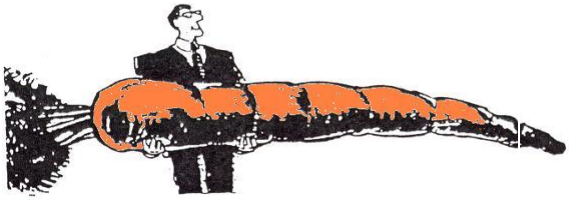

Carotenoid & Retinoid News

August 2017
Vol. 26, No. 2

"Nature itself is the best physician."
Hippocrates, Greek physician (460-370 BCE)

Medicine has made enormous progress since the time of Hippocrates, especially in the last century, but the more we know about human physiology the more appropriate seems his old maxim. Carotenoid researchers are especially aware of the role of these natural pigments in maintaining our health and preventing chronic disease. Recently, there was an abundance of research studies on macular pigments (lutein, zeaxanthin and meso-zeaxanthin) that can be measured by a noninvasive procedure (macular pigment optical density – MPOD) and are related to the concentrations of these pigments in the brain. Children with high MPOD tend to perform better in a challenging cognitive task as indicated by neuroelectric methods and on standardized academic tests. Supplementation with lutein and zeaxanthin was even found to decrease anxiety, serum cortisol and psychological stress scores in young adults (18-25 y old). In another study, macular pigments (24 mg/day) improved sleep quality, headache frequency, eye fatigue and strain in young adults self-exposed to LED screens for at least 6 hr/day. Healthy mature adults (25-45 y old) with higher MPOD exhibited enhanced neurocognition, while in older adults (65-75 y old) so-called crystallized intelligence and brain gray matter volume was positively associated with serum lutein. Lutein and zeaxanthin, dietary carotenoids obtained from green vegetables, yellow corn and eggs, may protect our vision from both sunlight and artificial glow of LED screens, preventing or delaying the onset and progression of macular degeneration in the old age. Therefore, adherence to Mediterranean diet, enriched by vegetables and fruits from the New World, is still our best insurance for a long and happy life, as advised by Hippocrates.

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 2018 on Friday, April 20, 2018. 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'2018, 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: Elizabeth Johnson (Elizabeth.Johnson@tufts.edu).

News from CARIG Steering Committee

In June 2017 CARIG RIS held election by electronic ballot for leadership positions and for new members of its Steering Committee. Current RIS Chair will serve through July 2018 and Chair-Elect will begin her stewardship at that time.

RIS Officers 2017-2018:
Chair – Elizabeth Johnson, Tufts University
Chair Elect – Nancy Moran, USDA/ARS Children Nutrition Research Center at Baylor College of Medicine
Past Chair – Lisa Jahns, USDA-ARS, North Dakota
Secretary – Jessica Copperstone, Ohio State University
Treasurer - Bryan Gannon, University of Wisconsin
Postdoc representatives:
Emily Mohn - Tufts University
Matthew Toomey – Washington University
Student representatives:
Darwin Ortiz-Osorio – Purdue University
Jirayu Tanprasertsuk – Tufts University
The current membership of the Committee includes, in addition to the above mentioned RIS officers:
Jessica Campbell, General Mills
Neal Craft – Craft Technologies Inc.
Helen Everts – Ohio State 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)
Sherry Tanumihardjo, University of Wisconsin-Madison
Wendy White – Iowa State University

Registration for CARIG RIS

Many of ICS members are also participants in the Carotenoid and Retinoid Interactive Research Group (CARIG) RIS associated with the American Society of Nutrition. If you happen to attend Experimental Biology meetings and the CARIG meeting and are also a member of ASN, it is important that you log onto your ASN profile and select membership in the CARIG RIS. We receive benefits from ASN including the opportunity to schedule space during the EB meeting for the CARIG meeting, so it is extremely important for members to identify their participation in the CARIG RIS. Apparently, membership in the RIS has declined because members did not update profiles during their renewal process.

UPCOMING EVENTS

October 9-12, 2017
17th International Nutrition & Diagnostics Conference, Prague, Czech Republic. Website: www.indc.cz

October 16-17, 2017
Production of Carotenoids Workshop – from Biosynthesis to Biotechnology, Trogir, Croatia. Contact COST Action EUROCAROTEN https://www.eurocaroten.eu/?q=node/110

April 20, 2018
CARIG Annual Conference, San Diego, CA. Contact**:** Elizabeth Johnson, CARIG RIS Chair, **Email**: Elizabeth.Johnson@tufts.edu

April 21-25, 2018
Experimental Biology 2018, San Diego, CA. Contact: EB2018, FASEB Office of Scientific Meetings & Conferences, 950 Rockville Pike, Bethesda, MD 20814-3998, **e-mail:** eb@faseb.org, **website:** www.experimentalbiology.org

June 10-15, 2018
4th International FASEB Conference on Retinoids. Steamboat Springs, CO. Website: www.faseb.org/SRC

June 16-22, 2018
Gordon Research Conference & Seminar on Carotenoids, Newry, ME. Website: www.grc.org

July 11-13, 2018
Brain and Ocular Nutrition 2018, Cambridge, UK. Website: www.bonconference.org

FORTHCOMING / RECENT PUBLICATIONS

SIGHT AND LIFE Magazine 31 (1) 2017. PO Box 2116, 4002 Basel, Switzerland, **tel:** 41-61-815-8756, **website:** www.sightandlife.org

Canthaxanthin: from molecule to function. Esatbeyoglu T, Rimbach G. *Mol Nutr Food Res 61, 2017, doi: 10.1002/mnfr.201600469*

Host-related factors explaining interindividual variability of carotenoid bioavailabiliy and tissue concentrations in humans. A review. Bohn T, Desmarchelier C, Dragsted O, et al. *Mol Nutr Food Res 61, 2017, doi: 10.1002/mnfr.201600685*

Lutein – the less explored carotenoid. Hirdyani H, Sheth M. *World J Pharm Res 6:528-53, 2017.*

Should we restrict vitamin A Intake, a minor contributor to plasma retinol turnover, when using retinol isotope dilution equations to estimate an individual's vitamin A status, or should vitamin A balance be maintained? Ford JL, Balmer Green J, Green MH. *J Nutr 147:1483-86, 2017.*

Metabolic effects of inflammation on vitamin A and carotenoids in humans and animal models. Rubin LP, Ross AC, CB, et al. *Adv Nutr 8:197-212, 2017*

A simple plasma retinol isotope ratio method for estimating β-carotene relative bioefficacy in humans: Validation with the use of model-based compartmental analysis. Ford JL, Balmer Green J, Lietz G, et al. *J Nutr 147 (9) 2017.* [forthcoming]

MEETING REPORTS

ASN CARIG Annual Symposium at Experimental Biology 2017

This year Symposium was aimed at summarizing the research to date on the absorption, digestion, metabolism and excretion of the dietary carotenoids ("Moving towards personalized nutrition of dietary carotenoids: a review of the genetic and non-genetic factors impacting absorption, metabolism and health impacts"). The symposium opened with the James A. Olson Memorial Lecture given by A. Heather Eliassen, from Harvard School of Public Health ("New epidemiological evidence on the relationship between carotenoids and breast cancer risk"). Factors impacting carotenes and xanthophylls were presented by Nancy Moran and Elizabeth Johnson, respectively. John Erdman discussed health aspects

of carotenoids, with a focus on lycopene. The CARIG poster competition for graduate students and post doctorate fellows had three 1st place winners: Boluwatiwi Olalekan Durojaye (Ohio State University), Chelsee T.L. Smuut Holloway (Rutgers University) and Darwin Ortiz-Osorio (Purdue University).

The Emerging Leaders in Nutrition Competition is intended to highlight the very best research submitted by students and young investigators to ASN's Scientific Sessions at the Experimental Biology meetings. Bryan Gannon (Cornell University), Emily Mohn (Tufts University), Rachel Chiaverelli (Tufts University), Sookyoung Jeon (University of Illinois) and Yan Yuan (Ohio State University) were recognized as the Emerging Leaders.

The 18th International Carotenoids Symposium

The 18th International Carotenoids Symposium in Lucerne, Switzerland (July 9-14, 2017) offered a variety of plenary talks and sessions ranging from nutrition and health, to photochemistry and metabolism. Over 80 excellent talks were provided along an attractive program of 14 sessions and there was plenty of time to meet, network, view and discuss posters. Nearly 300 individuals involved in carotenoid research participated in this event. A highlight of the last day was a talk presented by George Britton on the history of carotenoids. Synnove Liaaen-Jensen was also acknowledged on this last day for her many years of contributions to the carotenoid field. New to the International Carotenoid Society was the distinction of "Fellow of the International Carotenoid Society" in recognition of members whose consistent contributions to the Society, the scientific community, and the general public demonstrate a commitment to excellence, leadership, and sound scientific ethics. This honor along with special medallions was presented to 52 distinguished ICS members. A video of pictures from the Symposium can be found at: www.icslucerne2017.org/home.html

TECHNICAL NOTES

Thermal and ultraviolet–visible light stability kinetics of co-nanoencapsulated carotenoids

Lipid-core nanocapsules loaded with β-carotene and α-carotene, and lutein (NCs) were produced with monomodal particle size distribution. Their mean diameter was 151.33 ± 5.03 nm (D4,3) and 180.30 ± 0.70 nm (z-average), zeta potential was −22.63 ± 0.52 mV, and pH was 3.21 ± 0.04. The stability of NCs was studied under different simulated industrial treatments, such as thermal and ultraviolet (UV)-visible light treatment. Regardless of the temperature and incubation time of the samples, higher carotenoids retention (%) was observed in NCs than ethanol extract (EE) under UV-visible light treatment, and under thermal treatment. In addition, NCs when exposed to UV-visible light treatment had higher activation energy and lower constant rate (k) than EE. In conclusion, nanoencapsulation offers greater stability to the β-carotene, α-carotene, and lutein upon exposure to conditions similar to those used in the food processing (heat) and storage (UV-visible light).

da *Silva MM et al.*
Food Bioproducts Processing 105:86-94 (2017)

Synthesis of apo-13- and apo-15-lycopenoids, cleavage products of lycopene that are retinoic acid antagonists

Consumption of the tomato carotenoid, lycopene, has been associated with favorable health benefits. Some of lycopene biological activity may be due to metabolites resulting from cleavage of the lycopene molecule. Because of their structural similarity to the retinoic acid receptor antagonist β-apo-13-carotenone, the first half putative oxidative cleavage products of the symmetrical lycopene have been synthesized. All transformations proceed in moderate to good yield and some with high stereochemical integrity allowing ready access to these otherwise difficult to obtain terpenoids. In particular, the methods described allow ready access to the *trans* isomers of citral (geranial) and pseudoionone, important flavor and fragrance compounds that are not readily available isomerically pure and are building blocks for many of the longer apolycopenoids. In addition, all of the apo-11-, apo-13, and apo-15 lycopenals/lycopenones/lycopenoic acids have been prepared. These compounds have been evaluated for their effect on retinoic acid receptor (RAR) induced genes in cultured hepatoma cells, and much like β-apo-13-carotenone, the comparable apo-13-lycopenone, and the apo-15-lycopenoids, behave as RAR antagonists. Furthermore, molecular modelling studies demonstrate that the apo-13-lycopenone efficiently docked into the ligand binding site of RARβ. Finally, isothermal calorimetry (ITC) studies reveal that apo-13-lycopenone acts as an antagonist of RAR by inhibiting coactivator recruitment to the receptor.

Narayanasamy S et al.
J Lipid Res 58:1021-29 (2017)

NEWS AND VIEWS

Lycopene extracts from tomato-based food products induce apoptosis in cultured prostate cancer cells and regulate TP53, Bax and Bcl-2 transcript expression

Lycopene is more bioavailable from tomato processed products than from raw tomatos, since formation of lycopene *cis*-isomers during food processing and storage may increase its biological activity. In the current study, we evaluated the influence of lycopene extracts (5 mg/mL) from different tomato-based food products (paste, sauce, extract and ketchup) on cell viability and apoptosis in primary human prostate cancer cells (PCa cells) for 96 h. Using MTT assay, we observed a significant decrease on primary PCa cell viability upon treatment with lycopene extracted from either of the four tomato-based food products. Flow cytometric analysis revealed that lycopene from tomato extract and tomato sauce promoted up to 50x increase on the proportion of apoptotic cells, when compared to the control group. Using real time PCR assay, we found that lycopene promoted an upregulation of TP53 and Bax transcript expression and also downregulation of Bcl-2 expression in PCa cells. In conclusion, our data indicate that *cis*-lycopene may promote a significant inhibition on primary PCa cell viability, as well as increase their apoptotic rates, evidencing that cis-lycopene contained in tomato sauce and extract can modulate of primary human prostate cancer cell survival.

Soares ND et al.
Asian Pac J Cancer Prev 18: 339-45 (2017)

Supplementation of lycopene in maturation media improves bovine embryo quality *in vitro*

This study sought to modulate factors that reduce embryo quality in *in vitro* culture (IVC) systems. Over eight replicates, 3075 oocytes were cultured in *in vitro* maturation media containing various concentrations of lycopene, followed by *in vitro* fertilization and culture. The percentages of MII-stage oocytes, the presumptive zygotes that underwent cleavage and developed into blastocysts were significantly ($P<0.05$) higher, the intracellular ROS concentrations reduced significantly ($P<0.05$) in oocytes/blastocysts, TUNEL assay demonstrated reduced apoptosis and increased total cell number per blastocyst ($P<0.05$). Immunocytochemistry confirmed that diminished protein expression of nuclear factor kappa B (NFκB), cyclooxygenase-2 (COX2), and 8-oxoguanine (indicated by ROS) and relative mRNA expression of the Caspase-3, NFκB, COX2, iNOS and BCL2-associated X (BAX) was significantly ($P<0.05$) lower, while the anti-apoptotic gene BCL2 was significantly ($P<0.05$) higher in the 0.2 μM lycopene-supplemented group than the control. In conclusion, lycopene improves blastocyst quality by overcoming unfavorable conditions in *in vitro* culture systems.

Chowdhury MR et al.Theriogenology 103 (2017)
DOI: 10.1016/j.theriogenology.2017.08.003

Macular pigment optical density is positively associated with academic performance among preadolescent children

Macular pigment optical density (MPOD) - a non-invasive indicator of retinal xanthophylls and correlate of brain lutein - has been associated with superior cognitive function among adult populations. Given that lutein accumulation in the brain occurs in early life, it is possible that the cognitive implications of greater MPOD may be evident in childhood. Participants aged 8-9 years ($n = 56$) completed MPOD measurements via heterochromatic flicker photometry. Academic performance was assessed using the Kaufman Test of Academic and Educational Achievement II (KTEA). Habitual dietary intake of lutein (L) and zeaxanthin (Z) was measured among a subsample of participants ($n = 35$) using averaged 3-day food records. Stepwise hierarchical regression models were developed to determine the relationship between MPOD and academic achievement tests, following the adjustment of key covariates including sex, aerobic fitness, body composition, and intelligence quotient (IQ). The regression analyses revealed that MPOD improved the model, beyond the covariates, for overall academic achievement ($\Delta R^2 = 0.10$, $P < 0.01$), mathematics ($\Delta R^2 = 0.07$, $P = 0.02$), and written language composite standard scores ($\Delta R^2 = 0.15$, $P < 0.01$). This is the first study to demonstrate that retinal L and Z, measured as MPOD, is positively related to academic achievement in children, even after accounting for the robust effects of IQ and other demographic factors. These findings extend the positive associations observed between MPOD and cognitive abilities to a pediatric population.

Barnett SM et al. ***Nutr Neurosci*** *2017 epub*
doi: 10.1080/1028415X.2017.1329976

The relationship between retinal carotenoids and behavioral and neuroelectric indices of cognitive control in childhood

Lutein and zeaxanthin are plant pigments known to preferentially accumulate in neural tissue. Macular Pigment Optical Density (MPOD), a non-invasive measure of retinal carotenoids and surrogate measure of brain carotenoid concentration, has been associated with disease prevention and cognitive health. Superior MPOD status in later adulthood has

been shown to provide neuroprotective effects on cognition. Given that childhood signifies a critical period for carotenoid accumulation in brain, it is likely that the beneficial impact would be evident during development, though this relationship has not been directly investigated. The present study investigated the relationship between MPOD and the behavioral and neuroelectric indices elicited during a cognitive control task in preadolescent children. Participants (n = 49) completed a modified flanker task while event-related potentials (ERPs) were recorded to assess the P3 component of the ERP waveform. MPOD was associated with both behavioral performance and P3 amplitude, such that children with higher MPOD had more accurate performance and lower P3 amplitudes. These relationships were more pronounced for trials requiring greater amounts of cognitive control. These results indicate that children with higher MPOD may respond to cognitive tasks more efficiently, maintaining high performance while displaying neural indices of lower cognitive load. These findings provide novel support for the neuroprotective influence of retinal carotenoids during preadolescence.

Walk AM et al. Int J Psychophysiol 118:1-8 (2017)

Macular carotenoid supplementation improves visual performance, sleep quality and adverse physical symptoms in people with high screen time exposure

The dramatic rise in the use of smartphones, tablets, and laptop computers over the past decade has raised concerns about potentially deleterious health effects of increased "screen time" (ST) and associated short-wavelength (blue) light exposure. We determined baseline associations and effects of 6 month supplementation with the macular carotenoids (MC) lutein, zeaxanthin, and meso-zeaxanthin, on the blue-absorbing macular pigment (MP) and on measures of sleep quality, visual performance, and physical indicators of excessive ST. Forty-eight healthy young adults with at least 6 h of daily near-field ST exposure participated in this placebo-controlled trial. Visual performance measures included contrast sensitivity, critical flicker fusion, disability glare, and photostress recovery. Physical indicators of excessive screen time and sleep quality were assessed via questionnaire. MP optical density (MPOD) was assessed via heterochromatic flicker photometry. At baseline, MPOD was correlated significantly with all visual performance measures (p <0.05 for all). MC supplementation (24 mg daily) yielded significant improvement in MPOD, overall sleep quality, headache frequency, eye strain, eye fatigue, and all visual performance measures, versus placebo (p < 0.05 for all). Increased MPOD significantly improves visual performance and, in turn, improves several undesirable physical outcomes associated with excessive ST. The improvement in sleep quality was not directly related to increases in MPOD, and may be due to systemic reduction in oxidative stress and inflammation.

*Stringham JM et al. Foods 6(7), 47 (**2017**)*
doi:10.3390/foods6070047

Supplementation with macular carotenoids reduces psychological stress, serum cortisol, and improves physical and emotional health in young adults

Oxidative stress and systemic inflammation are the root cause of several deleterious effects of chronic psychological stress. We hypothesize that the antioxidant and anti-inflammatory capabilities of the macular carotenoids (MC) lutein, zeaxanthin, and meso-zeaxanthin could, via daily supplementation, provide a dietary means of benefit. A total of 59 young healthy subjects participated in a 12-month, double-blind, placebo-controlled trial to evaluate the effects of MC supplementation on blood cortisol, psychological stress ratings, behavioral measures of mood, and symptoms of sub-optimal health. Subjects were randomly assigned to one of three groups: placebo, 13 mg, or 27 mg / day total MCs. All parameters were assessed at baseline, 6 months, and 12 months. Serum MC were determined via HPLC, serum cortisol via ELISA, and macular pigment optical density (MPOD) via customized heterochromatic flicker photometry. Behavioral data were obtained via questionnaire. Significant baseline correlations were found between MPOD and Beck anxiety scores (r = −0.28; P = 0.032), MPOD and Brief Symptom Inventory scores (r = 0.27; P = 0.037), and serum cortisol and psychological stress scores (r = 0.46; P < 0.001). Supplementation for 6 months improved psychological stress, serum cortisol, and measures of emotional and physical health (P < 0.05 for all), versus placebo. These outcomes were either maintained or improved further at 12 months. Supplementation with the MC significantly reduces stress, cortisol, and symptoms of sub-optimal emotional and physical health. Determining the basis for these effects, whether systemic or a more central (i.e. brain) is a question that warrants further study.

Stringham NT, et al. Nutr Neurosci 2017epub
doi:10.1080/1028415X.2017.1286445

Non-dietary correlates and determinants of plasma lutein and zeaxanthin concentrations in the Irish population

The objective of this cross-sectional study was to investigate non-dietary correlates and determinants

of plasma lutein (L) and zeaxanthin (Z) concentrations in The Irish Longitudinal Study on Ageing (TILDA) sample. TILDA is a nationally representative prospective cohort study of community dwelling adults ≥50 years old in the Republic of Ireland. Demographic and health variables were collected during a face-to-face interview carried out at home (n = 8175), and a substantial proportion of these (n = 5035; 62%) also attended a study visit in a health assessment center. Blood samples collected at baseline (wave 1, the subject of the current study), were analyzed for plasma concentrations of L and Z by reversed-phase HPLC, and macular pigment optical density (MPOD) was also measured (using customized heterochromatic flicker photometry). After excluding participants with eye disease, data from 3,681 participants were available for analysis. For this group of participants, plasma L and Z were inversely and significantly associated with body mass index (BMI), and were positively and significantly associated with MPOD, total cholesterol, HDL and LDL ($p < 0.001$, for all). Plasma L and Z were significantly lower in males, current smokers, participants reporting less physical exercise, and participants reporting lower levels of education ($p < 0.05$, for all). Plasma L was significantly higher in participants reporting a family history of age-related macular degeneration (AMD) ($p = 0.001$), and in the group of ≥75 years old ($p < 0.05$). For each of these variables, the significant associations remained after controlling for other potentially confounding variables. The findings of this large study indicate that plasma concentrations of L and Z were lower in association with indicators of a poor lifestyle (high BMI, tobacco use, and less physical exercise) and in association with lower education, indicating that modifying lifestyle in a positive way is likely to be reflected in higher concentrations of plasma carotenoids, with consequential and putative health benefits.

Moran R et al. Nutr Health Aging 21:254-61 (2017)

Relative contribution of α-carotene to postprandial vitamin A concentrations in healthy humans after carrot consumption

Asymmetric α-carotene, a provitamin A carotenoid, is cleaved to produce retinol (vitamin A) and α-retinol (with negligible vitamin A activity). The vitamin A activity of α-carotene–containing foods is likely overestimated, because traditional analytic methods do not separate α-retinol derivatives from active retinol. This study aimed to accurately characterize intestinal α-carotene cleavage and its relative contribution to postprandial vitamin A in humans after consumption of raw carrots. Healthy adults (n = 12) consumed a meal containing 300 g raw carrot (providing 27.3 mg β-carotene and 18.7 mg α-carotene). Triglyceride-rich lipoprotein fractions of plasma were isolated and extracted, and α-retinyl palmitate (αRP) and retinyl palmitate were measured over 12 h postprandially via HPLC-MS. The complete profile of all α-retinyl esters and retinyl esters was measured at 6 h, and total absorption of α- and β-carotene was calculated. αRP was identified and quantified in every subject. No difference in preference for absorption of β- over α-carotene was observed (adjusting for dose, 28% higher, P = 0.103). After absorption, β-carotene trended toward preferential cleavage compared with α-carotene (22% higher, P = 0.084). A large range of provitamin A carotenoid conversion efficiencies was observed, with α-carotene contributing 12–35% of newly converted vitamin A (predicted contribution = 25.5%). In all subjects, a majority of α-retinol was esterified to palmitic acid (as compared with other fatty acids). α-Retinol is esterified in the enterocyte and transported in the blood analogous to retinol. The percentage of absorption of α-carotene from raw carrots was not significantly different from β-carotene when adjusting for dose, although a trend toward higher cleavage of β-carotene was observed. The results demonstrate large inter-individual variability in α-carotene conversion. The contribution of newly absorbed α-carotene to postprandial vitamin A should not be estimated but should be measured directly to accurately assess the vitamin A capacity of α-carotene-containing foods.

Cooperstone JL, et al.
Am J Clin Nutr 106: 59-66 (2017)

Vitamin A-retinoic acid signaling regulates hematopoietic stem cell dormancy

Dormant hematopoietic stem cells (dHSCs) are atop the hematopoietic hierarchy. The molecular identity of dHSCs and the mechanisms regulating their maintenance or exit from dormancy remain uncertain. Here, we use single-cell RNA sequencing (RNA-seq) analysis to show that the transition from dormancy toward cell-cycle entry is a continuous developmental path associated with upregulation of biosynthetic processes rather than a stepwise progression. In addition, low Myc (a regulator gene that codes for a transcription factor) levels and high expression of a retinoic acid program are characteristic for dHSCs. To follow the behavior of dHSCs in situ, a *Gprc5c*-controlled reporter mouse was established. Treatment with all-*trans* retinoic acid antagonizes stress-induced activation of dHSCs by restricting protein translation and levels of reactive oxygen species (ROS) and Myc. Mice

maintained on a vitamin A-free diet lose HSCs and show a disrupted re-entry into dormancy after exposure to inflammatory stress stimuli. Our results highlight the impact of dietary vitamin A on the regulation of cell-cycle-mediated stem cell plasticity.

Cabezas-Wallscheid N et al. Cell 169:807-23 (2017)

Degradation of retinoic acid required for patterning a high-acuity area in the retina

Species that are highly reliant on their visual system have a specialized retinal area for high-acuity vision, e.g., the fovea in humans. Although of critical importance for our daily activities, little is known about the mechanisms driving the development of retinal high-acuity areas (HAAs). Using the chick as a model, we found a precise and dynamic expression pattern of fibroblast growth factor 8 (Fgf8) in the HAA anlage, which was regulated by enzymes that degrade retinoic acid (RA). Transient manipulation of RA signaling, or reduction of Fgf8 expression, disrupted several features of HAA patterning, including photoreceptor distribution, ganglion cell density, and organization of interneurons. Notably, patterned expression of RA signaling components was also found in humans, suggesting that RA also plays a role in setting up the human fovea.

da Silva S, Cepko CL
Developmental Cell 42 (1):68-81(2017)

Photocyclic behavior of rhodopsin induced by an atypical isomerization mechanism

Vertebrate rhodopsin (Rh) contains 11-*cis*-retinal as a chromophore to convert light energy into visual signals. On absorption of light, 11-*cis*-retinal is isomerized to all-*trans*-retinal, constituting a one-way reaction that activates transducin (G_t) followed by chromophore release. Here we report that bovine Rh, regenerated instead with a six-carbon-ring (cyclohexyl) retinal chromophore featuring a C^{11}=C^{12} double bond locked in its *cis* conformation (Rh6mr), employs an atypical isomerization mechanism by converting 11-*cis* to an 11,13-*dicis* configuration for prolonged G_t activation. Time-dependent UV-Vis spectroscopy, HPLC, and molecular mechanics analyses revealed an atypical thermal reisomerization of the 11,13-*dicis* to the 11-*cis* configuration on a slow timescale, which enables Rh6mr to function in a photocyclic manner similar to that of microbial Rhs, abrogating the necessity for a complex retinoid cycle to renew its chromophore. With this photocyclic behavior, Rh6mr repeatedly recruits and activates G_t in response to light stimuli, making it an excellent candidate for optogenetic tools based on retinal analog-bound vertebrate Rhs. Overall, these comprehensive structure-function studies unveil a unique photocyclic mechanism of Rh activation by an 11-*cis* to 11,13-*dicis* isomerization.

Gulati S et al. PNAS 114:E2608-15 (2017)

Structure of Phytoene Desaturase

Cyanobacteria and plants synthesize carotenoids via a poly-*cis* pathway starting with phytoene, a membrane-bound C40 hydrocarbon. Phytoene desaturase (PDS) introduces two double bonds and concomitantly isomerizes two neighboring double bonds from *trans* to *cis*. PDS assembles into homo-tetramers that interact monotopically with membranes. A long hydrophobic tunnel is proposed to function in the sequential binding of phytoene and the electron acceptor plastoquinone. The herbicidal inhibitor norflurazon binds at a plastoquinone site thereby blocking reoxidation of FAD_{red}. Comparison with the sequence-dissimilar bacterial carotene desaturase CRTI reveals substantial similarities in the overall protein fold, defining both as members of the GR2 family of flavoproteins. However, the PDS active center architecture is unprecedented: no functional groups are found in the immediate flavin vicinity that might participate in dehydrogenation and isomerization. This suggests that the isoalloxazine moiety is sufficient for catalysis. Despite mechanistic differences, an ancient evolutionary relation of PDS and CRTI is apparent.

Brausemann A et al, Structure 25:1222-32 (2017)

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