twofold role in the testes: 1) to maintain steroidogenesis as retinoic acid in Leydig cells; and 2) to maintain the germinal epithelium and sperm production in the seminiferous tubules as retinol.

More over Ahluwalia and Bieri found that injected testosterone could not restore spermatogenesis in vitamin A deficient rats. This strengthens two function hypothesis for retinol and retinoic acid in testes [20].

In conclusion the work of Chytil's group shows that retinol (bound to serum RBP) enters the testes by the interstitial cells, probably the Leydig cells, through specific cell surface receptor sites. Inside these cells it is oxidized to retinoic acid. Perhaps the intracellular binding of retinol and retinoic acid to specific proteins in testes is a necessary step in this metabolic reaction. Retinoic acid

ISSN: 2319-9865

then stimulates testosterone output of the Leydig cells. Retinol, either as such or in some other metabolic forms, also enters the seminiferous tubules in a receptor mediated step to maintain the germinal epithelium [18].

Since 1925 it has been recognized that Vitamin A is required for spermatogenesis [25]. Vitamin a is converted in tissues to its principal biologically active derivative, retinoic acid. In the testes retinoic acid is necessary both for the initiation of spermatogenesis and puberty and for the maintenance of spermatogenesis in adults [26,27,28]. Dietary beta carotene and retinol are transported to the testes where they are converted to retinoic acid within the developing germ cells by alcohol and aldehyde dehydrogenases [29,30,31].. Retinoic acid then binds one of the retinoic acid receptor that regulates gene expression [32,33].Among other effects, retinoic acid induces the spermatogonial differentiation protein stimulated by retinoic acid – 8(STRA8) within the developing germ cells. STRA8 appears to play a central role in spermatogonial differentiation [34].

Nearly a century ago, E V McCollum established that a fat soluble micronutrient ("Factor A") was necessary to sustain life and prevent blindness in cows and rats [35]. Since that time, vitamin A has been found to play essential roles not only in vision but also in skin, bone, immune system and reproductive health as well as many aspects of embryonic development. Because of the essential nature of this vitamin, all steps in its metabolism, including the absorption of precursors, storage of retinol esters, oxidation of these esters to the primary active metabolite retinoic acid (RA), and degradation of RA to inactive metabolites are subject to tight biological controls and protected by genetic redundancy. In the signaling cells conversion of ROL to RA requires two sequential oxidative steps catalyzed by retinol – or alcohol dehydrogenases (RDHs or ADHs) and retinaldehyde dehydrogenases (RALDHs), respectively. In the responding cells, RA serves as a ligand for two families of nuclear receptors, the RA receptors (RARs) and the retinoid X receptors (RXRs). The RA: RAR/RXR complex binds to RA response elements (RAREs) in target genes, recruiting co-repressors or co-activators and thereby bringing about transcriptional changes [36].

In recent years, independent studies from multiple laboratories have yielded a large body of evidence demonstrating that RA triggers the onset of Meiosis in both male and female mammals, including mice and rats as well as in other vertebrates including chickens and amphibians [37,38]. In humans the role of RA in meiosis has been demonstrated in the ovary [39,40]. In the mouse, the organism most thoroughly studied thus far, the evidence suggests that RA, produced in the adjacent mesonephrons, acts in the fetal ovary to trigger the onset of meiosis in germ cells. In the early post natal and adult testes, RA is also required to up regulate *STRA8* and sustain meiosis. As a result of these studies, the paradigm has become that the balance between RA synthesis and degradation in the developing reproductive system is required for appropriate control of the induction of *STRA8* expression and hence the timing of meiotic initiation [41, 42, 43].

Long term Vitamin A deprivation results in spermatogenetic arrest at the spermatogonial A – to-A1 transition (undifferentiated to differentiated spermatogonia) or at the pre-leptotene spermatocyte stage in rats, at primarily at the A -to- A1 transition in mice [11, 44,45,46,47,48]. When retinol is provided to vitamin A – deficient (VAD) rodents, meiosis is reinitiated promptly and synchronously [44,46,47]. Large doses of Retinoic acid can also induce resumption of meiosis in this system, suggesting that retinoic acid, and not its precursor retinol, is the active factor [48]. Recent findings have extended our understanding of this phenomenon: retinol injection into VAD mice dramatically induce Stra8 expression over a 24 hour period, indicating that Retinol rescue in VAD rodents involves induction of expression of this critical pre-meiotic gene [41]. Retinoic acid is also required for initiation of meiosis during the first wave of mouse spermatogenesis. In post natal male mice null for lecithin: retinol acyltransferase (Lrat), which are particularly susceptible to becoming VAD, dietary depletion of Vitamnin A resulted in loss Stra8 expression, the accumulation of undifferentiated spermatogonia and meiotic failure [49].

Li and Clagett – Dame [50] used vitamin A deficient rats to study germ cells in the developing ovary. They observed that the majority of the germ cells in ovaries from severely VAD embryos failed to induce Stra8, failed to enter meiosis, and remain undifferentiated. In addition in a group of animals that was moderately deficient in retinoic acid only about 30% of the oogonia entered meiosis compared with 75% in the controls. These in – vivo experiments demonstrated a dose – dependent requirement for retinoic acid to initiate meiosis in the fetal gonad at the exact developmental point that the established paradigm predicts. Moreover, they demonstrated that retinoic acid is necessary, not just sufficient, to initiate meiosis. It seems retinoic acid is the key for meiotic division. Stra8 was identified as a retinoic acid –responsive in P19embryonal carcinoma cells: retinoic acid treatment leads to up- regulation of Stra8 within 2 hours [51, 52].

Retinoids are perhaps essential for proper embryonic development in vertebrates. Retinoic acid (RA) is required as it is the ligand for two classes of nuclear receptors (retinoic acid receptors[RAR] and retinoid X receptors[RXRs]) regulating the transcription of about 500 target genes involved in biological process. These genes assist in regulating important signaling molecules for cell division, cellular differentiation, tissue function, growth and vision in the developing embryo [53,54,55,56,57]. Retinoids are provided from the maternal circulation via the placenta [58, 59,60], whereas in oviparous vertebrates embryos use retinoids and carotenoids stored in the egg yolk sometimes. While significant advances are made in recent years in resolving the pathways leading to the synthesis of retinoids required during embryonic development in zebra fish embryos [61, 62] and in trout ovarian follicles [60]. Recently a review has provided the main functions of retinoic acid embryogenesis together with RA biosynthesis degradation and the signaling pathway [64, 65].

ISSN: 2319-9865

General Significance

In summary, the combined weight of published data presents a strong case for the action of RA in triggering germ cell entry into meiosis. In particular, the block in meiotic progression in males and females as a result of dietary vitamin A insufficiency provide unequivocal evidence for the requirement for Retinoic acid to complete the crucial biological process. Nonetheless the recent findings of Kumar et al. [66] potentially cloud the issue. There are several reports that testosterone, FSH, retinoic acid act on testis for spermatogenesis. Retinol and retinoic acid increases basal testosterone secretion in adult Leydig cells but decrease it in fetus.([67]Haider, 2004) and Zheng et al([68] 1999) showed that in culture Luteal Cells and granulose cells can produce retinoic acid and hypothesized that local production of retinoic acid is intimately connected with various stages of reproduction on female rats. In adult rodents, vitamin A deficiency is followed by a loss of differentiated germ cells within the seminiferous tubules and disrupted spermatogenesis that can be restored by Vitamin A replacement. It was found that vitamin A depletion markedly decrease testicular expression of the all -trans retinoic acid-responsive gene, Stra8 and caused meiotic failure in prepubertal male mice [69]. Although much remains to be clarified but the emerging landscape discoveries are exciting.

REFERENCES

1. Bendich and Olson JA. Biological actions of carotenoids. FASEB J. 1989; 3(8): 1927-32.
2. Blomhoff R, Green MH, Green JB,Berg T and Norum KR. Vitamin A metabolism: new perspectives on absorption, transport and storage. Physiol Rev. 1991; 71: 951-990.
3. Wolf V. Multiple functions of vitamin A. Physiol Rev. 1984; 64: 873-937.
4. Bowen ID, Bowen SM, Jones AH. Mitosis and apoptosis: Matters of life and death. Chapman & Hall, London, 1998.
5. Fantes P and Brooks R. The cell cycle: a practical approach. Oxford University Press, New York .1994
6. Cooke HJ, Hargreave T and Elliott J. Understanding of the genes involved in spermatogenesis: a progress report. Fertil Steril. 1998; 69: 989-998.
7. Moore KL and Persaud TVN. The eveloping human. Saunders. Philadelphia.2003.
8. Moore T. Vitamin A. Elsevier, New York.1957.
9. Wolf G. Multiple functions of vitamin A. Physiol Rev. 1984; 64:873-938.
10. Zile MH. Vitamin A and embryonic development: An overview. J Nutr.1998; 128: 455S-458S.
11. Thomson JN, Howell JM and Pitt GAJ. Vitamin A and reproduction in rats. Proc. R. Soc. Lond (Biol). 1964; 159: 510-535.
12. Dowling JE & Wald G. The biological function of vitamin A acid. Proc Natn Acad Sci Wash. 1960; 46: 587-91.
13. Howell JM, Thompson JN & Pitt GAJ. Histology of the lesion produced in the reproductive tract of animals fed a diet deficient in Vitamin A alcohol but containing vitamin A acid. I. The male rat. J Reprod Fertil. 1963;5: 159-63.
14. Takahashi YI, Smith JE, Winick M, and Goodman DS. Vitamin A deficiency and fetal growth and development in the rat. J Nutr. 1975;105: 1299-1310.
15. Howell JM, Thompson JN & Pitt GAJ. Reproduction and vision in rats maintained on a retinol-free diet containing 3-dehydroretinol (vitamin A2). B J Nutr. 1967;21: 37-40.
16. Palludan B. A-Avitaminosis in Swine: A Study on the Importance of Vitamin A for reproduction. Copehegen: Munksgaard.1966.
17. Ganguly J, Rao MRS, Murthy SK & Sarada K. Systemic mode of action of vitamin A. Vitams Horm. 1980; 38: 1-54.
18. Appling DR and Chytil F. Evidence of a Role for Retinoic Acid (Vitamin A-Acid) in the Maintenance of Testosterone Production in Male Rats. Endocrinol.1981; 108: 2120-2123.
19. Coward WA, Howell JM, Pitt GAJ and Thompson JN. Effects of hormones on reproduction in rats fed a diet deficient in retinol (Vitamin A alcohol) but containing methyl retinoate (Vitamin A acid methyl ester). J Reprod Fertil. 1966;12:309-317.
20. Ahluwalia B and Bieri JG. Local stimulatory effect of Vitamin A on Spermatogenesis in the Rat. J Nutr. 1971; 101:141-151.
21. McGuire BW, Orgebin-Crist MC and Chytil F. Auto radiographic Localization of Serum Retinol-Binding Protein in Rat Testis Endocrinol. 1981;108:658-667.
22. Rajguru SU, Yuan-Hsu Kang, and Ahluwalia BS. Localization of Retinol (Vitamin A) in Rat Testes. J Nutr. 1982; 112: 1881-1891.
23. Ahluwalia B, Gambhir K and Sekhon H. Distribution of Labeled Retinyl Acetate and Retinoic Acid in Rat and Human Testes. A Possible Site of Retinyl Acetate Incorporation in Rat Testes. J Nutr. 1975; 105: 467-474.
24. Ong DE and Chytill F. Retinoic acid-binding protein in rat tissue. Partial purification and comparison to rat tissue retinol-binding protein. J Biol Chem. 1975; 250: 6113-6117.
25. Wolbach SB and Howe PR. Tissue changes following deprivation of fat soluble A vitamin. J Exp Med. 1925;42: 753-777.
26. Lufkin T, Lohnes D, Mark M, Dierich A, Gorry P, Gaub MP, et al. High postnatal lethality and testes degeneration in retinoic acid receptor alpha mutant mice. Proc Natl ACAD Sci USA.1993; 90: 7225-7229.
27. Ghyselinck NB, Vernet N, Dennefeld C, Giese N, Nau H, Chambon P, Viville S and Mark M. Retinoids and spermatogenesis: lessons from mutant mice lacking the plasma retinol binding protein. Dev Dyn.2006; 235: 1608-1622.
28. Vernet N, Dennefeld C, Rochett-egly C, Oulad-Abdelghani M, Chambon P, Ghyselinck NB and Mark M. Retinoic acid metabolism and signaling pathway in the adult and developing mouse testes. Endocrinol. 2006b;147: 96-110.
29. Bishop PD and Griswold MD. Uptake and metabolism of retinol in cultured Sertoli cells: Evidence for a kinetic model.

Biochem.1987; 26:7511-7518.

30. J.Napoli. Retinoic acid: its biosynthesis and metabolism. In: Moldave K, ed. Progress in Nucleic Acid Research and Molecular Biology. San Diego, CA: Academic Press, 2000,p 139-188.
31. Paik J, Vogel S, Quadro L, Piantedosi R, Gottesman M, Lai K, Hamberger L, Vieria MM, Blaner W. Vitamin A: Overlapping delivery pathways to tissues from the circulation. J Nutr. 2004;134: S276-S280.
32. Chung SS, Sung W, Wang X and Wolgemuth DJ. Retinoic acid receptor alpha is required for synchronization of spermatogenic cycles and its absence results in progressive breakdown of the spermatogenic process. Dev Dyn. 2004;230: 754-766.
33. Bowles J, Knight D, Smith C, Wilhelm D, Richman J, Mamiya S, Yashiro K, Chawengsaksophak K, Wilson MJ, Rossant J, Hamada V and Koopman P. Retinoic signaling determines celkl fate in mice. Science. 2006; 312: 596-600.
34. Zhou Q, Li Y, Nie R, Friel P, Mitchell D, Evanoff RM, Pouchnik D , Banasik B , McCarrey JR , Small C and Griswold MD. Expression of stimulated by retinoic acid gene 8 (Stra8) and maturation of murine gonocytes and spermatogonia induced by retinoic acid in vitro. Biol Reprod.2008; 78(3): 537-45.
35. Wolf G. Discovery of Vitamin A. In: eLS: John Wiley & Sons, Ltd; 2001.
36. Duester G. Retinoic acid synthesis and signaling during early organogenesis. Cell. 2008; 134:921-931.
37. Smith CA, Roeszler KN, Bowles J, Koopman P and Sinclair AH. Onset of meiosis in the chicken embryo; evidence of a role of retinoic acid. BMC Dev Biol. 2008; 8: 85-92.
38. Wallacides A, Chesnel A, Chardard D, Filament S, Dumond H. Evidence for a conserved role of retinoic acid in urodele amphibian meiosis onset. Dev Dyn.2009; 238: 1389-1398.
39. Childs AJ, Cowan V, Kinnell V, Anderson RA and Saunders PT. Retinoic acid signaling and the control of meiotic entry in the human fetal gonad. PLoS One. 2011; 6: e 20249.
40. Le Bouffant R, Guerquin MJ, Duquenne C, Frydman N, Coffigny H, Rouiller -Fabre V, Frydman R, Habert R and Livera G. Meiosis initiation in human ovary requires intrinsic retinoic acid synthesis. Hum Reprod. 2010; 25: 2579-2590.
41. Koubova V, Menke DB, Zhou Q , Capel B, Griswold MD and Page DC. Retinoic acid regulates sex-specific timing of meiotic initiation in mice. Proc Natl Acad Sci USA. 2006; 103: 2474-2479.
42. MacLean G, Li H, Metzger D, Chambon P and Petkovich M. Apoptotic extinction of germ cells in testes of Cyp26b1 knockout mice. Endocrinol. 2007;148: 4560-4567.
43. Snyder EM, Small C and Griswold MD. Retinoic acid availability drives the asynchronus initiation of spermatogonial differentiation in the mouse. Biol Reprod. 2010; 83: 783-790.
44. Griswold MD, Bishop PD, Kim KH, Ping R, Siiteri JE Morales C. Function of vitamin A in normal and synchronized seminiferous tubules. Ann N Y Acad Sci. 1989;564: 154-172.
45. Huang HF and Hembree WC. Spermatogenic response to vitamin A in vitamin A deficient rats. Biol Reprod. 1979;21: 891-904.
46. Morales C and Griswold MD. Retinol- induced stage synchronization in seminiferous tubules of the rat. Endocrinol. 1987; 121: 432-434.
47. van Pelt AM and De Rooij DG. Synchronization of the seminiferous epithelium after Vitamin A replacement in Vitamin A-deficient mice. Biol Reprod. 1990; 43: 363-367.
48. van Pelt AM and De Rooij DG . Retinoic acid is able to reinitiate spermatogenesis in Vitamin A deficient rats and high replicate does support the full development of spermatogenic cells. Endocrinol. 1991; 128: 697-704.
49. Li H, Palezewski K, Baehr W and Clagett-Dame M. Vitamin A deficiency results in meiotic failure and accumulation of undifferentiated spermatogonia in prepubertal mouse testis. Biol Reprod. 2011; 84: 336-341.
50. Li H and Clagett-Dame M. Vitamin A deficiency blocks the initiation of meiosis of germ cells in the developing rat ovary in vivo. Biol Reprod. 2009; 81: 996-1001.
51. Bouillet P and Oulad-Abdelghani M, Vicaire S, Garnier JM, Sscuhbaur B, Dolle P and Chambon P. Efficient cloning of cDNAs of retinoic acid-responsive genes in P19 embryonal carcinoma cells and characterization of novel mouse gene, Stra1 (mouse LERK -2/Eplg2). Dev Biol. 1995; 170: 420-433.
52. Oulad-Abdelghani M, Bouillet P, Decimo D, Gansmuller A, Heyberger S, Dolle P , Bronner S, Lutz Y and Chambon P. Characterization of a pre-meiotic germ cell-specific cytoplasmic protein encoded by Stra8, a novel retinoic acid responsive gene. J Cell Biology.1996; 135: 469-477.
53. Mangelsdorf DJ and Evans RM. The RXR heterodimers and orphan receptors. Cell. 1995; 83: 841-850.
54. Napoli JL. Interactions of retinoid binding proteins and enzymes in retinoid metabolism. Biochim Biophys Acta. 1999; 1440: 139-162.
55. Maden M. Vitamin A and the developing embryo. Postgrad Med J. 2001; 77: 489- 491.
56. Balmer JE and Blomhoff R. Gene expression regulation by retinoic acid. J Lipid Res. 2002; 43: 1773-1808.
57. Blomhoff R and Blomhoff HK. Overview of retinoid metabolism and function. J Neurobiol. 2006; 66: 606-630.
58. Morriss-Kay GM and Ward SJ. Retinoids and mammalians development. Int Rev Cytol. 1999; 188: 73-131.
59. Quadro L, Hamberger L, Gottesman ME, Colantuoni V, Ramakrishnan R and Blaner WS. Transplacental delivery of retinoid: the role of retinol-binding protein and lipoprotein retinyl ester. Am J Physiol Endocrinol Metab. 2004; 286: E844- E851.
60. Quadro L, Hamberger L, Gottesman ME, Wang F, Colantuoni V, Blaner WS and Mendelsohn CL. Pathways of vitamin A delivery to the embryo: insights from a new tunable model of embryonic vitamin A deficiency. Endocrinol. 2005; 146: 4479-4490.

ISSN: 2319-9865

61. Lampert JM, Holzschuh J, Hesse S, Driever W, Vogt K and Von Lintig J. Provitamin A conversion to retinal via the b,b-carotene-15,15'-oxygenase (bcox) is essential for pattern formation and differentiation during zebra fish embryogenesis. Development. 2003; 130: 2173-2186.
62. Isken A, Holzschuh J, Lampert JM, Fischer L, Oberhauser V, Krzysztof P and Von Lintig J. Sequestration of retinyl esters is essential for retinoid signaling in the zebra fish embryo. J Biol Chem. 2007; 282: 1144-1151.
63. Liraz Levi, Berta Levavi-Sivan and Esther Lubzens. Expression of Genes Associated with Retinoid Metabolism in the Trout Ovarian Follicle. Biology of Reproduction. 2008; 79: 570-577.
64. Rohinn M and Dolle P. Retinoic acid signaling during development. Development. 2012; 139(5): 843-858.
65. Hogarth CA and Griswold DM. The key role of vitamin A in spermatogenesis. J Clin Invest. 2012; 120(4): 956-962.
66. Kumar S, Chatzi C, Brade T, Cunningham TJ, Zhao and Duester G. Sex specific timing of meiotic initiation is regulated by CYP26b1 independent retinoic acid signaling. Nat Commum. 2011; 2: 15-20.
67. Syed Haider G. Cell biology of Leydig Cells in the testis. Int Rev Cytol. 2004; 233: 181-241.
68. Zheng WL, Bucco RA, Sierra-Rievera E, Osteen KG, Melner MH and Ong DE. Synthesis of retinoic acid by rat ovarian cells that express cellular retinoic acid-binding protein-II. Biol Reprod. 1999; 60(1): 110-114.
69. Li H, Palczewski K, Baehr W and Clagett-Dame M. Vitamin A deficiency results in meiotic failure and accumulation of undifferentiated spermatogonia in prepubertal mouse testis. Biol Reprod. 2011; 84(2): 336-341.