PANAMERICAN SOCIETY for PIGMENT CELL RESEARCH

PASPCR Newsletter

Volume 4 Number 3 September,1996

Introduction . . . by the Publications Committee

The **PASPCR** *Newsletter* is published quarterly and is intended to serve as a means of communication for the members of our Society. As such, we invite our membership to actively contribute to the *Newsletter*; help us to update the Job Listings, Calendar of Events, Meeting Reports, Abstracts in press and other items of general membership interest. If you attend a scientific meeting at which you heard about work which you think will be of interest to the membership of the **PASPCR**, please write a few paragraphs summarizing what was presented and share it with us. If you should have a change of affiliation or address, we'd like to know that, too. This is **your** *Newsletter*, and we depend upon you to help us make sure it best serves the Society's needs. Contributions and comments can be sent to any of the members of the Publications Committee.

NEW! WorldWideWeb Pages for the PASPCR. The PASPCR now has its own **WWW** home page. We plan this to be a major source of current information for the PASPCR membership. The address for the page is: **http://lenti.med.umn.edu/paspcr**. This site contains information on the goals of the society, future meetings, council information, past issues of the PASPCR newsletter as well as links to other sites including the InterPig DataBase, the International Pigment Cell Conference in Anaheim and the International Federation of Pigment Cell Societies (IFPCS).

We have now included the membership directory on that page; please notify us if you wish any or all of your information to be deleted or modified on that site.

The PASPCR WWW page system is still under construction and we want to know if there is any other information you would like located on this site.

Please check out the PASPCR web site and send any comments and/or suggestions to either the PASPCR WebMaster Bill Oetting at bill@lenti.med.umn.edu or to Vince Hearing at hearingv@dc37a.nci.nih.gov.

IN THIS ISSUE . . . . .

PanAmerican Society for Pigment Cell Research

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Calendar of Events :

Oct 29- Nov 3, 1996 XVIth International Pigment Cell Conference, to be held in Anaheim, California, (contact: MMC/UCI Center for Health Education, PO Box 1428, Long Beach, CA 90801-1428, FAX: 310/933-2012)

Dec 7 - 11, 1996 36th Annual Meeting of the American Society for Cell Biology and 6th International Congress on Cell Biology, to be held in San Francisco, CA, (contact: ASCB Secretariat, 9650 Rockville Pike, Bethesda, MD 20814-3992; FAX: 301/530-7139)

April 23 - 26, 1997 Annual meeting of the Society for Investigative Dermatology, Washington, DC, (contact: the SID, Suite 500A, 1101 Cedar Ave., Cleveland, OH 44106, FAX: 216: 844-6859)

Jun 10 - 14, 1997 4th World Conference on Melanoma to be held in Sydney, Australia (contact: The Melanoma Foundation, PO Box M123, Camperdown, NSW 2050 Australia; FAX: +61 2/550-6316)

Jun 15- 18, 1997 VIIth PASPCR Annual Meeting, to be held in Providence, RI (contact: Dr. Walter C Quevedo, Jr., Brown University, Division of Biology and Medicine, Providence, RI 02912; FAX: 401/863-1971)

Jun 22 - 24, 1997 International Meeting "Pigmentary Disorders from a Global Perspective" to be held in Bali, Indonesia (contact: Bureau PAOG, Tafelbergweg 25, 1105 BC Amsterdam, The Netherlands; FAX: +31 20/696-3229)

Oct 9- 11, 1997 7th ESPCR Annual Meeting, to be held in Bordeaux, France (contact: 7th ESPCR Meeting Bordeaux, c/o Congres Seminaires Organisation, 81, Boulevard, Pierre 1er, 33110 Le Bouscat, Bordeaux, France)

Welcome to New Members

by James J Nordlund

We welcome the following new members to the **PASPCR** . . .

Pearl Grimes	Susan Kidson
Nam Soo Kim	Weidong Xu

If anyone is interested in joining our Society or wishes to sponsor a member, application forms can be obtained from Dr. James J. Nordlund at the PASPCR Secretary/Treasurer's office.

Corporate Sponsors

by James J Nordlund

The PASPCR would like to acknowledge and thank our Corporate Sponsors; the list below reflects contributions over the past 2 years. Financial gifts from these sponsors have allowed our Society to increase benefits to the membership far out of proportion to the actual dues collected from members. Monies contributed by these sponsors have been used over the years to support various PASPCR functions including our Young Investigator Award program, meeting travel stipends, annual meeting expenses and this Newsletter.

GOLD Corporate Patrons	*SILVER Corporate Patrons*	*Corporate Patrons*
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XVIth IPCC (International Pigment Cell Conference)

by Frank Meyskens

The XVIth International Pigment Cell Conference will be held from October 29th to November 3rd, 1996 at the Disneyland Hotel in Anaheim, California. Frank Meyskens is the Organizer of this meeting with Roger Bowers and Alistair Cochran serving as co-chairs of the Organizing Committee. The PASPCR has established a Web page that contains relevant information for this meeting; take a look at: "**http://lenti.med.umn.edu/paspcr/ipcc.htm**".

PROGRAM XVIth International Pigment Cell Conference October 29 - November 3, 1996

Tuesday, October 29, 1996

3:00-7:00 pm Pre-registration/View Exhibits
7:00-10:00 pm Welcome Reception: Fashion Show: "*Safe and Sexy in the Sun*"

Wednesday, October 30, 1996

Accompanying Guests: 9:00 - 11:00 am Buffet Breakfast; 10:00 - 11:00 am Orientation; 11:00 am - 6:00 pm Group Activity

7:00-8:00 am Registration/Continental Breakfast/View Exhibits
8:00-8:05 am Welcome: Chairman, Frank L Meyskens, Jr
Introduction: Laurel Wilkening, Chancellor, University of California, Irvine
8:05-8:35 am Special Lecture, F Sherwood Rowland, Nobel Laureate, 1995, Chemistry
#1 "*Stratospheric Ozone Depletion and Increased UVB at Earth's Surface*"

Symposium I: Economic and Societal Implications of Melanin and Melanogenesis
Co-Chairs: Mac Hadley, JF Dore, Shosuke Ito

8:35-9:00 am Keynote Speaker

#2 Miles Chedekel: *"Commercial Applications of Melanins and Melanogenesis"*

9:00-10:30 am **Invited and Competitive Abstract Speakers**

#3 Genji Imokawa: *"The role of endothelin-1 in epidermal hyperpigmentation and signaling mechanism of mitogenesis and melanogenesis"*

#4 P Autier: *"Pigmented lesions of the skin in children, sunscreen use and exposure to sunlight"*

#5 Giuseppe Prota: *"Cosmetic applications of melanins and melanogenesis: status quo and prospects"*

10:30-11:00 am Break

11:00-12:30 pm ***Workshop A: Extracutaneous Melanin, Melanocytes and Melanogenesis***

Chair and Overview: Ralf-Uwe Peter, Co-Chairs: Helene Hill and Tadahisa Seikai

Invited and Competitive Abstract Speakers

#6 Helene Z Hill: *"Melanin--the two-edged sword?"*

#7 Tadahisa Seikai: *"Normal and abnormal pigmentation processes of flatfish in relation to larval metamorphosis"*

#8 Johan Stjernschantz: *"Prostaglandin-induced increase of iridial pigmentation"*

#9 Adelina Zuasti: *"Ultrastructure and histochemistry of the pigment cells in the stria vascularis of the mesocricetus auratus"*

Workshop B: Dynamics of Invertebrate Pigment Cells

Chair and Overvew: Sumiko Negishi, "Regulation of invertebrate pigmentation", Co-Chairs: K Ranga Rao, Detlef Buckmann

Invited and Competitive Abstract Speakers

#10 Luiz Nery: *"Cellular signalling in the crustacean erythrophore"*

#11 Detlef Buckmann: *"Hormonal control and pattern formation in insect pigmentation"*

#12 Y Hasegawa: *"Regulation of pigment genesis in albinism"*

#13 Masaaki Ashida: *"The insect prophenol oxidase is a protein homologous to arthropod hemocyanin and activated through the action of a cascade triggered by microbial cell wall components"*

11:00-12:00 pm ***Posters and Discussion #1: Melanoma Research: Basic and Applied***

Frank L Meyskens, Jr, Chair

11:00-12:00 pm Poster Viewing

12:00-12:30 pm Discussion

12:30-2:00 pm Lunch on your own

Symposium II: Molecular Biology of Pigment Cells

Co-Chairs: Shigeki Shibahara, Manfred Schartl, Vincent J Hearing

2:00-2:30 pm Keynote Speaker

#14 Nicolas Dracopali:*"Mutations in Genes Regulating the G_1 Checkpoint Account for Almost Half of Familial Melanomas"*

2:30-4:00 pm **Invited and Competitive Abstract Speakers**

#15 Manfred Schartl: *"Analysis of the molecular mechanisms leading to pigment cell transformation by the x^{mrk} receptor tyrosine kinase of xiphophorus"*

#16 Hiroaki Yamamoto: *"Evolution of developmental systems of pigment cells"*

#17 Kazutomo Toyofuku:*"Molecular chaperone, calnexin, associates with tyrosinase, the key enzyme in melanogenesis"*

#18 Dorothy C Bennett: *"Cloning and mapping of a human gene sequence that promotes differentiation of mouse melanoma cells and may retard tumor development"*

#19 Susan Porter: *"Complex regulatory properties of the distal upstream mouse tyrosinase enhancer"*

4:00-4:05 pm IFPCS/WWW: Vincent Hearing

4:05-4:15 pm Break

4:15-6:15 pm ***Workshop C: "Regulating Mechanisms of Melanocyte Proliferation"***

Chair and Overview: Zalfa Abdel-Malek, co-Chairs: Masako Mizoguchi, Anthony Thody

Invited and Competitive Abstract Speakers

#20 Masayoshi Tachibana: *"Expression of MITF induces melanocyte differentiation and haploinsufficiency of MITF causes Waardenburg Syndrome type 2A"*

#21 Sheila MacNeil: *" Effect of ECM proteins on melanocyte proliferation and tyrosinase activity in media of varying mitogenic potency"*

#22 Anthony J Thody: *"Why are melanocytes vulnerable to oxidative damage?"*

#23 Maher Haddad: *"Correlation of end-stage differentiation of human melanocytes with suppression of cylin D1 and induction of MITF, p21 waf-1/SDI-1 and P27 KIP-1"*

#24 Anton Platz: *"Evidence for UV-induction of mutations in genes related to the cell cycle G_1 checkpoint control in human cutaneous melanoma"*

4:15-6:00 pm ***Posters and Discussion #2: Melanogenesis:***
John Pawelek, Chair

4:15-5:30 pm Poster Viewing

5:30-6:00 pm Discussion

5:30-7:00 pm ***Workshop D: Biophysics and Chemistry of Melanin***
Chair and Overview: Tadeusz Sarna, Co-Chairs: Kazumasa Wakamatsu, Harold Swartz

Invited and Competitive Abstract Speakers

#25 Julian Menter: *"Electron transfer and photoprotective properties of melanins in solution"*

#26 Kazumasa Wakamatsu: *"Usefulness of spectrophotometric and HPLC methods in measuring hair melanins"*

#27 Martin G Peter: *"On the redox state of enzymatically generated tyrosine melanin"*

#28 Melvin Eisner: *"EXAFS studies of chelated Fe sites in natural and synthetic neuromelanins"*

#29 Harold M Swartz: *"Implications of the interactions of melanin with reactive species"*

Workshop E: Vitiligo
Chair and Overview: David Norris, "Factors which determine melanocyte survival", Co-Chairs: Karin U Schallreuter-Wood, Robert Aquaron

Invited and Competitive Abstract Speakers

#30 Wiete Westerhof: *"Treatment of vitiligo with UVB (311NM) versus topical puva"*

#31 James J Nordlund: *"Vitiligo: an analysis of proposed etiologies"*

#32 R van den Wijngaard: *"Melanocyte anti-oxidant defence and immune infiltrates in vitiligo"*

#33 Ram K Tripathi: *"Evaluation of MITF locus linkage to human vitiligo and ostepetrosis"*

#34 Alain Taieb: *"In vivo and ex vivo melanocyte transplants in vitiligo: an extrinsic factor is needed to trigger the disease"*

7:00 pm Adjourn Free evening

Thursday, October 31, 1996

7:00-8:00 am Continental Breakfast/View Exhibits

8:00-8:30 am Seiji Lectureship: *Introduction: Giuseppe Prota, President IFPCS*

#35 Richard A King: *"Albinism as a Model System of Melanin Regulation"*

Symposium III: Melanoma Research: Basic and Applied
Co-Chairs: Frank Meyskens, Eberhard Paul, Kowichi Jimbow

8:30-9:00 am Keynote Speaker

#36 Alistair Cochran: *"Predictions of Outcomes for Patients with Cutaneous Melanoma"*

9:00-10:30 am **Invited and Competitive Abstract Speakers**

#37 John Fruehauf: *"Selective cytotoxic action of BSO on human melanoma"*

#38 Yutaka Mishima: *"Selective eradication and diagnosis of malignant melanoma;melanogenesis investigations leading to novel neutron capture therapy"*

#39 Eva M Link: *"^{211}At-methylene blue for treatment of disseminated melanoma"*

#40 Juichiro Nakayama: *"Different pattern of modulation between cytokine-induced and hypertherma-induced ICAM-1 expression in human malignant melanoma cell lines in vitro"*

#41 Mei-Yu Hsu: *"The role of e-cadherin in keratinocyte-melanocyte cross-talk"*

10:30-11:00 am Break

11:00-12:30 pm ***Workshop F: Control of Melanogenesis***

Chair and Overview, John M Pawelek, "DHICA polymerization and the silver phenotype", Co-Chairs: Katsuhiko Tsukamoto, Brian Weatherhead

Invited and Competitive Speakers

#42 Hirofumi Kondoh*: "The role of TRPs (tyrosinase related proteins) in the control of eumelanogenesis"*

#43 Francisco Solano: *"Comparison and properties of TRPs from murine and human malignant melanocytes"*

#44 Michele Miranda: *"Melanogenesis, tyrosinase expression and reproductive differentiation in black and white truffles (ascomycotina)"*

#45 Harish Mahalingam: *"Interplay of signaling mechanisms regulating tyrosinase gene expression"*

#46 Hua Chen: *"Involvement of phosphatidylinositol 3-kinase activity in the sorting and transport of newly synthesized tyrosinase-related protein-1 in melanogenesis*

12:30-1:30 pm Simultaneous Business Meetings of Regional Societies

12:30-2:00 pm Lunch on your own

Symposium IV: Photobiology of Melanocytes: Etiology and Prevention

Co-Chairs: JP Cesarini, Masamitsu Ichihashi, Lisa Zeise

2:00-2:30 pm Keynote Speaker

#47 Nik Kollias

2:30-4:00 pm **Invited and Competitive Abstract Speakers**

#48 Yoko Funasaka: *"The effect of ultraviolet B induced adult T cell leukemia-derived factor on survival and growth of human melanocytes"*

#49 Frank L Meyskens Jr*: "Expression of NF-kB/IkB/c-Rel in human melanocytes and melanoma cells: changes in association and dissociation"*

#50 Mauro Picardo: *"Alteration of antioxidants in normal melanocytes from patients with melanoma"*

#51 Mayumi Fujita: *"Activation of p53 is required for ultraviolet radiation-induced cell cycle arrest, apoptosis and BCL-2 regulation in melanoma cells"*

#52 Ashok K Chakraborty: *"Production and release of proopimelanocortin (POMC) derived peptides by human melanocytes and keratinocytes in culture: regulation by UVB"*

4:00-7:00 pm ***Workshop G: The "Blues" Symposium***

Chair: Joseph T Bagnara, Co-Chairs: Jean L Bolognia, Yoshiaki Hori

#53 Joseph T Bagnara: *"Introduction and overview of blue pigmentation"*

#54 Craig Bohren: *"A brief tour of light scattering with a side trip into colorimetry Human Cerulodermas*

#55 Jean L Bolognia: *"Blue nevi and Mongolian spots"*

#56 Yoshiaki Hori: *"The nevus of Ota and other nevus fuscocaeruleus*

#57 Ryozo Fujii: *"The blue colors of fish"*

#58 Philip J Fernandez: *"Blue skin color in amphibians"*

#59 Randall L Morrison: *"Mechanisms of structural color production in the skin of reptiles and birds*

#60 Walter C Quevedo, Jr: *" The blue colors of mammals"*

4:00-7:00 pm Poster Viewing

7:00 pm Adjourn Free evening

Friday, November 1, 1996

7:00-8:00 am Continental Breakfast/View Exhibits

8:00-8:30 am Introduction: Vincent Hearing, past-President PASPCR

#61 *Gelb Lectureship*: Seth Orlow : *"The Biogenesis of Melanosomes"*

Symposium V: Melanogenesis and Pigmentary Disorders

Co-Chairs: James Nordlund, Wiete Westerhof, Yoshiaki Hori

8:30-9:00 am Keynote Speaker

#62 Raymond E Boissy: "*Melanogenesis and Pigmentary Disorders*"

9:00-10:30 am **Invited and Competitive Abstract Speakers**

#63 Masako Mizoguchi : "*Melanogenesis in acquired dermal melanocytosis*"

#64 Richard Spritz: "*Mapping and mutation analyses of the genes for Hermansky-Pudlak Syndrome and Chediak-Higashi Syndrome*"

#65 James P Fryer: "*Analysis of splice site mutations in individuals with OCA1 using illegitimate transcription as a source of tyrosinase RNA in lymphocytes*"

#66 Vincent J Hearing: "*Mutational analysis of copper-binding by human tyrosinase and differential binding of divalent metal cations by the tyrosinase-related proteins*"

10:30-11:00 am Break

11:00-12:30 pm ***Workshop H: Biology and Biochemistry of Melanosomes***

Chair and Overview: Yutaka Mishima, "Melanosomes as a specialized lysosomes - transfection of melanogenic genes into melanin-deficient pigment cells and fibroblasts",

Co-chairs: Seth Orlow, Jan Borovansky

Invited and Competitive Abstract Speakers

#67 Kowichi Jimbow:"*Molecular biology of tyrosinase-related protein, assessment of biological role, biosynthesis and transport from TGN to pre-stage I melanosome through gene transfection*"

#68 Keishi Araki: "*Analysis of the role of small GTP binding protein RAB in intracellular melanosome transport*"

#69 Chie Sakai: "*Modulation of expression and activity of melanosomal proteins in murine melanocytes by agouti signal protein*"

#70 John A Hammer: "*The absence of a myosin V dependent transport system underlies in part the coat color defect in dilute mice*"

#71 Paul F Gomez: "*A small molecular weight, GTP-binding protein, rab-7, is involved in the transport of TRP-1 from TGN to melanosomes*"

11:00-12:30 pm ***Posters and Discussion #3: Biophysics and Chemistry of Melanin***

Patrick A Riley, Chair

11:00-12:00 pm Poster Viewing

12:00-12:30 pm Discussion

12:30 pm Adjourn Scientific Session

12:30-1:30 pm Simultaneous Business Meetings of Regional Societies

1:30-6:30 pm Break

6:30-7:30 pm Reception

7:30-midnight Banquet, Awards and Dancing

IFPCS Awards to Be Presented:

Myron Gordon Award - to Jiro Matsumoto

Seiji Memorial Lecture Award - to Richard A King

Raper Medal - recipient to be announced

Takeuchi Medal - recipient to be announced

IFPCS Special Awards:

to Joseph T Bagnara, Founding Editor, *Pigment Cell Research*

to Yoshiaki Hori, Chairman, *International Symposium on Melanogenesis and Malignant Melanoma*

to Frank L Meyskens, Jr, Alistair J Cochran & Roger R Bowers, Chair and Co-Chairs, *XVIth IPCC*

Saturday, November 2, 1996

7:00-8:00 am Continental Breakfast/View Exhibits

8:00-8:30 am Presidential Address: Giuseppe Prota, President IFPCS

#72 *"Pigment Cell Research: What Directions?"*

Symposium VI: Comparative Developmental Biology of Pigment Cells

Co-Chairs: Roger Bowers, Masataka Obika, Dorothy Bennett

8:30-9:00 am Keynote Speaker

#73 Jiro Matsumoto*: "Molecular Biology of Fish Pigmentation: Up-to-Date"*

9:00-10:30 am **Invited and Competitive Abstract Speakers**

#74 Sally Frost-Mason: *"From three pigment cell types to one. An evolutionary perspective of vertebrate chromatophore development"*

#75 Dorothy Bennett: *"Differential gene expression in immortal melanocytes, melanoblasts and melanoblast precursors"*

#76 Bernard Wehrle-Haller: *"Early melanocyte precursor migration is directed by localized steel factor"*

#77 Mark Moody: *"Enhancement of the xanthophore lineage in guanosine-treated axolotl neural crest cells in vitro"*

#78 William Pavan: *"Genetic regulation of melanocyte patterning"*

10:30-11:00 am Break

11:00-12:30 pm ***Workshop I: Genetic Aspects of Albinism***

Chair and Overview: Richard A King, Co-Chairs: Fritz Anders, Yasushi Tomita

Invited and Competitive Abstract Speakers

#*79* Jun Matsunaga: *"Sequence analysis of the human tyrosine promoter from a patient with tyrosinase-negative oculocutaneous albinism"*

#*80* Friedrich Beermann: *"Regulation of tyrosinase expression in transgenic mice"*

#*81* Julie M Newton: *"Molecular characterization of a mouse homolog for the human ocular albinism 1 (OA1) gene"*

#*82* William S Oetting: *"Analysis of the P gene in individuals with tyrosinase positive oculocutaneous albinism (OCA2)"*

Workshop J: Melanocytic Nevi: Clinical and Laboratory Investigations

Chair and Overview: Stan Pavel, "Melanocytic neve: clinical and laboratory investigation", Co-Chairs: Shinji Shimada, Arthur R Rhodes

Invited and Competitive Abstract Speakers

#*83* W Bergman: *"The relationship of atypical nevi and multiple mole melanoma in the FAMMM syndrome"*

#*84* R Akasu: *"Videomicroscopic features of melanocytic plantar nevi"*

#*85* Jerry O'Connell: *"Chimeric nevi: collision tumors that are variants of combined nevus"*

#*86* Paolo Antonio: *"The epiluminescence microscopy in the diagnosis of pigmented cutaneous lesions: the experience of National Cancer Institute of Naples, Italy"*

#*87* Zhao-lun Chen: *"An immunohistoschemical study on the expression of p53 protein, c-erb-2, and PCNA in malignant and benign melanocytic lesions"*

11:00-12:30 pm ***Posters and Discussion #4: Pigment Cell Development and Dysfunction***: *Walter C Quevedo, Jr, Chair*

11:00-12:00 pm Poster Viewing

12:00-12:30 pm Discussion

12:30-2:00 pm Lunch on your own

2:00-4:00 pm *Educational Forum: "Living with the Sun"*

4:00-6:00 pm Family Farewell Reception

Sunday, November 3, 1996

8:00 am-5:00 pm

1. *Satellite Meeting (all day): Classification of Cutaneous Melanoma*: Alistair Cochran
2. *Satellite Meeting (3 hours): Safety of Sunscreens and Tanning Parlors*: J.P. Césarini

Positions - Wanted and Available :

Cell Biologists - Unilever's Research and Engineering Division has two openings for the following position description. Changes in pigmentation of the skin are part of the adaptation response to a variety of conditions. These changes are caused and characterized by very marked changes in skin cell biology and biochemistry. We wish to recruit two scientists to be part of a new project team researching mechanisms of pigmentation and mode of action of certain skin lightening agents *in vivo*. The project will require the establishment and investigation of appropriate *in vitro* and *in vivo* models for pigmentation research. Expertise required: Candidates must have a good honours degree and PhD in a biochemical or cell biology subject with at least 3 years of research training in a good laboratory. The candidate must have a proven research record. Postdoctoral experience would be advantageous. Please send your CV quoting the Reference number MM960604 to: Bryony Leleux, Personnel Department, Unilever Research, Colworth Laboratory, Sharnbrook, Bedfordshire, MK44 1LQ; Email bryony.leleux@urcgb.sprint.com.

Predoctoral and Postdoctoral Positions - available for molecular biologists in the areas of drug discovery and metabolism research. Requires experience in gene cloning, DNA sequencing, recombinant protein expression and cell culture methods. Prior experience in dermatology research is desirable. Southern Research Institute is a diversified research and development organization. Our Life Sciences Division provides comprehensive preclinical drug development and testing capabilities as well as basic research in drug design and synthesis, pharmaceutical formulations, toxicology, virology, microbiology, and pharmacology. To apply, send resume or curriculum vitae to: Southern Research Institute, Attention: Suzann Allen, Human Resources, Department 118, P.O. Box 55305, Birmingham, AL, 35255-5305.

Faculty Position - Massachusetts General Hospital, Harvard Medical School, Cutaneous Biology Research Center. The Cutaneous Biology Research Center (CBRC) seeks a molecular, cellular or developmental biologist to establish a program in fundamental research relevant to skin pigmentation. Areas of reseearch can include but are not limited to pigment synthesis and transfer in melanocytes, genetics of mouse coat color and development/migration of neural crest cells. Applicants must have a Ph.D. and/or M.D. degree and relevant postdoctoral experience. Only applicants with a strong research record and the potential to develop extramurally supported research programs will be considered. Individuals with a demonstrated ability to develop imaginative approaches to important biological questions are particularly encouraged to apply. Rank/salary/start-up funds and space are negotiable depending on experience and qualifications. The CBRC occupies 45,000 square feet of fully equipped laboratory space in a new multidisciplinary research facility. Interested individuals should send curriculum vitae, reprints, a statement of research and future directions, along with the names, addresses and telephone numbers of three references to: Dr. Paul F. Goetinck, Chair, Faculty Search Committee, Cutaneous Biology Research Center, Massachusetts General Hospital - East, Building 149, 13th Street, Charlestown, MA 02129

INTERPIG DataBase

by Vincent Hearing

The INTERPIG database is on the InterNet! You can now access the InterPig DataBase at the following address: **http://lenti.med.umn.edu/paspcr/interpig.html**. Please note that as of this time, I estimate that less than 5% of the various IFPCS members have contributed entries. Think of how useful and complete this list would be if everyone took the time to supply their own information. Please take a moment to fill out the database data entry form (either online through the Web page or via Email) and send it back to Dr. Hearing. Please contact Vince Hearing or Bill Oetting if you need more information about these mechanisms of submission.

Meeting Report

by Helene Z Hill

Annual Meeting for American Society for Photobiology
Division V: Environmental Photobiology and UVR Effects

Highlights of the meeting included a workshop on Solar UV Impacts on Aquatic Microorganisms, a two part affair chaired by Tom Coohill. We learned of the difficulties measuring UV penetration and microorganism populations in the water column. Winds, wave motion and cloud cover are among the effects that alter sunlight penetration and the distribution of organisms. Many aquatic microorganisms are already under UVB stress so that sporadic spikes of UVB that occur in the southern hemisphere in October can profoundly affect the ecological balance. Since 30% of the world's animal protein comes from the sea, it is important to predict the effects on productivity to be expected with the decrease in ozone. Decrease in marine productivity will decrease CO_2-fixation and contribute to the greenhouse effect. Bacterioplankton are little studied but important contributors to the productivity of the waters. They appear to have little capacity to repair DNA.

The Sunscreen Symposium had an impact not only on Photobiologists but also on the Press. It seems that some sunscreen ingredients can act as photosensitizers and produce thymine dimer damage in DNA. As seen on CNN, Lorrie Kligman said not to worry. The study was done *in vitro.* It may be irrelevant when it comes to skin.

The Symposium on Melanin was co-sponsored by the Pan-American Society for Pigment Cell Research and the ASP and generously supported by Clairol, L'Oreal and Shiseido America Technocenter. Melanin can act as both a photosensitizer and a photoprotector. *In vivo*, in tissue cultured melanoma cells stimulated to produce eumelanin it is photoprotective for mutations produced by monochromatic UVB but not by polychromatic UVB+A. Intense tan produced by furocoumarin is not photoprotective versus skin cancer in mice. Human melanocytes of skin type VI contain mainly eumelanin while those of skin type II contain both eu- and phaeomelanin. It is clear that it is important to understand the roles of the various types of pigment *in vivo*. Phaeomelanin is more likely to be photosensitizing and could contribute to skin cancer induction in skin types I, II and III.

The UVA Symposium was jointly sponsored by the American and European Societies for Photobiology. UVA is a major component of sunlight and is cause for concern because sunbathers who use sunscreens are protected from erythema caused by UVB. As a result, they spend more time in the sun with greater risk of UVA-induced cancers. UVA suntan parlors are now popular, posing additional skin cancer risks. UVA produces oxidative lesions in DNA by photosensitizations mediated by unknown intracellular photosensitizers. These lesions can be both lethal and mutagenic, hence carcinogenic. Epidemiological analysis of skin cancers in Norway reveal that melanoma induction has a greater UVA component than basal and squamous cell cancers.

Bibliography :

The Bibliography published in this issue covers the period February, 1996 through April, 1996. If you notice a paper that was not detected by this search that should be included, please send it to us and we will include it in the next issue. We have attempted to highlight any publications which include a member of the PASPCR with a star.

MELANINS, MELANOGENS & MELANOGENESIS

Adamse P, Britz SJ: Rapid fluence-dependent responses to ultraviolet-B radiation in cucumber leaves: The role of UV-absorbing pigments in damage protection. J Plant Physiol 148:57-62 (1996).

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Zinc in pigmented cells and structures, interactions and possible roles

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SUMMARY: Zinc is a feature trace element of pigment cells and tissues. Organelles, in which melanin is synthesized and stored, i.e. melanosomes, represent a zinc reservoir at the subcellular level. In order to understand function of metals in tissues, cells and their constituents, knowledge is needed on metal interactions with intracellular targets. The possible zinc ligands in pigment cells include melanin, metallothionein, melanotransferrin, B700 and related proteins, ferritin, zinc enzymes and low molecular weight ligands. Areas of a special interest in relation of pigment cells and structures to zinc - such as zinc effect on melanogenesis, zinc excretion and buffering by melanosomes, zinc function in free radical processes as well as zinc role in melanomas - have been reviewed. High level of zinc in pigment cells may indicate a physiological defense against the potential danger of oxidative stress.

1. ZINC IN PIGMENT CELLS AND TISSUES

The strikingly high zinc level in pigment tissues was first noticed in pigment structures of eye [17,19,36,58,59,85] and later demonstrated in pigmented normal [45] and tumour tissues [46,58,65]; high level of zinc was demonstrated also in pigmented regions of human brains [29,48]. Experiments with radioactive ^{65}Zn revealed high uptake of zinc into murine tumours - Cloudman S91 melanoma [65], B16 melanoma [10,75] and Harding-Passey melanoma [10]. Newsome and Rothman [63] described the ability of human retinal pigment epithelial cells *in vitro* to accumulate and retain zinc, later study of the same group verified *in vivo* that pigment eye tissues of humans and primates took up and retained zinc [62]. Dencker and Tjalve [28] mentioned retention of ^{65}Zn in hair of pigmented C57BL6 mice.

2. ZINC IN MELANOSOMES

With the development of cell fractination techniques it became obvious that at the subcellular level zinc was deposited especially in melanosomes [41,86,90]. Our comparative studies demonstrated that melanosomes represent unique subcellular storehouses of zinc because the Zn concentration in the isolated organelles exceeded that in the whole original pigment tissue 3-5 fold [12,46] - Tab. 1.

Table 1 - Zinc concentration in pigment tissues and in melanosomes isolated from them

SPECIMEN	TISSUE	MELANOSOME
bovine uvea	138.4 ± 2.3	598.0 ± 4.2
human hair	158.0 ± 23.2	664.0 ± 376.6
Harding-Passey mouse melanoma	75.5 ± 1.8	383.3 ± 2.2
horse melanoma	112.0 ± 1.9	544.3 ± 4.1
human melanoma	181.1 ± 7.5	612.1 ± 5.2
Bomirski hamster melanoma (line Ma)	185.0	417.1

The result s are expressed in μZn/g dry sample (x ± SD). Compiled from [12, 45, 46]

The initial data derived from colorimetric measurements were later confirmed by modern techniques such as neutron activation analysis [78] or mass spectrometry [92] but there still has persisted a question if the zinc was not absorbed artificially by melanosomes during isolation procedure. Only X-ray microanalysis of melanosomes *in situ* brought a conclusive evidence for the presence of zinc in trout skin melanosomes [72], in melanosomes of inner ear and uveal tract [60], in retinal and choroidal pig melanosomes [82] and in melanosomes of human retinal pigment epithelium [94]. Only Takaya [91] using X-ray microanalysis found neither zinc nor copper in hair melanosomes.

The presence of zinc was demonstrated also in the pigment extracted by a mild procedure from substantia nigra of human brains [101]. If zinc is the abundant trace element of melanosomes (e.g. its concentration in human hair melanosomes is the highest Zn concentration attained in a structural element of human body), the next question striking mind is where and why it is localized in these organelles.

Zinc-melanin and zinc-protein interactions can be expected to occur in melanosomes. What is the distribution of zinc between melanin and protein moieties of melanosomes has not been clearly

defined because only a few studies have addressed the cardinal question of zinc distribution within melanosomes.

Prochozkov *et al.* [77] having digested the isolated melanosomes of Harding-Passey mouse melanoma with chymotrypsin separated the proteins electrophoretically on agar and studied by neutron activation analysis the Zn distribution among protein fractions. All the protein fractions displayed the presence of zinc, but a colourless protein band with the highest anodic mobility contained more than a half of the zinc associated with melanosomal proteins.

Zinc pool of melanosomes seems to be quite labile: It was possible to remove all hot Zn by 5 day exchange diffusion against 1mmol/l $ZnCl_2$ from B16 mouse melanoma melanosomes labelled with ^{65}Zn *in vivo* [10,11]. Treatment with 0.5 mmol/l acetic acid released 100% of radioactive zinc from the melanosomes as well. If the B16 melanosome acetic acid supernatant was passed over a Biogel P-2 column, 55% of ^{65}Zn was eluted in the void volume indicating a bound form of ^{65}Zn, less than 50% of ^{65}Zn was eluted in the salt volume (free ^{65}Zn) [11]. When the supernatant of SDS-treated B16 mouse melanoma labelled melanosomes was passed over an Ultrogel AcA54 column, ^{65}Zn was eluted in a fraction of a molecular weight in the region 15,00 - 18,00 [11].

There have been also observations suggesting indirectly the importance of non-pigment moieties of melanosomes for zinc binding. To this category falls e.g. a report of Shibata *et al.* [87] showing that Zn level was higher in premelanosomes than in melanosomes of Green's hamster melanoma.

3. NATURALLY OCCURRING ZINC LIGANDS IN PIGMENT CELLS AND STRUCTURES

In order to understand the function of metals in living systems, knowledge is needed on the biochemical basis of metal interactions with intracellular targets. The balance between essentiality and toxicity of metals can be regulated by specific binding sites for metals and hence knowledge concerning intracellular biochemical speciation is of importance.

3.1. Melanin

Melanin behaves as a natural cation exchange material [97] and is therefore able to incorporate various ions both *in vitro* and *in vivo* [23]. The analysis of the affinity of synthetic and natural melanins for inorganic ions showed interestingly that zinc was on the lower scale of ionic affinity [74]. Detailed study on binding capacity of metal ions to synthetic dopa melanins demonstrated that two classes of independent binding sites participated in the interactions of cations with dopa-melanin, with association constants for Zn $K_1=5.87 \times 10^5 mol^{-1}$, $K_2=4.85 \times 10^3 mol^{-1}$ [25].

Situation *in vivo* is expected to be more complicated: 1) Competition between various metal ions for binding sites on melanin can influence the binding parameters as evidenced by model experiments *in vitro* [9]. 2) Melanin pigments in melanosomes *in vivo* are always associated with a protein moiety which can also influence metal ion - melanin interactions. Among various metals only zinc was found in a higher amount in the melanin-human albumin-Zn complexes, unlike Mn, Cu and Fe binding of which decreased in the presence of albumin [3]; recently the binding capacity of melanoprotein isolated from bovine eyes for Zn^{2+} was found to be by 10 - 20 % lower compared with that of protein-free melanins [2]. The importance of protein in melanin-protein complexes for zinc binding was emphasized already by Bowness and Morton [18] but their results are difficult to interpret due to the usage of phosphate buffers in their experiments.

3.2. Metallothionein

Metallothionein is an important intracellular ligand for zinc and copper as well as for some other transition metals [70]. It is believed to be involved in the homeostatic control of Zn absorption, in cellular detoxification, in the control of differentiation and in direct activation of Zn-dependent enzymes [21,31,79].

The metabolic and growth demands of neoplastic tissue may make tumours the predominant site of Zn uptake [10,70,96] which is accompanied by hypozincemia [26,31,70,89]. This is a result of a number of factors, some unrelated to tumour. Hypozincemia has been also recorded in melanoma patients [47]. Further zinc redistribution during tumour-related stress can be induced by a rise in the amount of hepatic metallothionein [70,93]. Some authors suppose [70] that release of Zn^{2+} from lysing tumour cells may subsequently enable hepatic metallothionen synthesis to proceed.

Quantification of the copper-binding compounds in equine melanoma tumours revealed that as much as 50 - 60 % of total tissue copper was associated with metallothionein whereas tyrosinase and Cu_2Zn_2-superoxide dismutase accounted for appr. 2% of total copper [56]. The same situation is assumed for human melanoma tissue. Zn binds less strongly than Cu to metallothionein and can, therefore, be readily displaced by Cu [21] but Krauter *et al.* [56] found equimolar concentrations of zinc and copper in their samples which suggested that metallothionein might be the major protein ligand for zinc in pigment cells.

This would be in accord with the generally accepted concept of metallothionein as an autoregulated intracellular zinc (and copper) buffer [79] establishing intracellular steady state kinetics for Zn and Cu levels. As for pigment cells there have been only rare reports dealing with a specific role of metallothionein in these types of cells: Koropatnick and Pearson [55] studied B16 melanoma

cells with low and high metallothionein constitutive expression and concluded that metallothionein was associated with cisplatin resistance. Oliver *et al.* [66] demonstrated that induction of metallothionein synthesis in human retinal pigment epithelial cells was correlated with an increased capacity for ^{65}Zn uptake into cultured cells.

Zinc bound to metallothionein is released after degradation of the metallothionein protein in lysosomes (unlike the fate of Cu-metallothionein which is different) [79], hence lysosomes may be involved in the accumulation of zinc [84]. If we accept the more and more common opinion that melanosomes are related to lysosomes [88,102], this mechanism would offer an explanation for high Zn level in melanosomes.

3.3. Melanotransferrin

Melanotransferrin, also known as the tumour-associated antigen p97, is a monomeric glycoprotein expressed at high levels in most human melanomas but present in only trace amounts in normal adult tissues [22]. The comparison of the primary structure of p97 with that of other members of the transferrin superfamily revealed a Zn-binding consensus sequence found in metallopeptidases within the N-terminal lobe and in the C-terminal lobe a glutamic acid residue capable of completing a potential thermolysin-like Zn binding site [37]. Thus p97 may have a Zn-binding potential, unique amongst the transferrin superfamily. In contrast to other transferrins, melanotransferrin binds only one Fe^{3+} ion per molecule [5]. Functional consequences for melanoma cells with high p97 expression in melanoma cells have not so far been investigated.

3.4. B700 and related proteins

B700 protein is the major protein of the murine melanoma cell's melanosomal membrane; it is also present in the membrane of other cytoplasmic organelles as well as in the plasma membrane [44]. There are related proteins in melanomas of other species [39]. It has become obvious that the B700 protein is part of the serum albumin family of proteins [38]. A number of studies underscored the importance of controlling the relative concentrations of Zn and its ligands in Zn transport kinetic research and suggested that varying their concentrations might be a method of regulating the distribution of Zn into specific cells and tissues [8]. Albumin belongs to Zn ligands with physiologically high Zn affinity (circa 107) [1,40]. There has been no information on the B700 affinity for zinc. However, if it maintained the Zn-ligand affinity typical of serum albumin, it would become another hot candidate to explain Zn presence both in melanosomes and pigment cells.

3.5. Ferritin

Ferritin is a "fashionable" molecule because it can be engaged in the deactivation of increased iron load. In the substantia nigra the disbalance between iron and transferrin levels has been suspected from triggering free radical damage in Parkinson's disease [29].

It is less known that ferritin may fulfill also zinc-sequestering and -dispensing tasks. It has been postulated that ferritin may serve as the initial chelator for Zn^{2+} (and other metal ions) prior to the synthesis of metallothionein is initiated as the second line of defence [76]. No data on the concentration of ferritin in pigment cells have been available, though.

3.6. Zn-enzymes

The magnitude of the stability constants of metal binding proteins varies quite widely and has served to differentiate operationally between two classes, metalloproteins and metal-protein complexes [95] with firm and loose metal binding, respectively. Zinc containing enzymes fall in both groups.

There has been no Zn enzyme described the concentration of which in pigment tissues would be profoundly different from other tissues. It is only possible to mention high α-D-mannosidase expression in melanomas [32], (this enzyme has been suggested as a possible general indicator of Zn status [34]), and early papers emphasizing the importance of carbonic anhydrase to explain high Zn level in eye pigment tissues [36,59].

The marker enzyme of melanogenesis - tyrosinase - belongs to copper-containing proteins. It would be interesting to ascertain whether the recently discovered tyrosinase-related proteins are metalloenzymes and if so, what is their metal dependence.

3.7. Binding of zinc to low-molecular-weight ligands

Metal ion interactions with low-molecular-weight ligands *in vivo* are extraordinarily difficult to study due to the very low concentrations which are involved and due to the labile nature of most such associations. Our present knowledge about the chemical binding which may, or may not, take place between zinc and low-molecular-weight agents has had to be inferred largely from computer simulations of the equilibria which are thought to dominate the low-molecular-weight fraction of the metal ion [21]. These studies have demonstrated that e.g. in blood binding is clearly dominated by cysteinate with histidine acting as the other important coordinating partner [21,40]. Reduced glutathionate seems likely to supersede cysteinate inside most, if not all cells [21]. The presence of Zn cysteinate was cytochemically confirmed in cat tapetum lucidum rod-shaped paraplasmic inclusions

considered by some authors as melanosomes [53]. ^{1}H and ^{13}C NMR studies revealed that Zn^{2+} binds also with oxidized glutathione in aqueous medium with 1:1 stoichiometry [73]. Taking into account a significant role of glutathione for pigment cell metabolism [6], Zn-glutathione complexes may make the metabolic relations still more complex.

In pigment cells zinc - dopa interactions are also to be expected since L-dopa can bind zinc using its orthophenolic groups [51].

According to the prevailing opinion the small Zn^{2+}-species are involved in processes which exploit their kinetic advantages over the complex formed by proteins. For the most part, these involve transport to or through membranes and exchange between high-molecular-weight species [21] (Figure1).

Fig. 1 - Points of special interest in zinc relation to pigment cells and structures.
B700 = B700 and related proteins,
E = zinc enzymes,
MF = melanotransferrin,
MT = metallothionein,
LML = low-molecular weight-Zn ligands,
ZG = zinc gene regulatory proteins.

4. FUNCTIONS OF ZINC

Physical and chemical properties of zinc, including its coordination flexibility, make it highly adaptable to meeting the needs of proteins and enzymes that carry diverse biological functions and are involved in the metabolism of proteins, nucleic acids, carbohydrates and lipids as well as in the control of gene transcription and other fundamental biological processes such as cell division, differentiation, development, immune phenomena and receptor activity. The advance in knowledge of zinc chemistry and biochemistry in the past two decades has been striking and reached a level that provides predictive capacity for both the physiology and pathology of zinc metabolism. The astoudingly large body of observations and an encyclopedic analysis of the data have been subject of numerous reviews [e.g.4,27,95,98], but surprisingly no attempt to discuss the roles of zinc in melanin-containing structures has been made.

4.1. Participation of Zn^{2+} in melanogenesis

Catalytic function of Zn^{2+} in the synthesis of 5,6-dihydroxindole derivatives was noticed as early as 1950 [43] and included as a fact in the Raper-Mason scheme of melanogenesis. Observations of Prota and his associates have recently revived attention to the role of zinc in biosynthesis of melanins. They observed that various transition metals including Zn^{2+} affected markedly the chemical properties of melanin formed by the tyrosinase-catalyzed oxidation of L-dopa by increasing the incorporation of 5,6-dihydroxyindole-2-carboxylic acid into the pigment polymer [67,68]. Zn^{2+} can thus imitate function of dopachrome oxidoreductase. When acting together the inhibition of 5,6-dihydroxyindole-2-carboxylic acid decarboxylation was greater than that produced by Zn^{2+} or dopachrome oxidoreductase separately [50]. The suggestion that the presence of carboxylated indole units in natural melanins is due to the intervention in the melanogenesis of metal ions can be accepted. However, the role of Zn^{2+} namely in this respect appears to be uncertain because the free Zn^{2+} cation is damaging to biological systems and thus is associated with other molecules as Zn-ligand complex (see the section 3) resulting in a actual free Zn^{2+} ion concentration that is 10^{-3} - 10^{-6} that of the total zinc concentration [8,98]. Whether Zn^{2+}-ligand complexes can influence melanogenesis it has not been tested. Zn^{2+} ions were shown to inhibit the initial rate-limiting reaction of melanogenesis - tyrosine hydroxylation and thus to have a role in the regulation of melanogenesis [50].

4.2. Excretory function of melanosomes and pigment tissues

Melanin can participate in excretion of some substances under physiological conditions [81]. As hair melanosomes represent rich tissue reservoirs of zinc lost during removal of keratin structures, we tried to quantitate the Zn excretion via hair [12]. The daily Zn loss in man by this way varies around 20 mg which compared to the major Zn^{2+} portion excreted via pancreatic juice (10 mg/day) and to the output via urine (0.5 mg/day) is low. However, if we add also Zn^{2+} loss by means of epidermal melanosomes, the value will increase.

4.3. Zinc and free radical processes

Since the 1970s it has been anticipated that an essential biochemical function of zinc is to serve as a natural antioxidant [20,99,100]. Two mechanisms of zinc action have been elucidated - the protection of sulfhydryl groups against oxidation and the inhibition of the production of reactive oxygen species catalyzed by some transition metals, especially by displaced iron [20,42,100].

On this basis it was predicted that relatively high concentration of zinc might be present in those tissues vulnerable to oxidation such as the hair, skin, eye and spermatozoa. When this was shown to be the case, Willson [100] proposed the following corrolaries: 1 -"in healthy cells, vital molecules are protected from the action of decompartmentalized iron by the presence of zinc"; 2 -"normal cells are designed in such a way that division is not initiated until the zinc concentration at critical sites within the cell is sufficient to protect them from decompartmentalized iron that might normally be present. Zinc thus plays protective and stimulatory role".

The frequent occurence of necroses in melanoma tissue [13] and the presence of H_2O_2 [24] make the metal driven free radical processes in pigmented tumours probable. Moreover, increased malondialdehyde levels found in the livers of B16 and S91 melanoma-bearing mice [13,71] suggest that the tumours alter host antioxidant defenses. Alteration of iron metabolism and increased levels of lipid peroxidation are characteristic of substantia nigra in Parkinson's disease [30] and the fact that also zinc levels in substantia nigra are markedly increased under these circumstances may indicate a physiological response to oxidative stress [29].

Melanin in melanosomes in pigment cells and tissues represents another source of free radical activity. The melanin polymer has long been known to exhibit stable free radical properties, because of semiquinones, which appear to have a protective action in cells probably by acting as a sink for diffusible free radical species [80]. Data derived from *in vitro* experiments have indicated that melanins can function as a scavenger of the superoxide anion radical and can protect cellular structures against photochemically induced lipid peroxidation also due to the absorption of light energy [35]. Zn^{2+} ions were shown to stabilize semiquinone anion radicals in melanin and to increase free radical activity in melanosomes [2,83]. Melanin polymerization is thought to occur by a free radical process in which semiquinones are formed by redox equilibration interactions between melanin precursors which as reactive species are strictly compartmentalized [13,80], and if leaked metabolically detoxified [13].

Evidence documenting that a number of catecholic melanin precursors, including cysteinyldopas and dihydroxyindoles, are photochemically unstable *in vitro* in the presence of biologically relevant ultraviolet radiation was presented by Koch and Chedekel [52]. Definitive evidence of occurrence of these reactions *in vivo* is currently unavailable, nevertheless these photochemical processes are expected to have a role in the pathogenesis of various pathological processes. The high level of zinc in epidermal and eye pigment cells may again indicate a physiological defense against the potential danger of oxidative stress.

4.4. Metal ion "buffering" by melanosomes - mobile pool of Zn^{2+}

Melanosomes have been proposed to represent a physiologically important "reservoir" for essential trace elements, a short term storage deposits, which by binding or releasing the metal ions may play a key role in the control of various processes, e.g. in the action of ionic pumps. Such mechanism is believed to be involved in the secretion of endolymphatic fluid in inner ear [60].

According to Pffeifer and Mailloux [69] melanin should be investigated as a storage bank for useful cations such as calcium, potassium, sodium and zinc. The binding of these ions would prevent a disruption in the body's osmotic balance. If the mineral balance was disrupted by dietary or physiological causes, the increased concentration of copper and lead with their greater affinity for melanin would lead to the displacement of more favourable cations - Zn^{2+} and Ca^{2+} which may have implication for hypertension and its therapy [69].

Scavenging role in the elimination of metals, when they reach too high levels in the cell, was ascribed to neuromelanin granules [101].

The complexity of zinc intercellular transport can be illustrated by earlier work of O'Rourke *et al* [64] demonstrating that zinc secreted by the ciliary body is made bioavailable and absorbed by the chorioretinal complex.

However interesting these theories sound, until zinc melanosomal binding sites and their binding parameters are clearly defined, we can hardly ponder upon the importance of these proposals. All we can say is that the melanosome pool of zinc is mobile as evidenced by the zinc release from eye melanosomes in the face of reduced amounts of bioavailable zinc, for example with a deficient diet [82].

4.5. Zinc and melanomas

Inhibition of tumour growth by dietary zinc deficiency appears to be a general effect irrespective of cell type, species or site of growth [49,89,96]. This may be mediated by the direct requirements for zinc for cellular proliferation as well as by indirect effects on immune function and the interaction with other trace elements.

As for melanoma, P51 mouse melanoma cells (derived from B16 melanoma) when grown in zinc-depleted media had longer doubling time and a decreased thymidine uptake [61]. On the contrary it was reported that the addition of zinc and iron tartrate complexes to Eagle's minimal essential medium was sufficient to support the proliferation of B16 melanoma cells in the absence of serum [54]. Altered organ distribution and survival of melanoma cells were observed in the Zn depleted dietary groups of P51 melanoma-bearing mice [61].

Zn^{2+} concentrations exceeding 10^{-4} mol/l are generally cytotoxic *in vitro* [14,15]. It is therefore not surprising that *in vitro* Zn^{2+} was shown to inhibit both the anchorage-dependent [14] and anchorage-independent growth [57] of Cloudman S91 melanoma. Attempts to suppress B16 and Cloudman S91 growth by zinc acetate administration in mice were unsuccessful because the necessary Zn^{2+} levels *in vivo* were difficult to reach [16]. Preincubation *in vitro* of cell suspensions with 10^{-4} mol/l zinc acetate prior to injecting tumour cells inhibited melanoma development in mice [16]. 10^{-4} mol/l zinc sulphate was shown to decrease the i.v. but not s.c. transplantability of B16 melanoma [33].

Strong homeostatic control of zinc levels [4,27,95] prevents direct therapeutic use of zinc. The increased zinc uptake by melanomas might be rendered suitable for tumour localization with ^{69}Zn [10] and for targetting tumour cells with chemotherapeutic agents since zinc may act as a carrier for pharmacologically active ligands [96].

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