The visual process is a paramount example for the complex interactions of our body with the environment. It acquires most of the brain’s sensory input and strictly depends on a dietary chromophore. To establish and sustain vision, animals have evolved pathways by which dietary chromophore precursors such as vitamin A (all-trans-retinol (ROL)) and provitamin A such as vitamin A (all-trans-retinal (RRA)) are absorbed, transported, and metabolized. Knowledge about this metabolism has exponentially increased over the past decade. Genetic manipulation of animal models provided insights into the metabolic flow of these compounds through the body and in the eyes, unraveling their regulatory aspects and aberrant side reactions. The scheme that emerges reveals a common origin of key components for chromophore metabolism that have been adapted to the specific requirements of retinoid biology in different animal classes.

The third family member, RPE65 (retinal pigment epithelium 65-kDa protein), was the first animal CCE molecularly identified (15), but RPE65 was regarded for a long time as a retinoid-binding protein (16, 17). Mutations in RPE65 can cause Leber congenital amaurosis in humans (18). Analysis of mouse models revealed that this enzyme’s dysfunction disrupts chromophore synthesis and leads to the accumulation of retinyl esters (REs) in the retinal pigment epithelium (RPE) (19). It was later shown that RPE65 is the retinoid isomerase in the vertebrate visual cycle that catalyzes the conversion of all-trans-REs to 11-cis-retinol (20–22).

Monophyletic Origin of Carotenoid/Retinoid Metabolism

Carotenoids and their retinoid metabolites are isoprenoids that can undergo only a limited number of chemical transformations, and just a few of these occur naturally (Fig. 1A). The formal first step in chromophore metabolism is the conversion of the parent C₄₀ carotenoid precursor into a C₂₀ retinaldehyde by symmetric oxidative cleavage at C15/C15’ in the carbon backbone. Enzymatic oxidative cleavage of carotenoids at a specific position of the polyene chain has been proposed for all existing kingdoms of nature as a method for the synthesis of apocarotenoids, including retinoids. The first carotenoid-cleaving enzyme (CCE) was molecularly identified by analysis of a maize mutant deficient in the apocarotenoid abscisic acid (6). This breakthrough was followed by the molecular cloning and biochemical characterization of structurally related enzymes in different living kingdoms of nature (7).

Insect genomes encode only one and vertebrate genomes encode three distinct CCE family members. The β,β-carotene 15,15’-monooxygenase BCMO1 converts a limited number of provitamin A carotenoids such as β,β-carotene to retinaldehyde by symmetric oxidative cleavage at C15/C15’ (8). The role of BCMO1 as the key enzyme for retinoid production has been well established (9). The β,β-carotene 9,10-dioxygenase BCD02 catalyzes cleavage of carotenoids at the C9’/C10’ double bond (10) and displays broad substrate specificity (11–13). BCD02 can further metabolize its primary cleavage product by oxidative tailoring at C9/C10, indicating that the enzyme also plays a role in apocarotenoid metabolism (13). There also is a marked difference in the subcellular localization of the two vertebrate carotenoid oxygenases. BCMO1 is a cytoplasmic protein (8), whereas BCD02 localizes to mitochondria (13). Analysis of a knock-out mouse model for Bcdo2 demonstrated a critical role of the second CCE for carotenoid homeostasis in tissues (13, 14).

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The insect CCE, encoded by *ninaB* (neither inactivation or after potential gene B), catalyzes a combined oxidative cleavage at C15/C15’/H11032 and isomerization at C10/C11, yielding one molecule each of the *cis*- and *trans*-chromophores (23). Like RPE65 for vertebrates, NinaB is critical for insect vision (24, 25). Thus, both oxidative cleavage and *trans*-to-*cis* double bond conversion of carotenoids and retinoids are intrinsic catalytic activities of animal CCE family members (Fig. 1B).

The structural scaffold is well conserved between CCE family members of different kingdoms, the basic motif being a seven-bladed β-propeller (Fig. 1B) (26–28). The iron cofactor is coordinated by four conserved histidine residues and three second-shell glutamate residues and is accessible through a long non-polar tunnel. The essential role of ferrous iron for enzymatic catalysis was demonstrated for BCMO1 and RPE65 (29, 30). However, the precise mechanism of the isomerization and oxidative cleavage reaction remained unproven (31).

Upon oxidative cleavage, the aldehyde end group of all-trans-retinal (RAL) can undergo catalytic reduction/oxidation to form either ROL or RA. Comparative analysis of apocarotenoid metabolism revealed that these steps are catalyzed by related dehydrogenases in plants, fungi, and bacteria, and these are catalyzed by related enzymes. Step 1, oxidative cleavage of double bonds; steps 2 and 3, oxidation and reduction of oxygen end groups; step 4, introduction of oxygen into the ionone ring; step 5, esterification of hydroxyl groups; step 6, *trans*-to-*cis* isomerization of double bonds of the polyene chain (23). Like RPE65 for vertebrates, NinaB is critical for insect vision (24, 25). Thus, both oxidative cleavage and *trans*-to-*cis* double bond conversion of carotenoids and retinoids are intrinsic catalytic activities of animal CCE family members (Fig. 1B).

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The absorption and transport of carotenoids are evolutionarily well conserved in different kingdoms. Animals took advantage of this ancestral gene pool to evolve enzymes specific for chromophore metabolism.

**Absorption and Transport of Carotenoids**

In contrast to carotenogenic organisms, animals must acquire carotenoids from the diet. Initially, it was proposed that absorption of such lipids took place by passive non-ionic diffusion. However, increasing evidence indicates that this absorption is a protein-facilitated process (Fig. 2) (33). The protein dependence of carotenoid absorption was demonstrated by the chromatophore deficiency and blindness of the *Drosophila* mutant *ninaD* (34). The *ninaD* gene has been molecularly identified and encodes a cytoplasmic transmembrane protein expressed in the gut (35, 36). Carotenoids are then transported to neuronal and glial cells adjacent to the eyes. Uptake of circulating carotenoids by these cells is facilitated by the NinaD-related protein SANTA MARIA (36). Upon absorption by SANTA MARIA, carotenoids are metabolized by NinaB to yield the chromophore (supplemental Fig. S1).

Mutant analyses of the silk worm *Bombyx mori* identified molecular players in a pathway for tissue-specific accumulation of carotenoids in the silk gland. In this pathway, carotenoid absorption is mediated by a NinaD-related protein encoded by the Yellow Cocoon gene (37). For cellular accumulation, *Bom-
This regulation depends on the vitamin A status of the diet. When preformed vitamin A is present, Isx expression is induced, and both SR-BI and Bcmo1 expression are decreased. However, in the absence of dietary retinoids, the expression patterns of these genes are reversed (45). The molecular basis of this dietary responsiveness was found in the RAR-binding site in the Isx promoter (46). Thus, RA via RARs induces Isx expression and controls vitamin A production by negative feedback regulation.

**Mammals Possess Transport and Storage Systems Specific for Retinoids**

Insects absorb carotenoids intact, whereas vertebrates metabolize most of the absorbed provitamin A in enterocytes of the intestine. RAL is then converted into ROL and REs in a stepwise fashion (47). The resulting REs are packaged into chylomicrons that are secreted into the lymph (48). A smaller fraction of these circulating REs are taken up by peripheral tissue in a process that likely involves lipoprotein lipase (49). The remainder (~70%) are cleared by hepatocytes and hydrolyzed back to ROL (50), which is then transferred into hepatic stellate cells and esterified by lecithin:retinol acyltransferase (LRAT) for storage (supplemental Fig. S2) (51).

During fasting, ROL bound to the 21-kDa serum retinol-binding protein (RBP; hol-RBP) is the major retinoid found in the circulation. The liver expresses RBP, which is secreted from hepatocytes into the circulation in an ROL-dependent manner. Once in the blood, ROL-RBP forms a protein–protein complex with 55-kDa transthyretin (supplemental Fig. S2) (52). Transthyretin is required for normal blood ROL homeostasis and prevents excessive loss of the relatively small RBP molecule by glomerular filtration (52). RBP-deficient mice develop normally on retinoid-sufficient diets but suffer from visual chromophore deficiency early in life (53). Later in life, this deficiency is corrected when animals are kept on vitamin A-sufficient diets, demonstrating that, analogous to RA-dependent processes, other blood retinoid transport systems can substitute for RBP deficiency. Similarly, patients with RBP deficiency display only mild ocular defects (54).

A receptor for the hol-RBP complex has recently been identified as being encoded by the Stra6 (stimulated by retinoic acid 6) gene (55). Cell culture studies showed that ROL uptake via this transmembrane-spanning protein is driven by metabolic conversion of ROL to RE by LRAT. These studies also provided biochemical evidence that the STRA6-dependent flux of ROL between RBP and cells is bidirectional, indicating that STRA6 is a retinoid transporter (supplemental Fig. S2) (56, 57).

**Stra6 is expressed in several but not all retinoid-metabolizing tissues, including the eyes (55). Interestingly, the liver as the major organ for retinoid storage does not express STRA6, indicating that this receptor is required mainly for the delivery of ROL from the liver to peripheral tissues.**

A critical physiological role for STRA6 in retinoid metabolism is supported by genetic analyses in humans. Postulated loss-of-function mutations were found in individuals with Matthew-Wood syndrome, characterized by anophthalmia/microphthalmia in association with variable malformations of the heart, lungs, and diaphragm (58, 59). Similar developmental
Malformations can result from the maternal retinoid deficiency syndrome (60). Thus, it has been proposed that STRA6 is required for ROL uptake for subsequent RA production. However, the consequences of STRA6 deficiency are surprising because genetic disruption of its ligand RBP results only in a mild ocular defect (54). Furthermore, the RA-induced expression of \( \text{Stra6} \) is problematic if we would consider this transporter as being required for the production of this hormone in tissues. Thus, the role of STRA6 in retinoid homeostasis needs to be further defined.

**“Canonical” Visual Cycle**

Once absorbed by vertebrate eyes, ROL must be converted to the chromophore to establish and sustain vision. Individual steps in the canonical visual cycle have been delineated in biochemical detail, and the function of key enzymes has been confirmed in mouse models (Fig. 3). Mutations in genes encoding these proteins are associated with various blinding diseases in humans (supplemental Fig. S3) (3). In the disc membranes of rod outer segments (ROS), rhodopsin exists as an integral membrane protein, and the chromophore is covalently bound via a Schiff base linkage. Light induces a \( \text{cis} \)-to-\( \text{trans} \) isomerization of the protein-bound chromophore to initiate phototransduction (61). Hydrolysis of the Schiff base linkage by bulk water entering from the cytoplasmic side liberates the RAL photoproduct (62). Part of RAL is released into the disc lumen and must be transferred to the cytosol by ABCA4 (ATP-binding cassette transporter) (63). The first step in the visual cycle involves reduction of RAL to ROL catalyzed by retinol dehydrogenases (RDHs) (64, 65). Two enzymes, RDH8 in photoreceptor outer segments and RDH12 in photoreceptor inner segments, that belong to the short-chain dehydrogenase/reductase family and employ NADPH as a cofactor are mainly responsible for catalyzing this reaction in mouse photoreceptors (66). However, the redundancy of retinal reductase activity shown in mice suggests that photoreceptors contain additional functional RDHs besides RDH12 and RDH8 (67). This redundancy could be due to the need for a large enzymatic capacity to convert the chemically reactive aldehyde group of the photoproduct to the corresponding alcohol under bright light conditions. After bright light bleaching of rhodopsin, the photoproduct can exist in millimolar concentrations within cells. The aldehyde group of the photoproduct can form adducts with primary amino groups that exist in many cellular molecules, including lipids, proteins, and ribonucleotides. The natural occurrence of such an aberrant side reaction is documented by the presence of the bisretinoid A2E, formed by a condensation reaction of two molecules of RAL with the membrane lipid phosphatidylethanolamine. Ocular accumulation of A2E and A2E-mediated redox reactions have been implicated in the pathology of eye diseases such as age-related macular degeneration (68). The importance for rapid clearance of the photoproduct is also demonstrated by the consequences of mutations in \( \text{RDH12} \) and \( \text{ABCA4} \) in humans (69, 70). Mouse models with impaired retinal clearance have been established to characterize the underlying pathology.
(71). However, the mechanisms by which the photoproduction induces photoreceptor cell death remain controversial (72).

ROL formed in ROS is transported to the RPE, where it is esterified. This process is facilitated by two retinoid-binding proteins: interphotoreceptor retinoid-binding protein, which binds retinoids in the extracellular space, and CRBP1 (cellular retinol-binding protein-1), located within RPE cells (73, 74). The major ester synthase in RPE is LRAT (75, 76). The LRAT reaction constitutes an important intersection in ocular retinoid metabolism. This enzyme is required for the clearance of ROL from ROS and for the uptake of ROL from the blood. Because of their high hydrophobicity, all-trans-REs constitute a stable storage form of vitamin A within internal membranes and oil droplet-like structures called retinosomes (77). Additionally, all-trans-RE serves as a substrate for RPE65, which catalyzes the endothermic transformation of all-trans-retinoid to its 11-cis transformation. The product of this isomerization reaction is 11-cis-retinol, which is subsequently oxidized in the final catalytic step of the visual cycle to 11-cis-retinal. The enzymatic activities of short-chain dehydrogenases/reductases such as RDH5, RDH10, and RDH11 are mainly responsible for this reaction (78), but additional 11-cis-RDHs may participate within the RPE (67). Newly synthesized 11-cis-retinal is protected by binding to cellular retinaldehyde-binding protein (CRALBP), which mediates its transport back to photoreceptor ROS, where the chromophore couples to opsin, thereby completing the cycle (80). Disrupting the enzymatic steps of chromophore regeneration in the RPE, especially those involving LRAT and/or RPE65, has severe consequences for retinal health. The resulting chromophore deficiency causes slow progressive death of rods that is attributed to continuous activation of visual phototransduction by unliganded opsin (81). Moreover, disordered vectorial transport of cone visual pigments lacking bound chromophore leads to very rapid cone degeneration (82).

Alternative Visual Cycle for Cones?

Although outnumbered by more than 20:1 by rod photoreceptors, cone photoreceptors in the human eye mediate daylight vision and are critical for visual acuity and color discrimination (83). Cones operate under bright light that saturates rods, but rods still consume 11-cis-retinal. This scenario might require an additional cone-specific chromatophore regeneration pathway to avoid competition for 11-cis-retinal. Such competition has demonstrated in the eyes of R91W Rpe65 mutant mice, which produce only minute amounts of chromophore (84).

Older studies in lower vertebrates indicate that cone (but not rod) visual pigment regenerates in isolated neuronal retinas independent of the RPE (reviewed in Ref. (85), but recent work provides evidence that an intraretinal pathway for cone visual pigment regeneration also exists in mice and humans (86). Biochemical analysis of cone-dominant ground squirrels and chickens led to the identification of retinoid-metabolizing enzymes in the neuronal retina and the proposal of a cone-specific pathway (Fig. 3) (87). In this alternative cone-specific visual cycle, ROL released from cone outer segments is taken up by Müller cells, where, in contrast to the RPE, it is directly isomerized back to the 11-cis configuration and subsequently esterified to 11-cis-REs by acyl-CoA:retinol acyltransferase. 11-cis-REs can be mobilized by 11-cis-RE hydrolase to yield 11-cis-retinol, which then binds to CRALBP and is transported back to cone photoreceptors. Finally, NADP⁺/NADPH-dependent 11-cis-RDH activity found exclusively in cone photoreceptors expedites regeneration of visual chromophore from 11-cis-retinol (87). Studies of the cone-dominated retinas of zebrafish larvae provided in vivo evidence for this alternative cycle. Disruption of the function of RPE65, the canonical visual cycle isomerase, did not completely abolish chromophore regeneration and adversely affected rod rather than cone photoreceptor function (88). Additionally, genetic disruption of Müller glial cell-specific CRALBP did affect cone visual pigment regeneration in fish larvae (89).

In contrast, genetic disruption of RPE65 abolishes both cone and rod vision in mice. In Rpe65−/− mice, some residual light sensitivity has been attributed to rods (90) and is mediated by 9-cis-retinal and isorhodopsin (91). Furthermore, RPE65 is critical for chromophore production and vision in Nrl−/− mice, which possess a cone-only retina due to developmental defects (92). However, this dependence of chromophore production on RPE65 does not contradict an additional cone-specific pathway if we consider that ROL uptake in the eyes occurs via the RPE and is driven by esterification by LRAT (76). This all-trans-RE must be metabolized by RPE65 to the cis-chromophore as noted by the tremendous accumulation of REs in Rpe65−/− mice (19). This bottleneck would explain why both rods and cones are affected in RPE65 deficiency. Additionally, a previous study proposed that cone-specific RPE65 expression contributes to chromophore regeneration (93). The ultimate description of the alternative visual cycle requires identification of genes that encode proteins responsible for the key enzymatic steps.

Visual Cycle in Invertebrate Eyes

In contrast to vertebrates, retinoid production and function are restricted to the eyes in Drosophila (94). This feature is demonstrable by the absence of retinoids in the sine oculis mutant, which lacks compound eyes (Fig. 4A) (24). Genomewide microarray analysis of this mutant also revealed eye-enriched expression of genes that have homologs in the vertebrate visual cycle, including ninaB (Rpe65), pinta (CRALBP), and pigment-cell-enriched dehydrogenase (PDH; RDH12) (95). NinaB catalyzes the conversion of carotenoids such as zeaxanthin into 11-cis- and all-trans-3-hydroxyretinal in a 1:1 molar ratio (Fig. 4C) (24). The all-trans-3-hydroxyretinal cleavage product is then converted to the chromophore in a light-dependent pathway that lacks molecular description (96). As in vertebrates, a retinaldehyde-binding protein, encoded by the pinta gene, protects the newly synthesized chromophore. PINTA mutants display significantly reduced light sensitivity and evidence a strong reduction of rhodopsin levels (97). Because pinta flies can produce the chromophore, PINTA is likely required for transport of the chromophore from pigment cells to the photoreceptor cells to promote rhodopsin production (24).
Once bound to opsin, the chromophore can be regenerated by invertebrate photoreceptors after bleaching by absorption of another photon (5). Therefore, it was believed that invertebrate eyes do not employ enzymes for chromophore regeneration. Identification of an RDH12 homolog in insects and generation of the corresponding mutant provided evidence that a chromophore regeneration pathway also exists in the fly (98). In PDH mutants, de novo synthesis of the chromophore is not affected. However, illumination leads to a progressive loss of rhodopsin, which is accompanied by degeneration of photoreceptors. Biochemical evidence indicates that PDH catalyzes RAL to ROL conversion. Furthermore, retinal degeneration can be prevented by expressing human RDH12 in the PDH mutant (98).

Flies likely require this pathway to recycle RAL from internalized rhodopsin (98), and the pathway may also prevent RAL toxicity. Such toxicity has been demonstrated in sinaE flies, which lack the major opsin Rh1. Retinal degeneration in this mutant can be prevented by chromophore deficiency, indicating that, as in vertebrates, the aldehyde group of this compound can undergo aberrant side reactions (24). Furthermore, recycling of the chromophore allows adult flies to maintain normal rhodopsin levels when they are exposed to continuous dietary vitamin A deficiency (98). Thus, the pigment cells of the ommatidium, expressing PINTA and PDH, display an analogous function to the RPE in the vertebrate eyes by regenerating and supplying the photoreceptor cells with the chromophore (Fig. 4B).

**Conclusions**

There has been substantial progress in elucidating the metabolism of retinoids and carotenoids related to vision. These studies have revealed an intriguing evolutionary conservation of key components involved in chromophore production and recycling in animals. However, it is also evident that the same genes have adapted to the specific requirements of retinoid biology in invertebrates and vertebrates. Vertebrates have evolved a unique transport, uptake, and storage system for retinoids. Disruption of this system can cause a broad spectrum of pathologies ranging from mild ocular defects to fatal outcomes. The canonical visual cycle of the vertebrate eyes has been described in functional detail. Increasing evidence for an addi-
tional cone-specific pathway exists, but this cycle still lacks detailed molecular description. Although insects possess bistable visual pigments, a pathway for chromophore regeneration is still required, indicating that such pathways are intrinsic to vision. Studies in mouse models have helped to understand the pathogenesis of human blinding diseases caused by mutations of genes encoding key components of the canonical retinoid cycle. This knowledge can expedite the development of pharmacological therapies for the prevention and cure of such diseases (79). Only advances in knowledge about the basic chemistry of vision can guarantee that drug discovery and development will progress in parallel.

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