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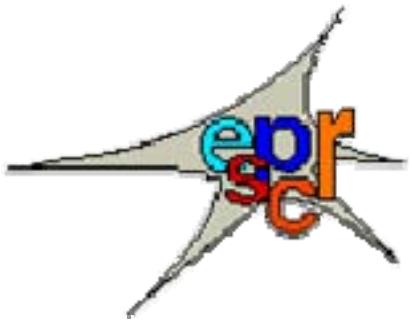

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH *BULLETIN*

N° 40 - August 2001

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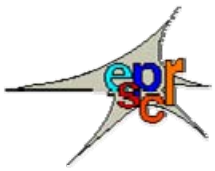

LETTER TO THE EDITOR
DISCUSSION, REVIEW,
SHORT COMMUNICATION, ...

MEETING REPORT

by Dr J. Borovansky

INTERNATIONAL SYMPOSIUM ON PHOTOPROTECTION

Krakow, Poland, May 19 -22, 2001

The symposium was organized by the European Society for Photobiology (ESP) and Jagiellonian University with two main organizers - Prof. Tadeusz Sarna and Prof. T.George Truscott. The cooperation between the European Society for Pigment Cell Research and the European Society for Photobiology dates from the 8th ESPCR Meeting in Prague 1998 where the ESP prepared a special session also devoted to photoprotection. Although this time the ESPCR was not an official partner, the symposium attracted many ESPCR members, particularly to Session I.

Session I "Natural Sunscreens" was opened by *Prof. P.A. Riley* who presented a plenary lecture "Photoprotection: Melanin, Mechanisms & Myths". In his brilliant concise style he summarized factors involved in photoprotection, with a special emphasis on melanin properties. *Simon* described the structural organization of eumelanin based on atomic force microscopy measurements and discussed the role of pigment aggregation in the photogeneration of ROS (reactive oxygen species). *Sarna et al*. reviewed the antioxidant properties of melanin; the ability of melanin to sequester redox active metal ions and to neutralize ROS are of key importance in melanin photoprotection. *Ramsden* in his lecture "Mechanistic Studies of Tyrosinase Oxidation" demonstrated that tyrosinase oxidizes phenols to o-quinones in one step and not via intermediate catechols as was widely claimed. *Pavel and Smit* ("The Role of Melanin in Protection against UV Radiation") discussed the leakage of reactive melanin precursors and showed that these compounds could liberate iron from its ferritin stores, which could substantially increase the cytotoxic effect of UV radiation. *Schallreuter* ("Thioredoxin Reductase - Its Role in Epidermal Redox Status) emphasized that UVB-generated H_2O_2 in the epidermis is involved in the control of thioredoxin reductase and showed that oxidation of 6-tetrahydrobiopterin to 6-biopterin by hydrogen peroxide could lead to a cytotoxic environment for epidermal melanocytes. *Leszczynski & Pastilla* reported that UVA radiation enhanced metastatic properties of B16 melanoma cells probably due to an alteration in expression of adhesion molecules. *Haywood & Linge* spoke on thermolysis of hair melanin induced by the 694nm ruby laser. *Borovansky & Elleder* characterized in detail the autofluorescence of synthetic and natural eu-, pheo- and neuromelanins, which can be induced in vitro by UV and near UV-light with ~~a~~ production of hydrogen peroxide, associated with photodegradation of pigment structures.

The principal speaker in Session II "Commercial Sunscreens" was *Prof. Urbach* who gave the plenary lecture "The Historical Aspects of Sunscreens".

Session III "Dietary and Enzymic Aspects" concentrated mainly on photoprotection by dietary ß-carotene and lycopene. *Picardo et al.* studied the role of antioxidant enzymes in photoprotection in melanocyte cultures and in biological samples from subjects with different phototypes and from melanoma patients.

Session IV dealt with ”Photoprotection of the eye”. *Boulton* characterized photodamage to the RPE as an oxygen dependent phenomenon which involves the photoinduction of ROS from a chromophore(s) located within the RPE. He suggested that lipofuscin and not melanin is the major chromophore responsible for the ensuing cytotoxicity.

In the Poster Session *Land and Riley* exhibited a poster ”Spontaneous Redox Reactions of Dopaquinone and the Balance between the Eumelanic and Phaeomelanic Pathways”, *Jastrzebska et al.* contributed ”Photoconductivity of Synthetic Dopa Melanin” and *Smit et al.* showed a poster devoted to elemental analysis of cultured melanocytes.

The symposium was partly situated in the picturesque historical buildings of the Jagiellonian University. The organization was perfect and the well set up programme was enjoyed by more than 70 scientists from four continents. Many participants left Krakow with a desire to return in the near future, e.g. on the occasion of an ESPCR Meeting.

Jan Borovansky

CURRENT LITERATURE

1. Chemistry of melanins and other pigments

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2. Biology of pigment cells and pigmentary disorders

(Dr. M. Picardo)

Meyskens Jr and co-workers reviewed the implications of oxidative stress in melanocytes and the possible consequences of intracellular redox alteration in melanocyte transformation and melanoma cell proliferation. The topics reported in this review included: melanogenesis, melanin synthesis and glutathione, melanin as an antioxidant and cellular pro-oxidant, response of melanin UV, anti-oxidant levels and melanogenesis, redox regulation of transcription factors, and data supporting the hypothesis for the pathogenesis of melanoma based on altered redox control. **Hachiya et al** demonstrated that endothelin-converting-enzyme (ECE) 1alpha in keratinocytes plays a pivotal role in the induction of pigmentation following UVB irradiation and that an extract of Sanguisorba officinalis, which inhibits ET-1 production in human keratinocytes, could be a good ingredient for a whitening agent. **Berking and Herlyn** illustrated the advantages of the development of organotypic cultures of human skin in melanoma research. Long-term in vivo studies, especially important for melanogenesis and melanoma metastasis, were realised by grafting of skin reconstructs to immunodeficient laboratory animals. In this review, principles and different methods of skin reconstruction were introduced with a focus on applications in pigmentary biology. **Kawaguchi and co-workers** proposed a hypothetical scheme of melanocyte proliferation caused by UV exposure. In normal epidermis, TRP-1+ mature melanocytes and Kit+ melanocyte precursors are identified. Stem cell factor is released by keratinocytes and activates Kit receptor on melanocyte precursors following UV exposure. The~~,~~ Kit+ melanocyte precursors first differentiate into Mitf+ and TRP-2+ melanoblasts that have proliferative potential, then become mature TRP-1+ melanocytes, which recapitulates the differentiation steps of melanocytes in normal development.

Oculocutaneous albinism type 2 results from mutation at the p locus. **Manga et al** proposed that p is required by melanocytes for transport of melanosomal proteins. In its absence, tyrosinase accumulates in vesicles and, in cultured melanocytes, is proteolysed and secreted. Posterior uveal melanoma is the most common intraocular tumour in adults, responsible for the death of approximately 35% of patients. **Elshaw and co-workers** studied the involvement of integrins in uveal melanoma and correlated expression with invasive potential in vitro. They found that the laminin binding alpha 6 beta1 integrin was not expressed by either melanocytes and tumours with spindle morphology, which are considered to have a better prognosis. This finding suggest that the expression of alpha 6 beta1 could be a useful prognostic indicator.

In malignant melanomas, loss or down-regulation of E-cadherin was observed both in vitro and in vivo. Several studies revealed that down-regulation of E-cadherin leads to defects in control of melanocyte proliferation by keratinocytes and to acquisition of an invasive tumor cell phenotype. **Poser et al** provided further insights into the regulation of E-cadherin expression in malignant melanoma cells and revealed that up-regulation of factor Snail could play a role in switching off E-cadherin expression in malignant melanoma cells. In blood samples from metastatic melanoma patients, **Bohm and co-workers** found elevated levels of alpha-MSH, HGF and Endothelin-1. They suggested that aberrant production of these factors could be responsible not only for activation of the pigment system in diffuse melanosis of metastatic melanoma, but also for increased proliferation, motility and pigment incontinence of normal and malignant melanocytes.

Kageshita et al studied the serum tissue factor (TF) levels in patients with melanoma. They found that TF was ubiquitously expressed in melanocytic cells and its expression was not correlated with serum 5-S-CD, one of the melanoma progression marker, suggesting serum TF level was not useful as a melanoma progression marker. **Deffrennes V et al** have analysed in different melanoma cell lines the molecular mechanisms leading to an abnormal pattern of MHC class II expression. They showed the constitutive expression of class II transactivator transcripts from promoter II, mainly used constitutively in B lymphocytes. The hypothesis was that this phenomenon might be linked to the neoplastic state of the melanoma cells. In eight melanoma cell lines, **Yang and Richmond** reported an increased IkappaB (IKK) activity, enhanced phosphorylation of IkappaBalpha and p65, and an enhanced nuclear localisation of p65/p50 in comparison to normal human epidermal melanocytes. Moreover antibody to the chemokine, CXC ligand 1, was able to block IKK activity and to inhibit the proliferation of melanoma, suggesting that the constitutive activation of NF-kappaB and autocrine effects of CXCL1 could play an important role in the pathogenesis of melanoma. The non-selective endothelin-B (ETB) receptor is the major receptor in melanocytes and malignant melanoma cells. **Demunter and co-workers** combined immunohistochemistry and reverse transcriptase-polymerase chain reaction to study ETB receptor expression in benign and malignant pigment cell lesions and in normal skin. Their data demonstrated that ETB could be added to the growing list of tumor progression markers in malignant melanoma, suggesting that endothelins play a role in melanoma progression in the skin. **Fang et al** described induction of a juvenile isoform of a microtubule-associated protein 2 (MAP-2c) in cultured metastatic melanoma

cells by the differentiation inducer hexamethylene bisacetamide. Up-regulation of this MAP-2 isoform, a marker for immature neurons, is accompanied by extended dendritic morphology and down-regulation of tyrosinase-related protein 1 (TYRP1/gp75), a melanocyte differentiation marker. They showed that neoplastic melanocytes, particularly at early stages, retained the plasticity to express the neuron-specific marker MAP-2. Hepatocyte growth factor (HGF) is a mitogen for human melanocytes and has been implicated as an important factor for the development and dissemination of melanomas. **Hamoen and co-workers** suggested that expression of HGF, by virtue of its ability to enhance proliferation and cell clustering may play a role in the multi-step process of transformation, even if an autocrine signal through HGF alone was not sufficient for malignant transformation. **Ivanova et al** analyzed in vitro the differences in cGMP formation in nonmetastatic and metastatic melanoma cell lines compared with normal melanocytes in culture. Their data suggested that: soluble guanylyl cyclase could be considered an important target for the signaling activities of nitric oxide in melanocytic cells and in the absence of NO-sensitive guanylyl cyclase, but upregulated activities of natriuretic-peptide-sensitive membrane -bound guanylyl cyclase isoforms were associated with the metastasis of melanoma

Massi D et al found that nitric oxide synthase (iNOS) was constantly absent in melanocytic naevi, whereas it was frequently expressed in melanomas, with up-regulation of the enzyme paralleling tumour progression. Thus, a fundamental role of iNOS in the malignant transformation of melanocytes and in tumour growth was suggested. In addition, iNOS could be useful as an immunohistochemical marker for malignant melanocytic lesions.

In normal human melanocytes, **Rocha and Guillo** reported the induction of nitric oxide synthase (NOS), with the consequent production of nitric oxide (NO), after treatment with lipopolysaccharide and cytokines. Their results suggest that NO could lead to autodestruction of melanocytes causing skin depigmentation. The possibility of a therapy with NOS-inhibitors in vitiligo was put forward. To correlate the occurrence of skin-homing melanocyte-specific CTL with the vitiligo state, **Lang et al** established a sensitive enzyme-linked immunospot (ELISPOT) assay for detection of CD8+ T cells specific for 11 different peptides presented by melanocytes from MelanA/MART1, tyrosinase and gp100. Furthermore, they applied IFN-γ staining as an additional marker for antigen specificity, and they examined the expression of the skin homing marker cutaneous lymphocyte antigen (CLA) on these cells. Their findings support the hypothesis that vitiligo is a CD8+ T cell-mediated autoimmune disease. **Phillips J and co-workers** tried to develop an improved culture strategy for grafting of vitiligo patients. They reported that irradiated donor fibroblasts can enhance melanocyte number within keratinocyte/melanocyte co-culture. However they found that a high content of keratinocytes induced a down-regulation of both melanocyte number and pigmentary function, as revealed by the loss of TRP-1 expression.

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  Expression of microtubule-associated protein 2 in benign and malignant melanocytes: implications for differentiation and progression of cutaneous melanoma. Am J Pathol, 158(6): 2107-2115, 2001.

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Generalized hyperpigmentation of the skin due to vitamin B12 deficiency. J Dermatol, 28(5): 282-5, 2001.

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Vitiligo: the evolution of cultured epidermal autografts and other surgical treatment modalities. Arch Dermatol, 137(3): 348-349, 2001.

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Constitutive IkappaB kinase activity correlates with nuclear factor-kappaB activation in human melanoma cells. Cancer Res, 61 (12): 4901-4909, 2001.

3. MSH, MCH, other hormones, differentiation

(Dr. B. Loir)

- Bastiaens MT, ter Huurne JA, Kielich C, Gruis NA, Westendorp RG, Vermeer BJ, Bavinck JN; The Leiden Skin Cancer Study Team.
Melanocortin-1 receptor gene variants determine the risk of nonmelanoma skin cancer independently of fair skin and red hair. Am J Hum Genet 68(4):884-94, 2001.
Comments: see in Box et al

- Bohm M, Schiller M, Nashan D, Stadler R, Luger TA, Metze D.
Diffuse melanosis arising from metastatic melanoma: pathogenetic function of elevated melanocyte peptide growth factors. J Am Acad Dermatol 44(5):747-54, 2001.
Summary: The origin of diffuse melanosis resulting from metastatic melanoma is unknown. The authors examined the changes in the skin of one affected patient and determined that the peripheral blood levels of alpha-MSH, hepatocyte growth factor, and endothelin-1 were significantly elevated in this patient. They concluded that « aberrant production of these factors may not only be responsible for activation of the pigment system in diffuse melanosis of metastatic melanoma, but also for increased proliferation, motility, and pigment incontinence of normal and malignant melanocytes. »

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Melanocortin-1 receptor genotype is a risk factor for basal and squamous cell carcinoma. J Invest Dermatol 116(2):224-9, 2001.
Comments : Melanocortin-1 receptor (MC1R) gene variants have previously been associated with fair skin and red hair and, independently of these, with cutaneous malignant melanoma. Both studies (Bastiaens et al ; Box et al) indicate that MC1R gene variants are also important independent risk factors for nonmelanoma skin cancer.

- Carlson KW, Nawy SS, Wei ET, Sadee W, Filov VA, Rezsova VV, Slominski A, Quillan JM.
Inhibition of mouse melanoma cell proliferation by corticotropin-releasing hormone and its analogs. Anticancer Res 21(2A):1173-9, 2001.

- Chluba J, Lima de Souza D, Frisch B, Schuber F.
Enhancement of gene delivery by an analogue of alpha-MSH in a receptor-independent fashion. Biochim Biophys Acta 1510(1-2):198-208, 2001.

- Fang D, Hallman J, Sangha N, Kute TE, Hammarback JA, White WL, Setaluri V.
Expression of microtubule-associated protein 2 in benign and malignant melanocytes: implications for differentiation and progression of cutaneous melanoma. Am J Pathol 158(6):2107-15, 2001.
Summary: « The authors describe induction of a juvenile isoform of microtubule-associated protein 2 (MAP-2c) in cultured metastatic melanoma cells by the differentiation inducer hexamethylene bisacetamide. Up-regulation of

this MAP-2 isoform, a marker for immature neurons, is accompanied by extended dendritic morphology and down-regulation of tyrosinase-related protein 1 (TYRP1/gp75), a melanocyte differentiation marker. » Moreover, their data show that neoplastic melanocytes, particularly at early stages, retain the plasticity to express the neuronal marker MAP-2 and that a similar reciprocal staining pattern MAP-2 vs TYRP1 was confirmed in vivo.

- Hamoen KE, Borel Rinkes IH, Morgan JR.
  Hepatocyte growth factor and melanoma: gene transfer studies in human melanocytes. Melanoma Res 11(2):89-97, 2001.
  Summary: « Hepatocyte growth factor (HGF), a fibroblast-derived protein that affects the growth, motility and differentiation of epithelial cells, is a mitogen for human melanocytes and has recently been implicated as an important factor for the development and dissemination of melanomas. The authors used retrovirus-mediated gene transfer to introduce the gene encoding human HGF into normal human melanocytes. Their results suggest that expression of HGF, by virtue of its ability to enhance proliferation and cell clustering, may play a role in the multi-step process of transformation, but an autocrine signal of HGF alone is not sufficient for malignant transformation. »

4. Photobiology

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5. Neuromelanins

(Prof. M. d'Ischia)

Current research in the field of neuromelanin focuses attention to a number of issues that are closely associated as potential etiopathogenetical factors in Parkinson's disease and related neurodegenerative disorders. This is well apparent in the early papers of 2001, featuring studies on neurotrophic factor loss during neuron degeneration, metal accumulation and redox state, and effects of nitric oxide on dopamine conversion. Chauhan et al. (J. Chem. Neuroanat. 2001, 21(4), 277-288) investigated the distribution of neurotrophic factors, including nerve growth factor, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor, brain derived neurotrophic factor, neurotrophin-3 and neurotrophin-4 in the neuromelanin-containing substantia nigra pars compacta (SNc) of Parkinson's disease brains by immunofluorescence. The results indicated that glial cell line-derived neurotrophic factor, of the tested neurotrophic factors, is probably the most susceptible and the earliest to decrease in the surviving neurons of SNc. On this basis, it was concluded that decreased availability of this growth factor may play a role in the process of SNc neurodegeneration in Parkinson's disease.
Nappi and Vass (J. Biol. Chem., 2001, 276(14), 11214-11222) compared the effects of nitric oxide (NO) on both tyrosinase/O_2-and horseradish peroxidase/H_2O_2-mediated oxidations of dopamine and its precursor L-dopa with those on autoxidative processes. The results of this investigation, carried out largely by electrochemical techniques, suggested that an oxidized nitrodopamine derivative, possibly the quinone or semiquinone of 6-nitrosodopamine, was generated in peroxidase/H_2O_2/NO-mediated reactions with dopamine, along with two oxidized melanin precursors, dopamine quinone and dopaminechrome. The observed chemistry, if confirmed in subsequent work, would highlight novel possible adverse effects of NO-promoted oxidations of dopamine and other catechols on cellular integrity and function, due to formation of reactive quinones and potentially cytotoxic noncyclized nitroso derivatives.
The issue of metals and neuromelanin in parkinsonian substantia nigra and other brain regions was addressed by Zecca et al. (J. Radioanal. Nucl. Chem. 2001, 248(1), 129-131) and by Yoshida et al. (J. Synchrotron Radiat. 2001, 8(2), 998-1000). The former authors measured the concentration of 18 elements in cortex, cerebellum and putamen of human brain and in their neuromelanins by instrumental neutron activation analysis, whereas the latter investigated the redox state of iron in a single neuron of the substantia nigra (SN) from a patient with Parkinson's disease (PD) using autopsy midbrain specimens including SN. X-ray absorption near-edge structure (XANES) spectroscopy results showed that the iron in the neuromelanin granules within SN neurons changed from ferrous (Fe2+) to ferric (Fe3+) ion in the process of neuronal degeneration. These results would further corroborate the critical role of the iron-neuromelanin interaction and reinforce the notion of oxidative stress as a most important biochemical correlate of Parkinson's disease.
As a last remark, a patent (Nelson, Jodi. (USA). PCT Int. Appl. (2001)) attempting to exploit neuromelanin as a target for melanin-binding quinolines in the treatment of Parkinson's disease is worthy of critical interest. The method is based on administering to the patients an effective amount of a neuromelanin-binding compound having a quinoline ring in a suitable pharmaceutical carrier. Enantiomers of chloroquine phosphate were tested with respect to their ability to inhibit diamine oxidase and bind to neuromelanin.

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  Depletion of glial cell line-derived neurotrophic factor in substantia nigra neurons of -Parkinson's disease brain. J. Chem. Neuroanat. 21(4), 277-288., 2001.

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The effects of nitric oxide on the oxidations of L-dopa and dopamine mediated by tyrosinase and peroxidase. Biol. Chem. 276(14), 11214-11222, 2001.

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Quinolines for the treatment of Parkinson's disease. (USA). PCT Int. Appl. Application: WO 2000-2000US40385 20000713. Priority: US 99-143767 19990713; US 2000-175051 20000107; US 2000-202140 20000505, 2001.

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6. Genetics, molecular and developmental biology

(Dr. F. Beermann)

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Dual inactivation of RB and p53 pathways in RAS-induced melanomas. Molecular & Cellular Biology 21(6):2144-2153, 2001.

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Increased transgene expression by the mouse tyrosinase enhancer is restricted to neural crest-derived pigment cells. Genesis 29(4):180-187, 2001.

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Analysis of melanocyte precursors in Nf1 mutants reveals that MGF/KIT signaling promotes directed cell migration independent of its function in cell survival. Developmental Biology 232(2):471-483, 2001.

7. Tyrosinase, TRPs, other enzymes

(Prof. J.C. Garcia-Borron)

The realization that aberrant processing of tyrosinase and the tyrps are causative of a variety of pathological states has prompted an increased interest in the molecular mechanisms underlying these complex pathways. This interest is further explained by the demonstration that tyrosinase, as well as the tyrps and other melanocyte differentiation markers are major sources of melanoma-derived antigenic peptides, thus contributing to the cellular immune response. As a result of this interest, and owing to the availability of new powerful experimental approaches, the knowledge of the processing of melanosomal proteins is increasing exponentially, and the burst of new information is quite impressive. Just as an example, 8 out of 35 papers referenced in this issue deal with different aspects of the normal or aberrant folding, post-translational processing, trafficking and degradation of melanogenic proteins. And it can be anticipated that this flow of new information will not decrease for a while.

A role of tyrosine as a key regulator for several aspects of melanocyte biology was proposed some time ago by John Pawelek's group. Two new papers provide further evidence for such a role. Interestingly, although the matters approached in each paper are very different, their conclusions might be complementary. Schwahn et al (Pigment Cell Res 2001 Feb;14(1):32-9) report that high levels of tyrosine have an anti-proliferative effect in human melanocytes, and, at the same time, potentiate the melanogenic response to MSH. On the other hand, Halaban et al. (J Biol Chem 2001 Apr 13;276(15):11933-8) present evidence suggesting that the typical tyrosinase substrates, DOPA and tyrosine, promote proper folding and transport of the enzyme. It will be interesting to see whether these two observations are actually related, and whether the tyrosinase substrates, or even other melanogenic intermediates, have a similar effect on the tyrps. Two other independent papers provide evidence pointing to processing defects as the molecular basis of OCA 1 and 2 (Toyofuku K, et al, Biochem J 2001 Apr 15;355(Pt 2):259-69, Manga P et al., Exp Eye Res 2001 Jun;72(6):695-710). All this information is setting the stage for a new concept of the physiopathology of several pigmentation disorders, and we can certainly expect other exciting reports in this field, in the near future.
Good news for wine lovers. Many of us will agree in that a cup of good wine is an enjoyable experience, but it may turn out that it is also a healthy anti-melanoma practice. Indeed, Gomez-Cordoves et al (J Agric Food Chem 2001 Mar;49(3):1620-4) suggest that phenolic fractions from wine have several interesting effects on tyrosinase activity, and also decrease colony formation by human melanoma cells. In the light of these results, and since Italian wines are excellent, I would recommend all ESPCR members to attend the Rome Meeting and get there a little preventative anti-melanoma therapy!

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Mislocalization of melanosomal proteins in melanocytes from mice with oculocutaneous albinism type 2. Exp Eye Res 72(6):695-710, 2001.

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Diverse roles of conserved asparagine-linked glycan sites on tyrosinase family glycoproteins. Exp Cell Res 1;267(1):115-25, 2001.

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Possible involvement of ERK 1/2 in UVA-induced melanogenesis in cultured normal human epidermal melanocytes. Pigment Cell Res 14(2):103-9, 2001.

8. Melanosomes

(Dr. J. Borovansky)

The usual hot topics have been studied recently - melanosome transport *(Smith & Simmons)*, melanosome transfer from melanocytes to keratinocytes *(Minwalla et al., Scot & Zhao)* and traffic events endosomes/melanosomes *(Gomez et al., Overwijk & Restifo)*. Two papers devoted to the function of the mouse ocular albinism gene product *(Samaraweera et al., Surace et al.)* conclude that the protein plays a role particularly in the earliest steps of melanosome biogenesis. The acid intramelanosomal pH was shown to ensure maximum interaction between formed melanin and protein(s) *(Mani et al.)*. The electric charge of melanosomes was measured by *Testorf et al* and its origin was analyzed. The list of tumours containing melanosomes was extended by angiomyolipoma *(Barnard & Lajoie)*.

- Barnard M, Lajoie G.
Angiomyolipoma: immunohistochemical and ultrastructural study of 14 cases. Ultrastruct Pathology 25(1): 21-29, 2001.
Comments: Angiomyolipoma, a neoplasm likely derived from a single cell that shares homology with the pericyte, shows consistent immunopositivity for HMB45. This was associated with ultrastructural observation of melanosome-like structures in 7 of 14 tumours examined in this study.

- Gomez PF, Luo D, Hirosaki K, Shinoda K, Yamashita T, Suzuki JJ, Otsu K, Ishikawa K, Jimbow K
Identification of rab7 as a melanosome-associated protein involved in the intracellular transport of tyrosinase-related protein 1. J Invest Dermatol 117(1): 81-90, 2001.
Comments: The authors demonstrated the presence of rab3, rab7 and rab8 in the melanosomal fraction. Rab7 was colocalized with TRP-1 around the perinuclear area and in the perikaryon. A suggestion is made a) that rab7 is a melanosome-associated molecule, b) that TRP-1 is present in late endosome delineated granules and c) that rab7 is involved in the transport of TRP-1 from the late-endosome delineated granule to the melanosome.

- Mani I, Sharma V, Tamboli I, Raman G.
Interaction of melanin with proteins: The importance of an acidic intramelanosomal pH. Pigment Cell Res 14(3): 170-179, 2001.
Comments: Melanin formation in vitro is potentiated by an alkaline pH whereas melanogenesis in melanosomes takes place in an acidic environment. The effect of various model proteins on melanin synthesis and on their interaction with melanin was investigated. Many proteins increased melanin synthesis at an acidic pH. It appears that acid intramelanosomal pH is essential to ensure maximum interaction between melanin and protein and to ensure that all the melanin formed is protein bound.

- Minwalla L, Zhao Y, Cornelius J, Babcock GF, Wickett RR, Le Poole IC, Boissy RE.
Inhibition of melanosome transfer from melanocytes to keratinocytes by lectins and neoglycoproteins in an in vitro model system. Pigment Cell Res 14(3): 185-194, 2001.
Comments: A battery of lectins and neoglycoproteins was tested for their effect on melanosome transfer from melanocytes to keratinocytes in human cell cultures. Addition of the compounds mentioned above to cocultures inhibited the transfer of melanosomes by 67-93%, which supports the role of selected lectins and glycoproteins in melanosome transfer.

- Overwijk WW, Restifo NP.
Autoimmunity and the immunotherapy of cancer: Targeting the "self" to destroy the "other". Critical Reviews in Immunol 20(6): 433-450, 2000.
Comments: Review proposing that the intersection of protein transport to melanosomes and endosomes allows for the loading of MDA (melanocyte differentiation antigens) peptides on MHC class II molecules, resulting in the activation of MDA-specific CD4(+) "helper" cells that aid the induction of melanoma specific CD8(+) T cells. Thus, the immunogenicity of MDA may be a consequence of their unique cell biology.

- Samaraweera P, Shen B, Newton JM, Barsh GS, Orlow SJ.
The mouse ocular albinism gene product is an endolysosomal protein. Exp Eye Res 72(3): 319-329, 2001.
Comments: To gain insight into the role of Oa1, the mouse homolog of the human X-linked ocular albinism 1 protein, its properties and localization were investigated. The results indicate that Oa1 is a melanocyte-specific integral membrane glycoprotein localized to late endosomes/lysosomes but not mature melanosomes. The authors speculate that Oa1 may play a role in the trafficking of vesicles to developing melanosomes.

- Scott G, Zhao Q.
Rab 3a and SNARE proteins: Potential regulators of melanosome movement. J Invest Dermatol 116(2): 296-304, 2001.
Comments: Demonstration of the presence of rab3a and SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) on isolated melanosomes and SNARE complexes in melanocyte cell cultures is in accord with the expected role of these proteins in targetting melanosomes to the plasma membrane, to melanosome transfer to keratinocytes, or both.

- Smith DA, Simmons RM.
Models of motor-assisted transport of intracellular organelles. Biophys J 80(1): 45-68, 2001.
One-dimensional models are presented for macroscopic intracellular transport of organelles and vesicles by molecular motors on a network of aligned intracellular filaments. A motor-coated organelle or vesicle is described as a diffusing particle binding intermittently to filaments, when it is transported at the motor velocity. Two models are treated in detail - unidirectional and bidirectional ones. For each model mathematical characteristics with many equations were deduced. Melanin-producing cells are mentioned as a particularly attractive prospect for qualitative analysis and theoretical modeling.

- Surace EM, Angeletti B, Ballabio A, Marigo V.
Expression pattern of the ocular albinism type 1 (Oa1) gene in the murine retinal pigment epithelium. Invest Ophthalmol Vis Sci 41(13): 4333-4337, 2000.
Comments: To better understand the pathogenesis of the ocular albinism type 1 , the time of onset and the pattern of the expression of the mouse homolog of the OA1 gene were monitored during eye development. The localization of Oa1 mRNA was studied and compared with the expression of other genes (tyrosinase, pink eyed dilution) involved in melanosome biogenesis. Oa1 expression was detected at early stages of RPE development , together with other genes involved in pigmentation defects. Oa1 is likely to play an important function in the earliest steps of melanosome biogenesis.

- Testori MF, Lundström I, Oberg PA.
The electric charge of pigment granules in pigment cells. Biosensors & Bioelectronics 16(1-2): 31-36, 2001.
Comments: Melanosomes were isolated from cultured melanophores of Xenopus laevis and their electric charge was determined by electrophoresis. There was no significant charge difference between melanosomes isolated from cells with aggregated or dispersed pigment granules -1.5×10^{16}C and -1.7×10^{16}C, respectively. Negative charge of melanosomes can have 3 different origins: 1) melanin itself is negatively charged; 2) proteins associated with melanosomal membrane may have a negative charge; 3)motor proteins associated with melanosomes can be phosphorylated with negative phosphate groups. Since the charge was not proportional to melanosome volume, the charge of melanosomes is not likely to originate mainly from melanin.

9. Experimental melanoma, Cell culture

(Dr. N. Smit)

Melanocyte culture

Rocha and Guillo describe the production of nitric oxide by cultured human melanocytes after treatment with LPS, TNF-α and IFN-γ as demonstrated by measurement of nitrite production of the melanocytes after 96 h incubation. These results confirm earlier findings described by Tsatmali et al (J Invest Dermatol 114, 2000) who also suggested a melanogenic role for NO in melanocytes. The cellular signaling of NO is mediated by guanylyl cyclase (GC). **Ivanova et al** have studied GC in several melanocyte cultures by measurement of guanosine 3',5'-cyclic monophosphate (cGMP). In the normal melanocyte cultures NO donors induced strong increases of cGMP levels which could be related to the melanin content of the cells. **Jimbow et al** describe the culture of vitiligo melanocytes (VMC) in comparison to normal melanocytes (NMC). The MTT assay showed earlier cell death for the VMC after UVB irradiation than the NMC. It is suggested that the VMC are more sensitive to oxidative stress. In this light the demonstration of **Tobin et al** that the addition of bovine catalase protected vitiligo melanocytes in culture may be another indication of increased oxidative stress in these cells. As indicated by the authors, the presence of melanocytes in white vitiligo lesional skin is surprising and in contrast with earlier reports by Le Poole et al (Am J Pathol 148, 1996) who showed a complete absence of melanocytes in these lesions using a large number of monoclonal antibodies. The authors describe that depending on the size of the suction blisters 10 to 50 viable melanocytes are obtained per T_{25} flask from white lesional skin, while an order of magnitude more cells were obtained from pigmented vitiligo skin and healthy controls. **Le Poole** et al describe an immortalized melanocyte cell line PIG3V which was generated similarly to the PIG1 culture described earlier by the same author in 1997. These immortalized cultures will undoubtedly be very useful for study of human melanocytes, especially since the PIG3V shows characteristics typical for vitiligo melanocytes. A comparison between the effects of TGF-beta on normal melanocytes and compound type nevus cells is made in the study by **Alanko and Saksela**. The cells were grown between two layers of type I collagen and the rate of apoptosis after addition of TGF beta was found much higher for the normal melanocytes. Such a system could demonstrate the difference in behaviour of nevus cells in the dermal compartment. In this respect the skin equivalent model containing melanocytes described by **Gibbs et al** provides a good model system to study the interactions between epidermal cells. Melanin transport and formation of supranuclear melanin caps in the keratinocytes can thus be studied under various (culture) conditions. Another interesting approach was used by **Deveci et al** who examined epidermal melanocyte-keratinocyte interactions. In this case the effects of melanocyte conditioned medium on the keratinocytes was studied and a stimulation of keratinocyte proliferation was found. **Berking and Herlyn** reviewed different models of skin reconstruction and their application for pigment cell biology. Grafting of skin reconstructs to immunodeficient animals is presented as a method to study melanomagenesis and melanoma metastasis. Next to the monocultures of melanocytes of various skin types and pigmentary disorders these skin reconstruction models will bring further insight in the role and (dys)functioning of the melanocyte in skin.

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- Alanko T, Saksela O: **Transforming growth factor beta1 induces apoptosis in normal melanocytes but not in nevus cells grown in type I collagen gel**. J.Invest Dermatol. 115:286-291, 2000.

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ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events
New Members
Join ESPCR in October – 3 months' free membership!
Postdoctoral Position
ESPCR COUNCIL ELECTIONS

Calendar of events

2001 Stratum Corneum III
Basel, September 12-14

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2001 Xth Annual Meeting of the ESPCR
Rome, Italy, September 26-29

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Web-site: www.ulb.ac.be/medicine/loce/espcr.htm

2001 2nd Euroskin Conference: "Children Under the Sun - UV-radiation and children's skin"
Orvieto, Italy, October 1-5

Contact: Dr R. GREINERT, Centre of Dermatology,
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E-mail: euroskin@t-online.de
Web site: www.euroskin.org

2001 15th Japanese Society for Pigment Cell Research Meeting (JSPCR)
Sendai, Japan, December 1-2

Contact: Prof. S. SHIBAHARA
E-Mail : shibahar@mail.cc.tohoku.ac.jp

2002 XVIIIth International Pigment Cell Conference
Scheveningen, Holland

Contact: Dr. Stan PAVEL
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Tel: 31-(71) 526 1952 Fax: 31-(71) 524 8106
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2002 20th World Congress of Dermatology
COLLOQUIUM / WCD 2002, 1 – 5 July

Contact: Philippe FOURNIER
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2003 XIth Annual Meeting of the PanAmerican Society for Pigment Cell Research
Wood's Hole, MA, September 3-7

Contact: Dr. Jean BOLOGNIA
E-mail: jean_bolognia@qm.yale.edu

2003 XIth Meeting of the ESPCR
Gent, Belgium

Contact: Prof. JM NAEYAERT

2004 XIIth Meeting of the ESPCR
Paris, France

Contact: Dr. Lionel LARUE

2005 XIVth International Pigment Cell Conference (IPCC)
Bethesda, USA (to be confirmed)

Contact: Dr. V. HEARING

NEW MEMBERS

The ESPCR is delighted to welcome the following colleagues to membership and hope that they will play a full and active part in the Society.

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Join ESPCR in October – 3 months' free membership!

Did you know that if you are a new member joining ESPCR between October and December, after our annual meeting, your subscription will cover membership until December 2002, instead of December 2001? So, to all members, if you have colleagues who would benefit from joining ESPCR (surely you do?), please encourage them to join soon, and get the most out of their subscription. They can read about the benefits and find an application form at:

Http://www.ulb.ac.be/medecine/loce/espcr/gen_inf.htm#3

Alternatively, please contact our Treasurer for information and application forms:

Dr. Lionel Larue (Treasurer, ESPCR), Institut Curie – Section Recherche,
UMR146 CNRS, Bât 110, Centre Universitaire, 91405 Orsay, France

E-mail: Lionel.Larue@curie.u-psud.fr

Postdoctoral Position

Polarized Kit-ligand expression in the epidermis: Its role in human melanocyte homeostasis

A postdoctoral position (fully funded for the first year with the possibility of a 2 year extension) is immediately available in the Department of Pathology, Centre Medical Universitaire at the University of Geneva, Switzerland. The project is supervised by Dr. Bernhard Wehrle-Haller and Prof. Beat Imhof and is within the frame of a collaboration between the University of Geneva and Industry.

The aim of this project is to understand the role of kit-ligand in melanocyte homeostasis in the adult epidermis and how manipulation of kit-ligand expression or localization in keratinocytes affect melanocyte behavior. The project will employ cell-biological, pharmaceutical, biochemical as well transgenic approaches (mouse) to develop methods to modify Kit-ligand localization (polarity and cell surface expression) in vivo and to study melanocyte behavior in response to such altered Kit-ligand presentation. For references and rational see Wehrle-Haller and Imhof (2001, J. Biol. Chem. 276, 12667-74) and Grichnik et al., (1998, J. Invest. Dermatol. 111, 233-38).

The Centre Medical Universitaire provides a stimulatory research environment located within the City of Geneva. Research in the department is centered around problems of autoimmunity, wound healing, inflammation, cell-cell junctions and cell migration. Geneva, located at the lake of Geneva in close proximity to the French Alps, provides a rich multicultural environment facilitating social integration.

Interested candidates preferably having experience in one or more of the aforementioned domains should send their CV (e.g. e-mail) including names and contacting information of two references to:

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ESPCR COUNCIL ELECTIONS

Dear ESPCR members,

The deadline for presentation of candidates to the ESPCR Council expired on Friday July 20. Two nominations were duly presented. These correspond to:

- Dr. Colin Goding, from the Marie Curie Research Institute, UK.
- Prof. Jean Marie Naeyaert, from the University of Ghent, B.

Given that two positions were vacant, a formal election is not needed. The new composition of the Council will be presented for approval to the next General Assembly, to be held in Rome, on Friday September 28, at 18:00.

This new composition will be:

OFFICERS

President: Dorothy Bennett (London)
Secretary: José Carlos García-Borrón (Murcia)
Treasurer: Lionel Larue (Paris)

COUNCIL

F. Beermann (Lausanne)
G. Ghanem (Brussels)
C.R. Goding (Oxted)
J.M. Naeyaert (Ghent)
S. Pavel (Leiden)
M. Picardo (Rome)
A.J. Thody (Bradford)
W. Westerhof (Amsterdam)