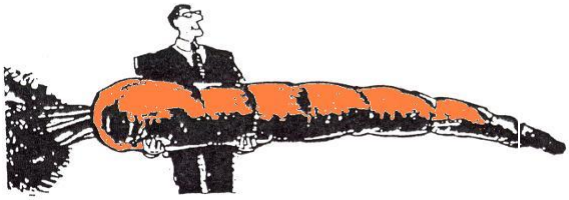


Carotenoid & Retinoid News

August 2016
Vol. 25, No. 2

From the editor:

"I am among those who think that science has great beauty. A scientist in his laboratory is not only a technician: he is also a child placed before natural phenomena which impress him like a fairy tale."
Maria Skłodowska-Curie
(1867-1934, physicist and chemist)

The famous Polish-French scientist Marie Curie never lost her fascination with nature and spent her life seeking to explain it and to use her knowledge for the benefit of humankind. Such attitude is an example for true scientists, not pursuing recognition and honors. These may come later, as in case of Marie Curie, who twice won the Nobel Prize. The satisfaction of a discovery is the best reward, and we may rejoice that there are constant new findings in our field of carotenoids and vitamin A research. Recently, electron microscopy revealed a structure of a protein in cell membrane that is responsible for the transport of vitamin A into the cell. Another interesting finding explains the bright red coloration of many birds. Apparently yellow dietary carotenoids are changed to red canthaxanthin by a special cytochrome P450 enzyme expressed locally in certain tissues (the skin and retina). The gene had probably originated about 250 million years ago, enabling color vision in archosaurs, since it is also present in turtles. The dinosaurs must have had it also, because they are closely related to birds. These and other recent discoveries are highlighted in this issue of our newsletter (News and Views section).

Maria S. Sapuntzakis (Chicago,IL)

CARIG Travel Awards

CARIG will award at least two monetary prizes, based on a poster competition to be held in conjunction with the CARIG Reception at Experimental Biology 2017 on Friday, April 21, 2017. Graduate students and postdoctoral trainees are eligible. Posters must address carotenoid and/or vitamin A research. For those assigned an oral presentation rather than a poster at EB'2017, printed copies of your slides with a print copy of your abstract and a small banner may be used for the CARIG poster competition. No advance registration is required to participate in the poster competition. Contact: Lisa Jahns (lisa.jahns@ars.usda.gov).

News from CARIG Steering and Advisory Committee

Several upcoming CARIG sponsored events will be held next spring at Experimental Biology 2017 in Chicago. The CARIG 2017 Conference will take place on April 21, Friday afternoon, before the Saturday opening of the ASN program. The tentative title of the 2017 Annual pre-EB Symposium is "Absorption, metabolism and health impact of dietary carotenoids" (proposed by Nancy Moran and John Erdman), and the Olson Lecturer is Heather Eliassen from Harvard School of Public Health, who will be speaking on carotenoids and breast cancer. We will have also a business meeting (5:30 pm) and a CARIG trainee poster and award session (6:30-8:30 pm) during the annual social following the CARIG Conference.

RIS Officers 2016-2017:

Chair– Lisa Jahns, USDA-ARS, North Dakota
Chair Elect - Elizabeth Johnson, Tufts University
Past Chair – Sherry Tanumihardjo, University of Wisconsin-Madison
Treasurer - Bryan Gannon, University of Wisconsin
The current membership of the Committee includes, in addition to the above mentioned RIS officers:
Jessica Campbell, General Mills
Helen Evert – Ohio State University
Mario Ferruzzi– Purdue University
Zeina E. Jouni - Kellogg Company
Klaus Kraemer – Task Force Sight and Life
Georg Lietz - Newcastle University
John Landrum - Florida International University (liaison to the International Carotenoid Society, ICS Secretary)
Lewis Rubin – Texas Tech University
Maria Stacewicz-Sapuntzakis (newsletter editor)

Postdoc representatives:
Jessica Copperstone - Ohio State University
Matthew Toomey – Washington University

Student representative: Kalina Hodges - Penn State University.

UPCOMING EVENTS

October 3-6, 2016
16th International Nutrition and Diagnostics Conference. Prague, Czech Republic.
Website: www.indc.cz

April 21, 2017
CARIG Annual Conference, Chicago, IL. Contact**:** Lisa Jahns, CARIG RIS Chair, **Email**: lisa.jahns@ars.usda.gov

April 22-26, 2017
Experimental Biology 2017, Chicago, IL. Contact: EB2017, FASEB Office of Scientific Meetings & Conferences, 950 Rockville Pike, Bethesda, MD 20814-3998, **e-mail:** eb@faseb.org, **website:** www.experimentalbiology.org

June 21-23, 2017
Oxygen Club of California 2017 World Congress, Berlin, Germany. Metabolic Stress and Redox Regulation. **Website**: www.occ-2017.com

July 9-14, 2017
18th International Symposium on Carotenoids. Lucerne, Switzerland. www.icslucerne2017.org

FORTHCOMING / RECENT PUBLICATIONS

SIGHT AND LIFE Magazine 30 (1) 2016. PO Box 2116, 4002 Basel, Switzerland, **tel:** 41-61-815-8756, **website:** www.sightandlife.org

Current capabilities and limitations of stable isotope techniques and applied mathematical equations in determining whole-body Vitamin A status, Lietz G, Furr HC, Gannon BM, et al. *Food Nutr Bull* 37:S87-S103, 2016.

Biomarkers of Nutrition for Development (BOND) – Vitamin A review. Tanumihardjo SA, Russell RM, Stephensen CB, et al. *J Nutr 146:1816S-48S,* 2016.

Carotenoids in staple cereals: metabolism, regulation and genetic manipulation. Xia X, He Z. *Front Plant Sci*, *August 2016, vol 7, doi: 10.3389/fpls.2016.01197*

Astaxanthin-producing green microalga *Haematococcus pluvialis*: from single cell to high value carotenoid products. Shah MMR, Liang Y, Cheng JJ, Daroch M. *Front Plant Sci, April 2016, vol 7, doi: 10.3389/fpls.2016.00531*

Carotenoids assist in cyanobacterial Photosystem II assembly and function. Zakar T, Laczko-Dobos H, Toth TN, Gombos Z. *Front Plant Sci, March 2016, vol 7, doi: 10.3389/fpls.2016.00295*

Lutein, zeaxanthin and meso-zeaxanthin supplementation associated with macular pigment optical density. Ma L, Liu R, Du JH, Liu XH. *Nutrients July 2016, vol 8 (7):426, doi: 10.3390/nu8070426* (a metaanalysis)

Industrial Biotechnology of Vitamins, Biopigments and Antioxidants. Eds. EJ Vandamme JL Revuelta. Wiley & Sons, Ltd. 2016. See especially: Ch.9, pp 229-64, Synthesis of β-carotene and other important carotenoids with bacteria. Albermann C, Beuttler H.
Ch.10, pp 265-86, β-Carotene and other carotenoids from microalgae. Grama BS, Delhaye A, Agathos SN, Jeffryes C.

Alphabetical Listing of Recent Publications may be found at www.carotenoidsociety.org/articles-books-and-databases**.** It is prepared by Dr. Harold Furr, Department of Nutritional Sciences, University of Wisconsin, Madison.

MEETING REPORTS

CARIG Conference at EB 2016

This year's symposium focused on "Inflammation Effects on Carotenoids and Retinoids" and covered a wide spectrum of disciplines, including epidemiology, mechanisms of action, fundamental, foundational and clinical research. The symposium opened with the James A. Olson Memorial Lecture given by Lewis Rubin (Texas Tech University Health Sciences Center). Other featured CARIG symposium presenters included Charles Stephensen (USDA Western Human Nutrition Research Center), Catherine Ross (Pennsylvania State University), Sherry Tanumihardjo (University of Wisconsin-Madison, and Torsten Bohn (Luxembourg Institute of Health).
Experimental Biology poster award winners:
Emily S. Mohn, Tufts University
Stephanie Mondloch, University of WI- Madison
Joshua Smith, University of Illinois-Urbana/Champagne.

Gordon Research Conference on Carotenoids

GRC on Carotenoids took place in Lucca (Barga), Tuscany region of Italy, on May 22- 27, 2016.
The GRC was attended by ~110 participants representing 15 countries from Asia, Australia, Europe, the Middle East and North and South America. Topics of discussion included the most

recent research in pathway engineering, biosynthesis, health and disease, provitamin A bioconversion regulation, and apocarotenoid metabolism and function. The venue for the next GRC is yet to be decided.

Gordon Research Conference award winners:

Rachel Kopec, French National Institute for Agricultural Research

Oussama Alrazem from the Universad de Castilla-La Mancha (Spain).

TECHNICAL NOTE

HPLC-MS/MS method for the separation of α-retinyl esters from retinyl esters

Enzymatic cleavage of the nonsymmetric provitamin A carotenoid α-carotene results in one molecule of retinal (vitamin A), and one molecule of α-retinal, a biologically inactive analog of true vitamin A. Due to structural similarities, α-retinyl esters and vitamin A esters typically coelute, resulting in the overestimation of vitamin A originating from α-carotene. Herein, we present a set of tools to identify and separate α-retinol products from vitamin A.

α-Retinyl palmitate (α-RP) standard was synthesized from α-ionone following a Wittig-Horner approach. A HPLC-MS/MS method employing a C30 column was then developed to separate the species. Authentic standards of retinyl esters and the synthesized α-RP confirmed respective identities, while other α-retinyl esters (i.e. myristate, linoleate, oleate, and stearate) were evidenced by their pseudomolecular ions observed in electrospray ionization (ESI) mode, fragmentation, and elution order. For quantitation, an atmospheric pressure chemical ionization (APCI) source operated in positive ion mode was used, and retinol, the predominant in-source parent ion was selected and fragmented. The application of this method to a chylomicron-rich fraction of human plasma is demonstrated. This method can be used to better determine the quantity of vitamin A derived from foods containing α-carotene.

Goetz HJ et al. J Chromatogr B June 2016
doi: 10.1016/j.jchromb.2016.06.043

NEWS AND VIEWS

^{13}C natural abundance in serum retinol is a novel biomarker for evaluating provitamin A carotenoid-biofortified maize consumption

Crops such as maize, sorghum, and millet are being biofortified with provitamin A carotenoids to ensure adequate vitamin A (VA) intakes. VA assessment can be challenging because serum retinol concentrations are homeostatically controlled and more sensitive techniques are resource-intensive. We investigated changes in serum retinol relative differences of isotope amount ratios of $^{13}C/^{12}C$ ($\delta^{13}C$), caused by natural ^{13}C fractionation in C_3 compared with C_4 plants, as a biomarker to detect provitamin A efficacy from biofortified (orange) maize and high-carotene carrots. The design was a 2 × 2 × 2 maize (orange compared with white) by carrot (orange compared with white) by a VA fortificant (VA+ compared with VA−) in weanling male Mongolian gerbils (n = 55), which included a 14-d VA depletion period and a 62-d treatment period (1 baseline and 8 treatment groups; n = 5−7 per group). Liver VA and serum retinol were quantified, purified by HPLC, and analyzed by GC combustion isotope ratio mass spectrometry for ^{13}C. Treatments affected liver VA concentrations (0.048 ± 0.039 to 0.79 ± 0.24 μmol/g; P<0.0001) but not overall serum retinol concentrations (1.38 ± 0.22 μmol/L). Serum retinol and liver VA $\delta^{13}C$ were significantly correlated (R^2 = 0.92; P<0.0001). Serum retinol $\delta^{13}C$ differentiated control groups that consumed white maize and white carrots (−27.1 ± 1.2 $\delta^{13}C$‰) from treated groups that consumed orange maize and white carrots (−21.6 ± 1.4 $\delta^{13}C$‰ P<0.0001) and white maize and orange carrots (−30.6 ± 0.7 $\delta^{13}C$‰ P<0.0001). A prediction model demonstrated the relative contribution of orange maize to total dietary VA for groups that consumed VA from mixed sources. Provitamin A efficacy and quantitative estimation of the relative contribution to dietary VA were demonstrated with the use of serum retinol $\delta^{13}C$. This method could be used for maize efficacy or effectiveness studies and with other C_4 crops biofortified with provitamin A carotenoids (e.g., millet, sorghum). Advantages include no extrinsic tracer dose, one blood sample, and higher sensitivity than serum retinol concentrations alone.

Gannon BM, et al. J Nutr 146:1290-97 (2016)

Dietary β-carotene and lutein metabolism is modulated by the APOE genotype

The human apolipoprotein E (APOE) genotype has been suggested to interact with nutrient metabolism, particularly with lipid soluble vitamins. Plasma carotenoid levels are determined by numerous dietary and genetic factors with high inter-individual variation; however, the APOE genotype has not been systematically examined so far. Our aim was to investigate the effect of the APOE genotype on dietary carotenoid metabolism with special regard to transcriptional regulation of carotenoid absorption, cleavage and adipocyte fat storage. We supplemented targeted replacement mice expressing human APOE3 and APOE4 isoforms with dietary β-carotene (BC) and lutein (LUT) for 8 weeks. Plasma BC and adipose tissue BC and LUT levels were in trend lower in APOE4 than APOE3 mice, while

hepatic expression of the β-carotene oxygenases BCO1 and BCO2 was significantly higher. In contrast to the liver, mRNA levels of proteins involved in carotenoid absorption and cleavage in the small intestinal mucosa, as well as of adipogenic markers in the adipose tissue, were not different between APOE3 and APOE4 mice. Our data suggest that the hepatic carotenoid cleavage activity is higher in APOE4 mice, partially reducing the circulation and extra-hepatic accumulation of intact carotenoids as compared to APOE3. Therefore we suggest considering the APOE genotype as modulator of carotenoid status in the future.

Huebbe P et al. BioFactors · April 2016
doi: 10.1002/biof.1284

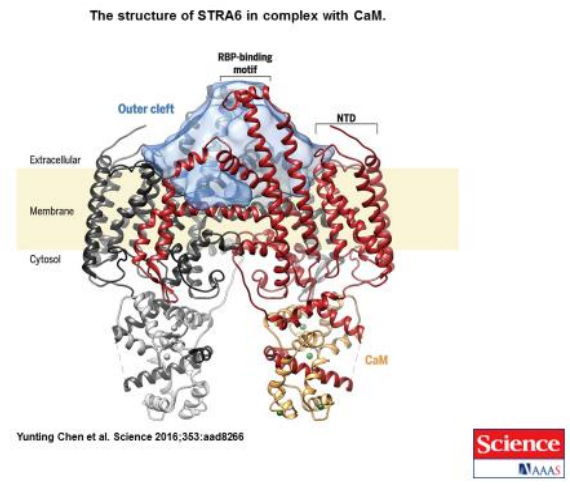
Substrate specificity of purified recombinant chicken β-carotene 9′,10′-Oxygenase (BCO2)

Provitamin A carotenoids are oxidatively cleaved by β-carotene 15-15'-dioxygenase (BCO1) at the central 15-15' double bond to form retinal (vitamin A aldehyde). Another carotenoid oxygenase, β-carotene 9'-10'-oxygenase (BCO2) catalyzes the oxidative cleavage of carotenoids at the 9'-10' bond to yield ionone and apo-10'-carotenoid. Previously published substrate specificity studies of BCO2 have been conducted using crude lysates from bacteria or insect cells expressing recombinant BCO2. Our attempts to obtain active recombinant human BCO2 expressed in *Escherichia coli* were unsuccessful. We have expressed recombinant chicken BCO2 in the strain *E.coli* BL21-Gold (DE3) and purified the enzyme by cobalt ion affinity chromatography. Like BCO1, purified recombinant chicken BCO2 reacts with the provitamin A carotenoids β-carotene, α-carotene, and β-cryptoxanthin. Its catalytic activity with β-carotene as substrate is at least 10-fold lower than that of BCO1. In further contrast to BCO1, purified recombinant chicken BCO2 also reacts with 9-cis-β-carotene and the non-provitamin A carotenoids zeaxanthin and lutein, and does not react with all-trans-lycopene and β-apocarotenoids. Apo-10'carotenoids were detected as enzymatic products by HPLC, and the identities were confirmed by LC-MS. Small amounts of 3-hydroxy-β-apo-8'-carotenal were also consistently detected in BCO2-β-cryptoxanthin reaction mixtures. With the exception of this activity with β-cryptoxanthin, BCO2 cleaves specifically at the 9'-10' bond to produce apo-10'-carotenoids. BCO2 has been shown to function in preventing the excessive accumulation of carotenoids, and its broad substrate specificity is consistent with this.

dela Sena C et al. J Biol Chem 291(28) 2016
doi: 10.1074/jbc.M116.723684

Structure of the STRA6 receptor for retinol uptake

Vitamin A homeostasis is critical to normal cellular function. Retinol-binding protein (RBP) is the sole specific carrier in the bloodstream for hydrophobic retinol, the main form in which vitamin A is transported. The integral membrane receptor STRA6 mediates cellular uptake of vitamin A by recognizing RBP-retinol to trigger release and internalization of retinol. We present the structure of zebrafish STRA6 determined to 3.9-angstrom resolution by single-particle cryo-electron microscopy. STRA6 has one intramembrane and nine transmembrane helices in an intricate dimeric assembly. Unexpectedly, calmodulin (CaM) is bound tightly to STRA6 in a noncanonical arrangement. Residues involved with RBP binding create an archlike structure that covers a deep lipophilic cleft. This cleft is open to the membrane, suggesting a possible mode for internalization of retinol through direct diffusion into the lipid bilayer.



The STRA6 dimer, drawn as a ribbon representation with one protomer in dark red and the other in black, is associated with two molecules of calmodulin, drawn in gray and gold. The internal volume of the outer cleft is represented as a semitransparent blue surface. Calcium ions are represented as green dots.

Chen Y et al. Science 353(6302) Aug 2016
doi: 10.1126/science.aad8266

Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression

There is limited evidence that supports etiologically distinct molecular subtypes of prostate cancer, the identification of which may improve prevention. Given their antioxidant properties, we hypothesized that lycopene and tomato sauce may be especially protective against diseases harboring the common gene fusion transmembrane protease, serine 2

(*TMPRSS2*):v-ets avian erythroblastosis virus E26 oncogene homolog (*ERG*). We aimed to examine associations between estimated lycopene and tomato sauce intake and the risk of prostate cancer defined by ERG protein expression subtype. Our study population consisted of a prospective cohort of 46,719 men from the Health Professionals Follow-Up Study. *TMPRSS2:ERG* was assessed by ERG immunohistochemistry on tumor tissue microarrays constructed from radical prostatectomy specimens. We used multivariable competing risk models to calculate HRs and 95% CIs for the risk of ERG-positive and, separately, ERG-negative disease. We implemented inverse probability weighting to account for evaluating ERG status only in surgically treated cases. During 23 y of follow-up, 5543 men were diagnosed with prostate cancer, among whom 884 were assayed for ERG (426 ERG-positive). With inclusion of only the latter cases, increasing cumulative average tomato sauce intake was associated with a decreased risk of prostate cancer overall (≥2 servings/week compared with <1 serving/month; multivariable HR: 0.70; 95% CI: 0.52, 0.95; *P*-trend = 0.002). With respect to molecular subtypes, cumulative average tomato sauce intake was associated with a decreased risk of ERG-positive disease (HR: 0.54; 95% CI: 0.37, 0.81; *P*-trend = 0.004) but not with ERG-negative disease (HR: 0.96; 95% CI: 0.62, 1.50; *P*-trend = 0.10; *P*-heterogeneity = 0.04). Increasing quintiles of lycopene intake were associated with a decreased risk of both subtypes (*P*-heterogeneity = 0.79). Inverse probability weighting did not materially change the results. Our results lend some support to the hypothesis that prostate cancers that harbor *TMPRSS2:ERG* may be etiologically distinct from fusion-negative cancers. In particular, tomato sauce consumption may play a role in reducing *TMPRSS2:ERG*-positive disease.

Graff RE et al. Am J Clin Nutr 103: 851-860 (2016)

Lutein and its binding protein in human brain tissue

Lutein selectively accumulates in human retina and brain. While many epidemiological studies show evidence of a relationship between lutein status and cognitive health, lutein's selective uptake in human brain tissue and its potential function in early neural development and in cognitive health have been poorly evaluated at a molecular level. The objective of this study was to evaluate the cross-sectional relationship between concentrations of brain lutein and StARD3 (identified as its binding protein in retinal tissue) among three age groups: infants (1-4 months, n = 10) older adults (55-86 years, n = 80), and centenarians (98-105 years, n = 10). Brain lutein concentrations were determined by HPLC, and StARD3 levels were analyzed by Western Blot analysis. The strong relationship in infant brains ($r = 75$, $P<0.001$) suggests that lutein has a role in neural development. The relationship remained significant but weaker in older adults ($r = 0.51$, $P<0.05$), and was insignificant in centenarians ($r = 0.08$, $P>0.05$), seven of whom had mild cognitive impairment or dementia. These exploratory findings suggest an age-related decrease or abnormality of StARD3 activity in human brain. Given that StARD3 is also involved in cholesterol transport, a process that is aberrant in neurodegenerative diseases, the potential protective function of lutein against these diseases remains to be explored.

Tanprasertsuk J et al. PLOS One (2016)
doi:10.1371/journal.pone.0155488

Association between leukocyte telomere length and serum carotenoids in US adults

Telomere length is a biomarker for aging. It is known that oxidative stress can accelerate telomere shortening, whereas antioxidants can delay their shortening. Carotenoids as antioxidants are favorably associated with health- and aging-related diseases caused by oxidative stress, but their association with telomere length is less certain. We investigated the association between blood carotenoid levels and leukocyte telomere length in a representative sample of US adults. We analyzed 3660 participants aged 20 years and older in the 1999–2002 National Health and Nutrition Examination Survey. The levels of carotenoids [α-carotene, β-carotene (*trans* + *cis*), β-cryptoxanthin, combined lutein/zeaxanthin, and *trans*-lycopene] were measured using HPLC. The leukocyte telomere length (*T*/*S* ratio) was assayed using the quantitative polymerase chain reaction method. A doubling of blood α-carotene, β-carotene (*trans* + *cis*), and β-cryptoxanthin was associated with approximately 2% longer telomeres. Compared with the lowest carotenoid quartile of α-carotene, β-carotene (*trans* + *cis*), and β-cryptoxanthin, telomere length for adults in the highest quartiles was significantly increased by 5–8%. We found that increasing levels of blood carotenoid were significantly associated with longer leukocyte telomeres in US adults. High intake of carotenoid-rich food may play a role in protecting telomeres and regulating telomere length.

Min KB, Min JY. Eur J Nutr 2016
doi: 10.1007/s00394-016-1152-x

Genetic Basis for Red Coloration in Birds

The yellow and red feather pigmentation of many bird species plays pivotal roles in social signaling and mate choice. To produce red pigments, birds ingest yellow carotenoids and endogenously convert them into red ketocarotenoids via an oxidation reaction catalyzed by a previously unknown ketolase. We investigated the genetic basis for red coloration in birds using whole-genome sequencing of red siskins (*Spinus cucullata*), common canaries (*Serinus canaria*), and "red factor" canaries, which are the hybrid product of crossing red siskins with common canaries. We identified two genomic regions introgressed from red siskins into red factor canaries that are required for red coloration. One of these regions contains a gene encoding a cytochrome P450 enzyme, *CYP2J19*. Transcriptome analysis demonstrates that *CYP2J19* is significantly upregulated in the skin and liver of red factor canaries, strongly implicating *CYP2J19* as the ketolase that mediates red coloration in birds. Interestingly, a second introgressed region required for red feathers resides within the epidermal differentiation complex, a cluster of genes involved in development of the integument. Lastly, we present evidence that *CYP2J19* is involved in ketocarotenoid formation in the retina. The discovery of the carotenoid ketolase has important implications for understanding sensory function and signaling mediated by carotenoid pigmentation.

Lopes RJ et al. Curr Biol 26:1427–34 (2016)

Bright-red colors in vertebrates are commonly involved in sexual, social, and interspecific signaling and are largely produced by ketocarotenoid pigments. In land birds, ketocarotenoids such as astaxanthin are usually metabolically derived via ketolation of dietary yellow carotenoids. However, the molecular basis of this gene-environment mechanism has remained obscure. Here we use the *yellowbeak* mutation in the zebra finch (*Taeniopygia guttata*) to investigate the genetic basis of red coloration. Wild-type ketocarotenoids were absent in the beak and tarsus of *yellowbeak* birds. The *yellowbeak* mutation mapped to chromosome 8, close to a cluster of cytochrome P450 loci (*CYP2J2*-like) that are candidates for carotenoid ketolases. The wild-type zebra finch genome was found to have three intact genes in this cluster: *CYP2J19A*, *CYP2J19B*, and *CYP2J40*. In *yellowbeak*, there are multiple mutations: loss of a complete *CYP2J19* gene, a modified remaining *CYP2J19* gene (*CYP2J19*^{yb}), and a non-synonymous SNP in *CYP2J40*. In wild-type birds, *CYP2J19* loci are expressed in ketocarotenoid-containing tissues: *CYP2J19A* only in the retina and *CYP2J19B* in the beak and tarsus and to a variable extent in the retina. In contrast, expression of *CYP2J19*^{yb} is barely detectable in the beak of *yellowbeak* birds. *CYP2J40* has broad tissue expression and shows no differences between wild-type and *yellowbeak*. Our results indicate that *CYP2J19* genes are strong candidates for the carotenoid ketolase and imply that ketolation occurs in the integument in zebra finches. Since cytochrome P450 enzymes include key detoxification enzymes, our results raise the intriguing possibility that red coloration may be an honest signal of detoxification ability.

Mundy NI et al. Curr Biol 26:1435–40 (2016)

Avian ketocarotenoid pigments occur in both the red retinal oil droplets that contribute to color vision and bright red coloration used in signaling. Turtles are the only other tetrapods with red retinal oil droplets, and some also display red carotenoid-based coloration. Recently, the *CYP2J19* gene was strongly implicated in ketocarotenoid synthesis in birds. Here, we investigate *CYP2J19* evolution in relation to color vision and red coloration in reptiles using genomic and expression data. We show that turtles, but not crocodiles or lepidosaurs, possess a *CYP2J19* orthologue, which arose via gene duplication before turtles and archosaurs split, and which is strongly and specifically expressed in the ketocarotenoid-containing retina and red integument. We infer that *CYP2J19* initially functioned in color vision in archelosaurs and conclude that red ketocarotenoid-based coloration evolved independently in birds and turtles via gene regulatory changes of *CYP2J19*. Our results suggest that red oil droplets contributed to color vision in dinosaurs and pterosaurs.

Twyman H et al. Proc Royal Soc B, Aug 2016
doi: 10.1098/rspb.2016.1208

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