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Understanding the physiological role of retinol-binding protein in vitamin A metabolism using transgenic and knockout mouse models

Loredana Quadro [a,b,*], Leora Hamberger [a], Vittorio Colantuoni [b], Max E. Gottesman [a], William S. Blaner [b,*]

[a] *Institute of Cancer Research, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA*

[b] *Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA*

Abstract

Retinoids (vitamin A and its derivatives) play an essential role in many biological functions. However mammals are incapable of de novo synthesis of vitamin A and must acquire it from the diet. In the intestine, dietary retinoids are incorporated in chylomicrons as retinyl esters, along with other dietary lipids. The majority of dietary retinoid is cleared by and stored within the liver. To meet vitamin A requirements of tissues, the liver secretes retinol (vitamin A alcohol) into the circulation bound to its sole specific carrier protein, retinol-binding protein (RBP). The single known function of this protein is to transport retinol from the hepatic stores to target tissues. Over the last few years, the generation of knockout and transgenic mouse models has significantly contributed to our understanding of RBP function in the metabolism of vitamin A. We discuss below the role of RBP in maintaining normal vision and a steady flux of retinol throughout the body in times of need.

* Corresponding authors. Address: College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA. Tel.: +1-212-3053705; fax: +1-212-3051741 (L. Quadro), Tel.: +1-212-3055429; fax: +1-212-3052801 (W.S. Blaner).

E-mail addresses: lq13@columbia.edu (L. Quadro), wsb2@columbia.edu (W.S. Blaner).

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1. Vitamin A metabolism and function

Vitamin A plays an essential role in maintaining mammalian health. It is required for many crucial biological functions such as vision, reproduction, growth and immunity (Goodman, 1984; Napoli, 1996). Since animals are incapable of vitamin A synthesis, all retinoids within the body (vitamin A and its metabolites) must be obtained from the diet as preformed vitamin A (retinyl esters, retinol and a very small amount of retinoic acid) from animal products or as provitamin A carotenoids from fruits and vegetables (Goodman, 1984).

While retinol (vitamin A alcohol), the major circulating form of vitamin A, is not biologically active, it serves as a metabolic precursor of active retinoids. These are generated intracellularly by two oxidative enzymatic reactions in which retinol is converted first to retinaldehyde and then to retinoic acid (Blaner and Olson, 1994). Retinaldehyde is active in the visual cycle (Saari, 1999; Wald, 1968). All-*trans* and 9-*cis*-retinoic acid are the ligands for specific classes of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs) respectively. These receptors regulate the transcription of many essential target genes (Chen and Evans, 1995; Kastner et al., 1995; Kurokawa et al., 1995; Leblanc and Stunnenberg, 1995; Mangelsdorf et al., 1995; Pfahl and Chytil, 1996).

Within the intestinal mucosa all retinol, regardless of its dietary origin, is re-esterified with long-chain fatty acids into retinyl esters by the enzyme lecithin:retinol acyltransferase (LRAT) (Ruiz et al., 1999; Zolfaghari and Ross, 2000). The newly synthesized retinyl esters are incorporated into chylomicrons along with other dietary lipids and secreted into the general circulation via the lymphatic system (Vogel et al., 1999). Once nascent chylomicrons enter the general circulation, hydrolysis of chylomicron triglyceride by lipoprotein lipase (LPL) bound to the luminal surface of the vascular endothelium, results in the formation of chylomicron remnants (Goldberg, 1996) still containing the newly absorbed retinyl esters. After chylomicron remnants acquire apolipoprotein E, either in the plasma or in the space of Disse, approximately 75% of chylomicron remnants are cleared by the liver, the major site of vitamin A storage and metabolism (Blaner and Olson, 1994; Cooper, 1997). The remaining 25% is cleared by extrahepatic tissues (Goodman et al., 1965). Dietary retinoic acid is absorbed as such in the intestine and distributed bound to albumin throughout the body (Eckhoff et al., 1991; Lehman et al., 1972; Smith et al., 1973).

To meet tissue vitamin A requirements, the liver secretes retinol into the circulation, bound to its specific transport protein, retinol-binding protein (RBP) (Soprano and Blaner, 1994). This 21 kDa protein with a single binding site for one molecule of all-*trans*-retinol, is mainly synthesized by the hepatocytes (Soprano and Blaner, 1994). Retinol–RBP circulates in the blood as a 1:1 molar complex with another serum protein, transthyretin (TTR) (Gaetani et al., 2002; Monaco et al., 1995). Under fasting condition, retinol–RBP accounts for approximately 99% of all retinoids present in the blood. However, after consumption of a vitamin A-rich meal, the amount of circulating retinol present as retinyl esters in chylomicrons and chylomicron remnants can greatly exceed that of retinol–RBP. In healthy individuals, the postprandial increase in circulating retinyl esters usually subsides 6–8 h after

consumption of dietary vitamin A (Vogel et al., 1999). In both humans and animals serum levels of retinol–RBP remain constant, except in extreme cases of nutrition and in certain disease states (Biesalski et al., 1999; Goodman, 1984). When dietary vitamin A is not available, RBP is able to mobilize retinol from vitamin A stores in the liver to supply peripheral cells and tissues with retinoids needed for various biological functions (Vogel et al., 1999). When hepatic vitamin A stores are exhausted, as they would upon continuous consumption of a retinoid-deficient diet (over a period of many months for most animal species and years for previously well nourished humans), serum levels of retinol–RBP decline to undetectable (Gamble and Blaner, 1999). As circulating levels of retinol–RBP decline, the health of cells and tissues is compromised due to the inability to support retinoid-dependent processes (Goodman, 1984). Other retinoids are also present in the circulation albeit at much lower levels compared to retinol–RBP: (1) retinyl esters incorporated in lipoprotein particles (especially in very low density lipoprotein, VLDL, and low density protein, LDL) (Goodman et al., 1965; Mahley and Hussain, 1991); (2) retinoic acid (both all-*trans* and 13-*cis*) in the fasting plasma of human, rodents and cow (Blaner and Olson, 1994); (3) fully water soluble glucuronides of both retinol and retinoic acid (Barua et al., 1988; Barua and Olson, 1989) and (4) provitamin A carotenoids (Napoli and Race, 1988; Olson, 1989).

2. Physiological function of retinol-binding protein

2.1. The role of RBP in vision

The visual cycle is driven by retinal derived from circulating retinol (Goodman, 1984; Wald, 1968). Within the retina, photoreceptor function depends on a specific vitamin A metabolite, 11-*cis*-retinal (Wald, 1968) which forms a Shiff's base with photoreceptor opsin to generate the visual pigment rhodopsin. Photoisomerization of the chromophore from 11-*cis* to all-*trans*-retinal is the initial event of the visual cycle. This light-catalized isomerization induces a conformational change in opsin that activates a photoreceptor-specific G-protein (Gregory-Evans and Bhattacharya, 1998). The G-protein activation then triggers a series of molecular events that result in a transmembrane hyperpolarization of rods and/or cones (Gregory-Evans and Bhattacharya, 1998). This signal is transmitted through a series of neurons to the central nervous system, where the visual information is integrated (Kelsey, 1997). Regeneration of the visual pigment requires release from the opsin of all-*trans*-retinal and binding of a new molecule of 11-*cis*-retinal. Once released, all-*trans*-retinal is reduced enzymatically to all-*trans*-retinol and then transported to the retinal pigment epithelium (RPE). Inside the RPE, all-*trans*-retinol is isomerized to 11-*cis*-retinol which is then oxidized to 11-*trans*-retinol. The newly regenerated 11-*trans*-retinol returns from RPE to the outer segment (photoreceptor layer) and joins with opsin, completing the visual cycle (Saari, 1999).

The targeted disruption of the RBP genomic locus in mouse has provided interesting insight into the function that this protein plays in vision. The RBP knockout

mice (RBP−/−) have low serum retinol levels (12.5% of wild-type animals) and impaired retinal function and visual acuity during the first months of life (Quadro et al., 1999). As a matter of fact, at weaning the knockout mice show abnormal electroretinograms (ERGs) and have low levels of retinol and retinal in the eye (Table 1). However, when these mice are maintained on a standard rodent chow diet, they accumulate sufficient eye retinol levels to achieve normal vision by 4–5 months of age (Table 1). Moreover, if maintained on a vitamin A-deficient diet (vitamin A: <0.22 IU/g) since weaning, vision of RBP−/− mice further deteriorates while no change in vision is seen in wild-type mice (Quadro et al., 1999). These data suggest that, in the knockout mice, an alternative, RBP-independent pathway(s) delivers retinol from recently ingested vitamin A to the eye. This pathway(s) however is rather inefficient, as RBP−/− mice are able to achieve normal vision only after several months on a vitamin A-sufficient diet while their eye retinol stores remain low throughout life (Quadro et al., 1999). This supports the notion that the lack of RBP generates an extremely tenuous vitamin A status in these mice, particularly with respect to the visual function.

Why does circulating retinol–RBP seem to be particularly important in maintaining visual function? What RBP-independent pathway(s) possibly deliver vitamin A to the eye of RBP−/− mice and why are they so inefficient compared to retinol–RBP? When RBP−/− mice are maintained on a standard rodent chow diet, the eye and other peripheral tissues have several potential RBP-independent sources for acquiring retinol: as retinyl esters packaged into chylomicrons and their remnants or bound to VLDL, LDL, and/or HDL, or as retinol bound to albumin (Vogel et al., 1999). Surprisingly, the literature describing how the RPE and the retina acquire lipids from circulating lipoproteins is very limited (Hayes et al., 1989; Noske et al., 1998; Wang and Anderson, 1993). Vogel et al. (2002) demonstrated that delivery of retinol to the eye as retinyl esters incorporated in chylomicrons is very inefficient. By following the plasma clearance and tissue uptake of ^{3}H-retinoid over time after administration of an oral bolus of ^{3}H-retinol via gavage, they show that retinyl esters incorporated in chylomicrons and lipoproteins account for a very small fraction of retinol delivered to the eye. In addition, the low levels of retinol, likely bound to albumin, that are present in the circulation of RBP−/− mice (Quadro et al., 1999) do not seem to be targeted to the eye. Thus, the eye must rely on retinol bound to RBP as its primary means for acquiring the retinoids needed for normal visual pigment

Table 1
Retinol and retinal levels in the eye cups of RBP−/− mice

Age	Genotype	Retinol (ng/eye cups)	Retinal (ng/eye cups)	*N*
4 weeks	wt	49.9 ± 3.2	57.3 ± 9.9	5
	RBP−/−	15.6 ± 2.5	10.7 ± 6.4	5
32 weeks	wt	53.3 ± 7.4	87.0 ± 16.1	4
	RBP−/−	56.0 ± 13.1	49.2 ± 19.0	4

Retinol levels were determined by reverse phase HPLC. Retinal levels were determined by normal phase HPLC. Values were expressed as mean ± SD. *N* = number of mice analyzed per each group. wt = wild-type mice.

formation. The poor uptake of postprandial retinoids by the eye is the basis of the visual phenotype of the RBP−/− mice.

The ability of the eyes of both RBP−/− and wild-type mice to take up ^{3}H-retinol from the circulation when it is present as retinol–RBP complex is very striking (Vogel et al., 2002). The rate of uptake of ^{3}H-retinol by the eye, when normalized per gram of tissues, markedly exceeds that of all the other tissues analyzed, except for kidney. Why does the eye possess such a great affinity for retinol delivered bound to RBP? Cell surface receptors for RBP are reported to be present on the basal surface of human and bovine RPE cells (Heller and Bok, 1976; Pfeffer et al., 1986) as well as in many other cells and tissues throughout the body (Soprano and Blaner, 1994; Vogel et al., 1999). However, no definitive reports of the cloning of this receptor have been published (Soprano and Blaner, 1994; Vogel et al., 1999). Nevertheless, the simplest and most compelling interpretation of these data would be to hypothesize that RPE cells are somehow able to specifically recognize and efficiently absorb retinol when bound to RBP.

Although the major site of RBP synthesis in the body is the hepatocyte, other cell types are reported to be capable of RBP expression (Soprano and Blaner, 1994). It is generally thought that the synthesis of RBP in extrahepatic tissues serves either to recycle retinol to the liver (Green et al., 1987) or to facilitate uptake of retinol by tissues with blood–tissue barriers (testes, eyes and brain) (Aldred et al., 1995; Das and Gouras, 1988; Flood et al., 1982, 1983; Herbert et al., 1991; MacDonald et al., 1990; Mark et al., 1993; Martone et al., 1988; McGuire et al., 1981; Ong et al., 1994; Shingleton et al., 1989; Zetterstrom et al., 1994; Zheng et al., 2001). Whether circulating RBP derived from different tissues performs the same basic physiological functions of the hepatic protein is still not clear. Further analysis of the role of RBP in assuring that the eye acquires and maintains normal vitamin A levels comes from the work of Quadro et al. (2002). In this paper the authors focus on the role of RBP synthesized in extrahepatic tissues. In particular, to investigate the role of circulating RBP of extrahepatic origin in maintaining visual responsiveness they generated a mouse strain that lacks functional RBP and carries a transgene that expresses human retinol-binding protein (hRBP) under the control of the mouse muscle creatine kinase (MCK) promoter (hRBP−/− mice). Unlike RBP−/−animals, hRBP−/− mice do not show visual defects in the first months of life, as assessed by ERGs, and have copious optic stores of retinol and retinyl esters. The amount of hRBP secreted into the bloodstream of these mice is very high and, correspondingly, the levels of serum retinol are 3-fold higher than wild-type animals and 30-fold higher than that of RBP knockout mice. The high concentrations of retinol bound to hRBP accounts for the suppression of the visual defect in RBP−/−animals. However, no detectable hRBP was found in the RPE of hRBP−/− mice, suggesting that the delivery of retinol to the eye might not entail endocytosis of an retinol–RBP complex (Quadro et al., 2002). These last data leave open the issue of how the retinol–hRBP is taken up by the RPE. Thus, if an RBP receptor exists, it might not function through an endocytotic pathway.

Among the tissues where the synthesis of extrahepatic RBP has been shown, the eye is one of the most difficult to understand. RBP is expressed in the RPE and from

there secreted into the interphotoreceptor matrix (IPM) (Adler and Edwards, 2000). However, little is known about the function that RBP serves in the eye. This study indicates that circulating hRBP of extrahepatic origin efficiently delivers vitamin A to the eye and rescues the visual defect of RBP−/− mice (Quadro et al., 2002). Whether RBP synthesized in the eye plays a role in maintaining the visual cycle has yet to be definitively proved.

Analysis of the visual function of the mice lacking TTR (TTR−/−) (Episkopou et al., 1993) further supports the conclusion that RBP is necessary for efficient delivery of retinol to the eye. Although, TTR−/− mice have low serum retinol, like RBP knockout mice, their vision is normal (Bui et al., 2001; Quadro et al., 1999).

All these data together support the idea that the absence of the complex retinol–RBP, rather than the low serum retinol levels per se, is responsible for the impaired vision of the RBP−/− mice.

2.2. The role of RBP in storage and mobilization of vitamin A

The RBP knockout mice display another remarkable feature. Postprandial vitamin A is delivered in chylomicron remnants to the liver where the majority of the body's retinol reserves are stored as lipid droplets in the nonparenchymal stellate cells (also called Ito cells, fat-storing cells or lipocytes) (Blaner et al., 1985). It is well established that chylomicron remnants are taken up by hepatocytes (Cooper, 1997) and it has long been thought that RBP facilitates the transfer of newly absorbed vitamin A from hepatocytes to stellate cells for storage (Blaner and Olson, 1994). Interestingly, though, hepatic stellate cells in the RBP−/− mice are filled with lipid droplets (Novikof P., personal communication). Moreover, by 5 months of age, hepatic total retinol stores significantly increase in RBP−/− mice compared to wild-type mice (Quadro et al., 1999). These data indicate that RBP is not required for movement of retinol between hepatocytes and stellate cells, and are in agreement with the report of Ghyselinck et al. (1999) that demonstrated that cellular retinol-binding protein I (CRBP-I) is the key player of this function.

On the other hand, their ability to mobilize retinol from hepatic stores is compromised (Quadro et al., 1999; Vogel et al., 2002). Therefore, in order to maintain normal retinoid dependent processes, RBP−/− mice rely primarily on recently absorbed dietary vitamin A. Indeed, dietary vitamin A is the origin of their residual circulating retinol that dramatically drops when the mice are maintained on a vitamin A-deficient diet for one week (Table 2) (Quadro et al., 1999).

These studies have revealed that the major physiological role of RBP is to mobilize the hepatic retinoid stores in order to maintain a steady flow of retinol throughout the body in times of insufficient vitamin A intake. Thus, RBP plays an essential function particularly in the wild where the availability of vitamin A in the diet of the animals can differ dramatically in different seasons. RBP frees the animals from dependence on dietary vitamin A availability. This has likely been the evolutionary advantage resulting in a protein highly conserved across species (Soprano and Blaner, 1994). This might be one of the reasons why the eye acquired a special affinity for RBP: vision is such a critical function in higher vertebrates, essential for

Table 2
Serum retinol levels in RBP−/− mice on a vitamin A-deficient diet for one week

Genotype	Diet	Retinol (μg/dl)	*N*
wt	Regular chow	20.1 ± 4.4	5
	Vit A-deficient	25.5 ± 4.5	5
		(p = NS)	
RBP−/−	Regular chow	1.37 ± 0.4	5
	Vit A-deficient	0.32 ± 0.2	4
		(p = 0.001)	

Retinol levels were determined by reverse phase HPLC and expressed as mean ± SD. N = number of 12-week old female mice analyzed per each age group. Vitamin A-deficient diet = <0.02 IU/g; Regular chow diet = 25 IU/g. wt = wild-type mice. Student's t test was used to calculate statistical significance.
NS = not significant ($p > 0.01$).

survival and fitness in the wild, that they couldn't afford to rely on a delivery system dependent on dietary vitamin A availability.

Thus, the lack of RBP makes these mice permanently living on the edge of vitamin A-deficiency and dependent on dietary vitamin A through delivery via chylomicrons and their remnants. Because RBP−/− mice maintained on a standard rodent chow diet are phenotypically normal with the exception of the impaired vision, tissues other than eye seem to be able to obtain sufficient vitamin A to meet their needs from recently ingested retinol. Studies investigating retinoid transport in RBP−/− mice and transgenic mice expressing hRBP promise to further unravel the role of RBP.

References

Adler, A.J., Edwards, R.B., 2000. Human interphotoreceptor matrix contains serum albumin and retinol-binding protein. Exp. Eye Res. 2, 227–234.

Aldred, A.R., Brack, C.M., Schreiber, G., 1995. The cerebral expression of plasma protein genes in different species. Comp. Biochem. Physiol. B. Biochem. Mol. Biol. 1, 1–15.

Barua, A.B., Olson, J.A., 1989. Chemical synthesis of all-*trans*-[11-3H]retinoyl beta-glucuronide and its metabolism in rats in vivo. Biochem. J. 2, 403–409.

Barua, A.B., Batres, R.O., Olson, J.A., 1988. Synthesis and metabolism of all-*trans*-[11-3H]retinyl beta-glucuronide in rats in vivo. Biochem. J. 2, 415–420.

Biesalski, H.K., Frank, J., Beck, S.C., Heinrich, F., Illek, B., Reifen, R., Gollnick, H., Seeliger, M.W., Wissinger, B., Zrenner, E., 1999. Biochemical but not clinical vitamin A deficiency results from mutations in the gene for retinol-binding protein. Am. J. Clin. Nutr. 69, 931–936.

Blaner, W.S., Olson, J.A., 1994. Retinol and retinoic acid metabolism. In: Sporn, M.B., Roberts, A.B., Goodman, D.S. (Eds.), The Retinoids, Biology, Chemistry and Medicine. Raven Press, New York, NY, pp. 229–256.

Blaner, W.S., Smith, J.E., Dell, R.B., Goodman, D.S., 1985. Spatial distribution of retinol-binding protein and retinyl palmitate hydrolase activity in normal and vitamin A-deficient rat liver. J. Nutr. 7, 856–864.

Bui, B.V., Armitage, J.A., Fletcher, E.L., Richardson, S.J., Schreiber, G., Vingrys, A.J., 2001. Retinal anatomy and function of the transthyretin null mouse. Exp. Eye Res. 5, 651–659.

Chen, J.D., Evans, R.M., 1995. A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature 377, 454–457.

Cooper, A.D., 1997. Hepatic uptake of chylomicron remnants. J. Lipid Res. 11, 2173–2192.
Das, S.R., Gouras, P., 1988. Retinoid metabolism in cultured human retinal pigment epithelium. Biochem. J. 2, 459–465.
Eckhoff, C., Collins, M.D., Nau, H., 1991. Human plasma all-*trans*, 13-*cis* and 10-*cis*-4-oxoretinoic acid profiles during subchronic vitamin A supplementation: comparison to retinol and retinyl plasma levels. J. Nutr. 121, 1016–1025.
Episkopou, V., Maeda, S., Nishiguchi, S., Shimada, K., Gaitanaris, G.A., Gottesman, M.E., Robertson, E.J., 1993. Disruption of the transthyretin gene results in mice with depressed levels of plasma retinol and thyroid hormone. Proc. Natl. Acad. Sci. USA 6, 2375–2379.
Flood, M.T., Gouras, P., Haley, J.E., Blaner, W.S., 1982. Human retinal pigment epithelium in vitro: organization, ultrastructure, and biochemistry. Birth Defects Orig. Artic. Ser. 6, 53–66.
Flood, M.T., Bridges, C.D., Alvarez, R.A., Blaner, W.S., Gouras, P., 1983. Vitamin A utilization in human retinal pigment epithelial cells in vitro. Invest. Ophthalmol. Vis. Sci. 9, 1227–1235.
Gaetani, S., Bellovino, D., Apreda, M., Devirgiliis, C., 2002. Hepatic synthesis, maturation and complex formation between retinol-binding protein and transthyretin. Clin. Chem. Lab. Med. 12, 1211–1220.
Gamble, M.V., Blaner, W.S., 1999. Factors affecting blood retinol levels of vitamin A. In: Livrea, M.A. (Ed.), Vitamin A and retinoids: an update of biological aspects and clinical applications. Birkhauser Publishing Ltd., Basel, pp. 1–18.
Ghyselinck, N.B., Bavik, C., Sapin, V., Mark, M., Bonnier, D., Hindelang, C., Dierich, A., Nilsson, C.B., Hakansson, H., Sauvant, P., Azais-Braesco, V., Frasson, M., Picaud, S., Chambon, P., 1999. Cellular retinol-binding protein is essential for vitamin A homeostasis. Embo J. 18, 4903–4914.
Goldberg, I.J., 1996. Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. J. Lipid Res. 4, 693–707.
Goodman, D.S., 1984. Vitamin A and retinoids in health and disease. N. Engl. J. Med. 16, 1023–1031.
Goodman, D.S., Huang, H.S., Shiratori, T., 1965. Tissue distribution of newly absorbed vitamin A in the rat. J. Lipid Res. 6, 390–396.
Green, M.H., Green, J.B., Lewis, K.C., 1987. Variation of retinol utilization rate with vitamin A status in the rat. J. Nutr. 117, 694–703.
Gregory-Evans, K., Bhattacharya, S.S., 1998. Genetic blindness: current concepts in the pathogenesis of human outer retinal dystrophies. Trends Genet. 3, 103–108.
Hayes, K.C., Lindsey, S., Stephan, Z.F., Brecker, D., 1989. Retinal pigment epithelium possesses both LDL and scavenger receptor activity. Invest. Ophthalmol. Vis. Sci. 2, 225–232.
Heller, M., Bok, D., 1976. A specific receptor for retinol binding protein as detected by the binding of human and bovine retinol binding protein to pigment epithelial cells. Am. J. Ophthalmol. 1, 93–97.
Herbert, J., Cavallaro, T., Martone, R., 1991. The distribution of retinol-binding protein and its mRNA in the rat eye. Invest. Ophthalmol. Vis. Sci. 2, 302–309.
Kastner, P., Mark, M., Chambon, P., 1995. Nonsteroid nuclear receptors: what are genetic studies telling us about their role in real life? Cell 6, 859–869.
Kelsey, C.A., 1997. Detection of vision information. In: Hendee, W.R., Wells, P.N.T. (Eds.), The Perception of Visual Information. Springer-Verlag, New York, NY, pp. 33–56.
Kurokawa, R., Soderstrom, M., Horlein, A., Halachmi, S., Brown, M., Rosenfeld, M.G., Glass, C.K., 1995. Polarity-specific activities of retinoic acid receptors determined by a co-repressor. Nature 377, 451–454.
Leblanc, B.P., Stunnenberg, H.G., 1995. 9-*cis* Retinoic acid signaling: changing partners causes some excitement. Genes Dev. 15, 1811–1816.
Lehman, E.D., Spivey, H.O., Thayer, R.H., Nelson, E.C., 1972. The binding of retinoic acid to serum albumin in plasma. Fed. Proc. 31, 672.
MacDonald, P.N., Bok, D., Ong, D.E., 1990. Localization of cellular retinol-binding protein and retinol-binding protein in cells comprising the blood-brain barrier of rat and human. Proc. Natl. Acad. Sci. USA 11, 4265–4269.
Mahley, R.W., Hussain, M.M., 1991. Chylomicron and chylomicron remnant catabolism. Curr. Opin. Lipidol. 2, 170–176.

Mangelsdorf, D.J., Thummel, C., Beato, M., Herrlich, P., Schutz, G., Umesono, K., Blumberg, B., Kastner, P., Mark, M., Chambon, P., Evans, R., 1995. The nuclear receptor superfamily: the second decade. Cell 6, 835–839.

Mark, M., Lufkin, T., Vonesch, J.-L., Ruberte, E., Olivo, J.-C., Dolle, P., Gorry, P., Lumsden, A., Chambon, P., 1993. Two rhombomers are altered in HOXA-1 mutant mice. Development 119, 319–338.

Martone, R.L., Schon, E.A., Goodman, D.S., Soprano, D.R., Herbert, J., 1988. Retinol-binding protein is synthesized in the mammalian eye. Biochem. Biophys. Res. Commun. 3, 1078–1084.

McGuire, B.W., Orgebin-Crist, M.C., Chytil, F., 1981. Autoradiographic localization of serum retinol-binding protein in rat testis. Endocrinology 2, 658–667.

Monaco, H.L., Rizzi, M., Coda, A., 1995. Structure of a complex of two plasma proteins: transthyretin and retinol-binding protein. Science 268, 1039–1041.

Napoli, J.L., 1996. Biochemical pathways of retinoid transport, metabolism, and signal transduction. Clin. Immunol. Immunopathol. 80, S52–S62.

Napoli, J.L., Race, K.R., 1988. Biogenesis of retinoic acid from β-carotene. J. Biol. Chem. 263, 17372–17377.

Noske, U.M., Schmidt-Erfurth, U., Meyer, C., Diddens, H., 1998. Lipid metabolism in retinal pigment epithelium. Possible significance of lipoprotein receptors. Ophthalmologe 95, 814–819.

Olson, J.A., 1989. Provitamin A functions of carotenoids: the conversion of β-carotene into vitamin A. J. Nutr. 119, 105–108.

Ong, D.E., Davis, J.T., O'Day, W.T., Bok, D., 1994. Synthesis and secretion of retinol-binding protein and transthyretin by cultured retinal pigment epithelium. Biochemistry 7, 1835–1842.

Pfahl, M., Chytil, F., 1996. Regulation of metabolism by retinoic acid and its nuclear receptors. Annu. Rev. Nutr. 16, 257–283.

Pfeffer, B.A., Clark, V.M., Flannery, J.G., Bok, D., 1986. Membrane receptors for retinol-binding protein in cultured human retinal pigment epithelium. Invest. Ophthalmol. Vis. Sci. 7, 1031–1040.

Quadro, L., Blaner, W.S., Salchow, D.J., Vogel, S., Piantedosi, R., Gouras, P., Freeman, S., Cosma, M.P., Colantuoni, V., Gottesman, M.E., 1999. Impaired retinal function and vitamin A availability in mice lacking retinol-binding protein. Embo J. 17, 4633–4644.

Quadro, L., Blaner, W.S., Hamberger, L., Van Gelder, R.N., Vogel, S., Piantedosi, R., Gouras, P., Colantuoni, V., Gottesman, M.E., 2002. Muscle expression of human retinol-binding protein (RBP). Suppression of the visual defect of RBP knockout mice. J. Biol. Chem. 277, 30191–30197.

Ruiz, A., Winston, A., Lim, Y.H., Gilbert, B.A., Rando, R.R., Bok, D., 1999. Molecular and biochemical characterization of lecithin retinol acyltransferase. J. Biol. Chem. 6, 3834–3841.

Saari, J.C., 1999. Retinoids in mammalian vision. In: Nau, H., Blaner, W.S. (Eds.), The Handbook of Experimental Pharmacology. Retinoids. Springer Verlag Publishing, Heidelberg, pp. 563–588.

Shingleton, J.L., Skinner, M.K., Ong, D.E., 1989. Characteristics of retinol accumulation from serum retinol-binding protein by cultured Sertoli cells. Biochemistry 25, 9641–9647.

Smith, J.E., Milch, P.O., Muto, Y., Goodman, D.S., 1973. The plasma transport and metabolism of retinoic acid in the rat. Biochem. J. 132, 821–827.

Soprano, D.R., Blaner, W.S., 1994. Plasma retinol-binding protein. In: Sporn, M.B., Roberts, A.B., Goodman, D.S. (Eds.), The Retinoids, Biology, Chemistry and Medicine. Raven Press, New York, NY, pp. 257–282.

Vogel, S., Gamble, M.V., Blaner, W.S., 1999. Biosynthesis, absorption, metabolism and transport of retinoids. In: Nau, H., Blaner, W.S. (Eds.), Handbook of Experimental Pharmacology. Retinoids. Springer Verlag Publishing, Heidelberg, pp. 31–95.

Vogel, S., Piantedosi, R., O'Byrne, S.M., Kako, Y., Quadro, L., Gottesman, M.E., Goldberg, I.J., Blaner, W.S., 2002. Retinol-binding protein-deficient mice: biochemical basis for impaired vision. Biochemistry 41, 15360–15368.

Wald, G., 1968. The molecular basis of visual excitation. Nature 156, 800–807.

Wang, N., Anderson, R.E., 1993. Transport of 22:6n-3 in the plasma and uptake into retinal pigment epithelium and retina. Exp. Eye Res. 2, 225–233.

Zetterstrom, R.H., Simon, A., Giacobini, M.M., Eriksson, U., Olson, L., 1994. Localization of cellular retinoid-binding proteins suggests specific roles for retinoids in the adult central nervous system. Neuroscience 3, 899–918.

Zheng, W., Lu, Y.M., Lu, G.Y., Zhao, Q., Cheung, O., Blaner, W.S., 2001. Transthyretin, thyroxine, and retinol-binding protein in human cerebrospinal fluid: effect of lead exposure. Toxicol. Sci. 1, 107–114.

Zolfaghari, R., Ross, A.C., 2000. Lecithin: retinol acyltransferase from mouse and rat liver. cDNA cloning and liver-specific regulation by dietary vitamin A and retinoic acid. J. Lipid Res. 12, 2024–2034.