Issue n° 37 - Aug 2000

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH *BULLETIN*

N° 37 - Aug 2000

Editorial Office: G. Ghanem (Editor), C. Meunier, R. Morandini (Production Team), Laboratory of Oncology and Experimental Surgery (L.O.C.E.), Université Libre de Bruxelles, Institut J. Bordet, Rue Héger-Bordet 1, B - 1000 Brussels, Belgium.
Phone: 32-2-541.32.96 Fax: 32-2-534.95.50 E-Mail: gghanem@ulb.ac.be

ESPCR and ESPCR Bulletin WEB site
http://www.ulb.ac.be/medecine/loce/espcr.htm

CONTENTS

HIGHLIGHTS

Large deletions of chromosome 9p in cutaneous malignant melanoma identify patients with a high risk of developing metastases

S. Puig*, J. Castro, P.J. Ventura, A. Ruiz, C. Ascaso, J. Malvehy, X. Estivill, J.M. Mascaro, M. Lecha and T. Castel.
*Department of Dermatology, Hospital Clinic Malignant Melanoma Group, University of Barcelona.

published in Melanoma Research 2000, 10, pp.231-236.

ABSTRACT

Cutaneous malignant melanoma (CMM) is an aggressive tumour with a high metastatic potential. Deletions of chromosome 9p have been detected in CMM, some of which involve the *CDKN2A/p14^{ARF}* genes. Loss of heterozygosity (LOH) of 16 microsatellite markers on 9p and mutations in the *CDKN2A/p14^{ARF}* genes had been previously studied in 32 melanoma patients by our group. 9p deletions were detected in 15 primary tumours (45.5%) and are here correlated with the clinical outcome over 5 years and compared with classical prognostic factors. Eight of the 32 patients developed metastases (25%). The metastases were all detected within 768 days of the initial diagnosis. The patients without metastases were last monitored at least 1621 days after diagnosis. None of the 21 patients with more than eight microsatellites conserved developed metastases, whereas all of the eight patients who developed metastases had eight or more markers deleted. The sensitivity of this analysis to predict metastases was 100% (specificity 84%), whereas the sensivity for the same sample using a Breslow thickness > 3 mm was 62.5% (specificity 68%). LOH of eight or more of the 9p microsatellite markers is therefore a useful prognostic factor to predict the development of metastases in the first 4.4-6.3 years (1621-2294 days).

2. Biology of pigment cells and pigmentary disorders

(Dr. M. Picardo)

Several authors have investigated the regulatory mechanism of melanoma progression, migration and invasion in vitro. Toschi E et al hypothesized that, in addition to its pro-apoptotic and antiangiogenetic effect, p53 overexpression in human melanoma cell lines can affect cells invasiveness trough modulation of matrix metalloproteinase-2 and 9. The authors demonstrated that the p53 overexpression gene, obtained by a recombinant vector, in human cell line carrying mutated gene caused a reduced invasiveness associated with a decreased matrix metalloproteinase-2 level without mRNA level modification. In addition, no further modulation of some wild-type p53-regulated pathways can be achieved by introduction of additional copies of the gene. The authors not found a modification of metalloproteinase-9 level after p53 overexpression. Thus, Toschi suggests a novel regulatory mechanism for p53 trough modification of metalloproteinase-2 secretion.

In the number of June 2000 of Pigment Cell Research several reviews focused on the melanocytes metabolism. Setaluri V. focused the attention on the cellular sorting machinery that recognise specific sorting signals and regulate the entry and exit of proteins trough intracellular compartments en route to melanosomes. As regard to tyrosinase, the biosynthesis appear to be regulated by quality-control event at endoplasmic reticulum. The di-leucine motif of cytplasmic tail of melanosomal proteins and its interaction with adaptor protein complexes (ie AP3) are critical. Defects in sorting signals cause several murine coat color phenotype and human pigmentary disorders. Rees JL reviews the available data on the "loss of function" mutations in melanocortin 1 receptor (MC1R) which is associated, in animal and man, with a switch from eumelanin to phaeomelanin production. The MC1R seems to be an important determinant of sun sensitivity and a genetic risk factor for melanoma and non melanoma skin cancer. The world wide pattern of MC1R diversity seems to be compatible with functional constraint operating in Africa, whereas the greater allelic diversity seen in non-African populations would be consistent with neutral predictions rather than selection.

The gene expression profile analysis was recently performed in pigment cells to investigate, on a genomic scale, the pigment cell function and development, as reported in the review from Loftus SK and Pavan WJ.

The Sasaki Minoru group have evaluated the tyrosinase gene expression within 24 h of NO-induced melanogenesis and found that mRNA expression for tyrosinase was induced 2h after and suppressed by a cGMP-dependent protein kinase inhibitor, suggesting that this enhancement of tyrosinase gene expression is a important mechanism for NO-induced melanogenesis.

Recent work showed that α-MSH or cholera toxin (CT) can activate a cAMP pathway that elicits proliferative arrest and senescence in normal melanocytes. Because senescence may be defence against malignant transformation, Bandyopadhyay and Medrano have examined the different responses of melanocytes derived from light and dark skin to CT. The authors demonstrated that in melanocytes from dark skin the CT-induced melanogenesis was associated with accumulation of the tumor suppressor p16NK4a and decreased expression of E2F1. On the contrary, melanocytes from light skin accumulate smaller amounts of melanin under the same condition and they continued to proliferate. This delayed senescence may be the consequence of a reduced association of p16 with CDK4 and steady levels of cyclin e and E2F1.

In the last number of J Invest Dermatol, Schallreuter KU respond to Fuller BB (same Journal, 114(2): 268-76, 2000) about the regulation of tyrosinase activity.

- Bandyopadhyay D and Medrano EE.
  Melanin accumulation accelerates melanocyte senescence by a mechanism involving p16NK4a/CDK4/pRB and E2F1. Ann N Y Acad Sci 908:71-84, 2000.

- Busca R., Abbe P. et al.
  Ras mediates the cAMP-dependent activation of extracellular signal-regulated kinases (ERKs) in melanocytes. EMBO J 19(12): 2900-10, 2000.

- Commo S and Bernard BA.
  Melanocyte subpopulation turnover during the human hair cycle: an immunohystochemical study. Pigment Cell Res 13: 253-259, 2000.

- Jegou S. Boutelet I. and Vaudry H.
  Melanocortin-3 receptor mRNA expression in pro-opiomelanocortin neurones of rat arcuate nucleus. J Neuroendocrinol 12(6): 501-5, 2000.

- Loftus SK and Pavan WJ.
  The use of expression profiling to study pigment cell biology and dysfunction. Pigment Cell Res. 13(3): 141-146, 2000.

- Pisarra P., Lupetti R. et al.
Human melanocytes and melanomas express novel mRNA isoforms of the tyrosinase-related protein-2/DOPAchrome tautomerase gene: molecular and functional characterization. J Invest Dermatol 115: 48-56, 2000.

- Rees JL.
The melanocortin 1 receptor (MC1R): more than just red hair. Pigment Cell Res. 13(3): 135-140, 2000.

- Sasaki M et al.
Up-regulation of tyrosinase gene by nitric oxide in human melanocytes. Pigment Cell Res. 13(4): 248-252, 2000.

- Schallreuter KU and Wood JM.
Downregulation of tyrosine activity in human melanocyte cell cultures by yohimbine. J Invest Dermatol. 115: 130, 2000.

- Setaluri V.
Sorting and targeting of melanosomal membrane proteins: signals, pathways, and mechanisms. Pigment Cell Res. 13(3): 128-134, 2000.

- Toschi E, Rota R., Antonini A., Melillo G., and Capogrossi M.
Wild-type p53 gene transfer inhibits invasion and reduces matrix metalloproteinase-2 levels in p53-mutated human melanoma cells. J Invest Dermatol. 114(6): 1188-94, 2000.

3. MSH, MCH, other hormones, differentiation

(Dr. B. Loir)

- Bandyopadhyay D, Medrano EE.
Melanin accumulation accelerates melanocyte senescence by a mechanism involving p16INK4a/CDK4/pRB and E2F1. Ann N Y Acad Sci. 908:71-84, 2000.
Shortened abstract: "Recent work has demonstrated that alpha-MSH or cholera toxin (CT) can activate a cAMP pathway that elicits proliferative arrest and senescence in normal human pigmented melanocytes. In these cells, senescence is associated with increased binding of the tumor suppressor p16INK4a to CDK4 and loss of E2F-binding activity. Because senescence may provide defense against malignant transformation of melanocytes, and because pigmentation is a strong defense against melanoma, the authors examined the ability of melanocytes derived from light and dark skin to respond to CT." They analysed the mechanism associated with the delayed senescence observed in melanocytes derived from light-skin in comparison with those from dark-skin.

- Graeven U, Rodeck U, Karpinski S, Jost M, Andre N, Schmiegel W.
Expression patterns of placenta growth factor in human melanocytic cell lines. J Invest Dermatol. 115(1):118-23, 2000.
Summary: The authors have assessed the mRNA expression of the angiogenic placenta growth factor and its receptor neuropilin-1 by RT-PCR as well as the secretion of this growth factor. Their findings "demonstrated that melanoma progression is accompagnied by deregulated, constitutive placenta growth factor expression. Placenta growth factor, however, serves no apparent autocrine role in melanoma proliferation."

- Haycock JW, Rowe SJ, Cartledge S, Wyatt A, Ghanem G, Morandini R, Rennie IG, MacNeil S.
Alpha-melanocyte-stimulating hormone reduces impact of proinflammatory cytokine and peroxide-generated oxidative stress on keratinocyte and melanoma cell lines. J Biol Chem. 275(21):15629-36, 2000.

- Hirobe T, Abe H.
ACTH(4-12) is the minimal message sequence required to induce the differentiation of mouse epidermal melanocytes in serum-free primary culture. J Exp Zool. 286(6):632-40, 2000.

- Lazar-Molnar E, Hegyesi H, Toth S, Falus A.
Autocrine and paracrine regulation by cytokines and growth factors in melanoma. Cytokine. 12(6):547-54, 2000. Review.

- Matsunaga N, Virador V, Santis C, Vieira WD, Furumura M, Matsunaga J, Kobayashi N, Hearing VJ.
In situ localization of agouti signal protein in murine skin using immunohistochemistry with an ASP-specific antibody. Biochem Biophys Res Commun. 270(1):176-82, 2000.
Summary: The authors have generated a rabbit antibody against the carboxyl terminus sequence of ASP. Then, they characterized the expression of ASP in the skin of newborn nonagouti (a/a), agouti (A/+) and lethal yellow (A(y)/a) mice. In the last one, the "expression patterns suggest that ASP is delivered quickly and efficiently to melanocytes and to hair matrix cells in the hair bulbs where it regulates melanin production."

- Mazurkiewicz JE, Corliss D, Slominski A.
Spatiotemporal expression, distribution, and processing of POMC and POMC-derived peptides in murine skin. J Histochem Cytochem. 48(7):905-14, 2000.
Summary: After depilation-induced anagen, the authors "found cell-specific variations in the expression of POMC mRNA that were consistent with immunoreactivities for POMC-derived peptides." Based on their results, they can also infer "that the activities of PC1 and PC2 are responsible for the cell-specific differential processing of POMC in murine skin."

- Misery L.
The neuro-immuno-cutaneous system and ultraviolet radiation. Photodermatol Photoimmunol Photomed. 16(2):78-81, 2000. Review.

- Shellman YG, Chapman JT, Fujita M, Norris DA, Maxwell IH.
Expression of activated N-ras in a primary melanoma cell line counteracts growth inhibition by transforming growth factor-beta. J Invest Dermatol. 114(6):1200-4, 2000.
Summary: "These data suggest that activated Ras plays an important part in melanoma progression from the radial growth phase to the vertical growth phase by counteracting inhibition by cytokines such as transforming growth factor-beta, thus providing a growth advantage."

- Singh RK, Varney ML.
IL-8 expression in malignant melanoma: implications in growth and metastasis. Histol Histopathol. 15(3):843-9, 2000.

- Slominski A, Wortsman J, Luger T, Paus R, Solomon S.
Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. Physiol Rev. 80(3):979-1020, 2000. Review.

- Smalley K, Eisen T.
The involvement of p38 mitogen-activated protein kinase in the alpha-melanocyte stimulating hormone (alpha-MSH)-induced melanogenic and anti-proliferative effects in B16 murine melanoma cells. FEBS Lett. 476(3):198-202, 2000.

- Tsatmali M, Graham A, Szatkowski D, Ancans J, Manning P, McNeil CJ, Graham AM, Thody AJ.
alpha-melanocyte-stimulating hormone modulates nitric oxide production in melanocytes. J Invest Dermatol. 114(3):520-6, 2000.
Summary: Their results suggest that "alpha-MSH regulates nitric oxide production in melanocytic cells by modulating the induction of inducible nitric oxide synthase. Additional experiments showed that nitric oxide increased melanin production by B16 cells and human melanocytes."

4. Photobiology

- Bataille V, Bykov VJ, Sasieni P, Harulow S, Cuzick J, Hemminki K.
Photoadaptation to ultraviolet (UV) radiation in vivo: photoproducts in epidermal cells following UVB therapy for psoriasis. Br J Dermatol. 143(3):477-483, 2000.

- Brown DB, Peritz AE, Mitchell DL, Chiarello S, Uitto J, Gasparro FP.
Common fluorescent sunlamps are an inappropriate substitute for sunlight. Photochem Photobiol. 72(3):340-4, 2000.

- Cattaruzza MS.
The relationship between melanoma and continuous or intermittent exposure to UV radiation. Arch Dermatol. 136(6):773-774, 2000.

- Cleaver JE.
Common pathways for ultraviolet skin carcinogenesis in the repair and replication defective groups of xeroderma pigmentosum. J Dermatol Sci. 23(1):1-11, 2000. Review.

- Gasparro FP.
Photodermatology: progress, problems and prospects. Eur J Dermatol. 10(4):250-4, 2000. Review.

- Gil EM, Kim TH.
UV-induced immune suppression and sunscreen. Photodermatol Photoimmunol Photomed. 16(3):101-10, 2000.

- Ivanov VN, Ronai Z.
p38 protects human melanoma cells from UV-induced apoptosis through down-regulation of NF-kappaB activity and Fas expression. Oncogene. 19(26):3003-12, 2000.

- Iyengar B.
Melatonin and melanocyte functions. Biol Signals Recept. 9(5):260-6, 2000.

- Noonan FP, Otsuka T, Bang S, Anver MR, Merlino G.
Accelerated ultraviolet radiation-induced carcinogenesis in hepatocyte growth factor/scatter factor transgenic mice. Cancer Res. 60(14):3738-43, 2000.

- Rieber M, Strasberg Rieber M.
Apoptosis-inducing levels of UV radiation and proteasome inhibitors produce opposite effects on p21(WAF1) in human melanoma cells. Int J Cancer. 86(4):462-7, 2000.

- Strickland FM, Muller HK, Stephens LC, Bucana CD, Donawho CK, Sun Y, Pelley RP.
Induction of primary cutaneous melanomas in C3H mice by combined treatment with ultraviolet radiation, ethanol and aloe emodin. Photochem Photobiol. 72(3):407-14, 2000.

- Van Den Wijngaard RM, Aten J, Scheepmaker A, Le Poole IC, Tigges AJ, Westerhof W, Das PK.
Expression and modulation of apoptosis regulatory molecules in human melanocytes: significance in vitiligo. Br J Dermatol. 143(3):573-581, 2000.

- Weichenthal M, Godorr M, Altenhoff J, Neuber K, Breitbart EW.
Effects of whole-body UVB irradiation on cytokine production by peripheral blood mononuclear cells from stage I melanoma patients. Arch Dermatol Res. 292(7):348-53, 2000.

- Westerdahl J, Ingvar C, Masback A, Jonsson N, Olsson H.
Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer. 82(9):1593-9, 2000.

5. Neuromelanins

- Braak H, Rub U, Sandmann-Keil D, Gai WP, de Vos RA, Jansen Steur EN, Arai K, Braak E.
Parkinson's disease: affection of brain stem nuclei controlling premotor and motor neurons of the somatomotor system. Acta Neuropathol (Berl). 99(5):489-95, 2000.

- Linert W, Jameson GN.
Redox reactions of neurotransmitters possibly involved in the progression of Parkinson's Disease. J Inorg Biochem. 79(1-4):319-26, 2000.

- Xin W, Shen XM, Li H, Dryhurst G.
Oxidative metabolites of 5-S-cysteinylnorepinephrine are irreversible inhibitors of mitochondrial complex I and the alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase complexes: possible implications for neurodegenerative brain disorders. Chem Res Toxicol. 13(8):749-760, 2000.

6. Genetics, molecular biology

(Dr. F. Beermann)

Two new coat color genes have been identified and cloned in mouse and human.
NEMO (NFκB-essential modulator) is an X-linked gene. Mutations of the gene are found in the human syndrome incontinentia pigmenti. When NEMO is mutated in transgenic mice by homologous recombination, symptoms similar to those of incontinentia pigmenti are observed (Makris et al., Schmidt-Supprian et al., Smashi et al.).
Rab27a is a vesicle transport protein. Mutations of the gene are found in Griselli syndrome and, in mouse, in the ashen mutation (now named *Rab27a^{ash}*) (see papers by Menasche et al., Pastural et al., Wilson et al.).

- Aigner B, Besenfelder U, Müller M, Brem G.
Tyrosinase gene variants in different rabbit strains. Mammalian Genome 11:700-702, 2000.

- Alexeev V, Yoon K.
Gene correction by RNA-DNA oligonucleotides [Review]. Pigment Cell Research 13(2):72-79, 2000.

- Amae S, Yasumoto K, Takeda K, Udono T, Takahashi K, Shibahara S.
Identification of a composite enhancer of the human tyrosinase-related protein 2/DOPAchrome tautomerase gene. Biochimica et Biophysica Acta 1492:505-508, 2000.

- Bumsted KM, Barnstable CJ.
Dorsal retinal pigment epithelium differentiates as neural retina in the Microphthalmia (mi/mi) mouse. Investigative Ophthalmology & Visual Science 41(3):903-908, 2000.

- Busca R, Ballotti R.
Cyclic AMP a key messenger in the regulation of skin pigmentation [Review]. Pigment Cell Research 13(2):60-69, 2000.

- Camacho-Hübner A, Beermann F.
Caractéristiques cellulaires et moléculaires de la pigmentation chez les mammifères - tyrosinase et TRP [Review]. Pathologie Biologie 48:577-583, 2000.

- Carreira S, Liu B, Goding C.
The gene encoding the T-box factor Tbx2 is a target for the microphthalmia-associated transcription factor in melanocytes. Journal of Biological Chemistry 275:21920-21927, 2000.
Summary: The T-box transcription factor family comprises several members and is conserved in evolution. In this paper, the authors show, that one T-box factor, Tbx2, is transcriptionally regulated by Mitf: a Mitf binding site is present in the mouse Tbx2 promoter, the promoter is bound by Mitf in vitro and expression of Tbx2 in melanoma cell lines is correlated to presence of Mitf. They conclude that Tbx2 is one of the first target genes of Mitf, which is not directly involved in pigment synthesis.

- Dupin E, Glavieux C, Vaigot P, Le Douarin NM.
Endothelin 3 induces the reversion of melanocytes to glia through a neural crest-derived glial-melanocytic progenitor. Proceedings of the National Academy of Sciences of the United States of America 97(14):7882-7887, 2000.

- Everts RE, Rothuizen J, van Oost BA.
Identification of a premature stop codon in the melanocyte-stimulating hormone receptor gene (MC1R) in Labrador and Golden retrievers with yellow coat colour. Animal Genetics 31(3):194-199, 2000.

- Goding CR.
Mitf from neural crest to melanoma: signal transduction and transcription in the melanocyte lineage [Review]. Genes & Development 14(14):1712-1728, 2000.

- Golob M, Buettner R, Bosserhoff AK.
Characterization of a transcription factor binding site, specifically activating MIA transcription in melanoma. Journal of Investigative Dermatology 115(1):42-47, 2000.

- Halaban R, Svedine S, Cheng E, Smicun Y, Aron R, Hebert DN.
Endoplasmic reticulum retention is a common defect associated with tyrosinase-negative albinism. Proceedings of the National Academy of Sciences of the United States of America 97(11):5889-5894, 2000.

- Jordan S, Beermann F.
Nomenclature for identified pigmentation genes in the mouse [Review]. Pigment Cell Research 13(2):70-71, 2000.

- Jordan SF, Jackson IJ.
A late wave of melanoblast differentiation and rostrocaudal migration revealed in patch and rump-white embryos. Mechanisms of Development 92(2):135-143, 2000.

- Kissel H, Timokhina I, Hardy MP, Rothschild G, Tajima Y, Soares V, Angeles M, Whitlow SR, Manova K, Besmer P.
Point mutation in Kit receptor tyrosine kinase reveals essential roles for Kit signaling in spermatogenesis and oogenesis without affecting other Kit responses. EMBO Journal 19(6):1312-1326, 2000.

- Kunisada T, Yamazaki H, Hirobe T, Kamei S, Omoteno N, Tagaya H, Hemmi H, Koshimizu U, Nakamura T, Hayashia SI.
Keratinocyte expression of transgenic hepatocyte growth factor affects melanocyte development, leading to dermal melanocytosis. Mechanisms of Development 94(1-2):67-78, 2000.

- Loftus SK, Pavan WJ.
The use of expression profiling to study pigment cell biology and dysfunction [Review]. Pigment Cell Research

13(3):141-146, 2000.

- Makris C, Godfrey V, Krähn-Senftleben G, Takahashi T, Roberts J, Schwarz T, Feng L, Johnson R, Karin M. **Female mice heterozygous for IKK/NEMO deficiencies develop a dermatopathy similar to the human X-linked disorder Incontinentia Pigmenti.** Molecular Cell 5:969-979, 2000.
  Shortened abstract: IKKγ/NEMO is the essential regulatory subunit of the IkB kinase (IKK), encoded by an X-linked gene in mice and humans. It is required for NFκ-B activation and resistance to TNF-induced apoptosis. Female mice heterozygous for Ikkγ/Nemo deficiency develop a unique dermatopathy characterized by keratinocyte hyperproliferation, skin inflammation, hyperkeratosis, and increased apoptosis. Although Ikkγ+/- females eventually recover, Ikkg- males die in utero. These symptoms and inheritance pattern are very similar to those of incontinentia pigmenti (IP), a human genodermatosis, synthenic with the IKKγ/NEMO locus.

- Menasche G, Pastural E, Feldmann J, Certain S, Ersoy F, Dupuis S, Wulffraat N, Bianchi D, Fischer A, Le Deist F, de Saint Basile G.
  Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nature Genetics 25(2):173-176, 2000.
  Shortened abstract: Griscelli syndrome (GS, MIM 214450), a rare, autosomal recessive disorder, results in pigmentary dilution of the skin and the hair, the presence of large clumps of pigment in hair shafts and an accumulation of melanosomes in melanocytes. We previously mapped the GS locus to chromosome 15q21 and found a mutation in a gene (MY05A) encoding a molecular motor in two patients. Further linkage analysis suggested a second gene associated with GS was in the same chromosomal region. We detected mutations in RAB27A, which lies within this interval, in 16 patients with GS. Unlike MYO5A, the GTP-binding protein RAB27A appears to be involved in the control of the immune system, as all patients with RAB27A mutations, but none with the MY05A mutation, developed HS (haemophagocytic syndrome).

- Oh J, Liu ZX, Feng GH, Raposo G, Spritz RA.
  The Hermansky-Pudlak syndrome (HPS) protein is part of a high molecular weight complex involved in biogenesis of early melanosomes. Human Molecular Genetics 9(3):375-385, 2000.

- Pastural E, Ersoy F, Yalman N, Wulffraat N, Grillo E, Ozkinay F, Tezcan I, Gedikoglu G, Philippe N, Fischer A, de St Basile G.
  Two genes are responsible for Griscelli syndrome at the same 15q21 locus. Genomics 63(3):299-306, 2000.

- Pisarra P, Lupetti R, Palumbo A, Napolitano A, Prota G, Parmiani G, Anichini A, Sensi M.
  Human melanocytes and melanomas express novel mRNA isoforms of the tyrosinase-related protein-2/DOPAchrome tautomerase gene: Molecular and functional characterization. Journal of Investigative Dermatology 115(1):48-56, 2000.

- Rhim H, Dunn KJ, Aronzon A, Mac S, Cheng M, Lamoreux ML, Tilghman SM, Pavan WJ.
  Spatially restricted hypopigmentation associated with an Ednrb(s)-modifying locus on mouse chromosome 10. Genome Research 10(1):17-29, 2000.

- Schmidt-Supprian M, Bloch W, Courtois G, Addicks K, Israël A, Rajewsky K, Pasparakis M.
  NEMO/IKKg-deficient mice model incontinentia pigmenti. Molecular Cell 5:981-992, 2000.
  Abstract: Disruption of the X-linked gene encoding NFκ-B essential modulator (NEMO) produces male embryonic lethality, completely blocks NFκ-B activation by proinflammatory cytokines, and interferes with the generation and/or persistence of lymphocytes. Heterozygous female mice develop patchy skin lesions with massive granulocyte infiltration and hyperproliferation and increased apoptosis of keratinocytes. Diseased animals present severe growth retardation and early mortality. Surviving mice recover almost completely, presumably through clearing the skin of NEMO-deficient keratinocytes. Male lethality and strikingly similar skin lesions in heterozygous females are hallmarks of the humangenetic disorder incontinentia pigmenti (IP). Together with the recent discovery that mutations in the human NEMO gene cause IP, our results indicate that we have created a mouse model for that disease.

- Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, Israel A, Heiss NS, Klauck SM, Kioschis P, Wiemann S, Poustka A, Esposito T, Bardaro T, Gianfrancesco F, Ciccodicola A, D'Urso M, Woffendin H, Jakins T, Donnai D, Stewart H, Kenwrick SJ, Aradhya S, Yamagata T, Levy M, Lewis RA, Nelson DL (The International Incontinentia Pigmenti (IP) Consortium).
  Genomic arrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. Nature 405: 466-472, 2000.
  Abstract: Familial incontinentia pigmenti (IP; MIM 308310) is a genodermatosis that segregates as an X-linked dominant disorder and is usually lethal prenatally in males. In affected females it causes highly variable abnormalities of the skin, hair, nails, teeth, eyes and central nervous system. The prominent skin signs occur in four classic cutaneous stages: perinatal inflammatory vesicles, verrucous patches, a distinctive pattern of hyperpigmentation and dermal scarring. Cells expressing the mutated X chromosome are eliminated selectively around the time of birth, so females with IP exhibit extremely skewed X-inactivation. The reasons for cell death

in females and in utero lethality in males are unknown. The locus for IP has been linked genetically to the factor VIII gene in Xq28. The gene for NEMO (NFκ-B essential modulator)/IKK (IκB kinase-γ) has been mapped to a position 200 kilobases proximal to the factor VIII locus. NEMO is required for the activation of the transcription factor NFk-B and is therefore central to many immune, inflammatory and apoptotic pathways. Here we show that most cases of IP are due to mutations of this locus and that a new genomic rearrangement accounts for 80% of new mutations. As a consequence, NFκ-B activation is defective in IP cells.

- Tachibana M.
  MITF: A stream flowing for pigment cells [Review]. Pigment Cell Research 13:230-240, 2000.

- Takeda K, Yasumoto K, Takada R, Takada S, Watanabe K, Udono T, Saito H, Takahashi K, Shibahara S.
  Induction of melanocyte-specific microphthalmia-associated transcription factor by Wnt-3a. Journal of Biological Chemistry 275(19):14013-14016, 2000.
  Shortened abstract: The melanocyte-specific promoter of the human MITF gene (MITF-M promoter) contains a functional LEF-1-binding site, which is bound in vitro by LEF-1 and confers the preferential expression on a reporter gene in melanocytes and melanoma cells, as judged by the transient transfection assays. Exogenously added Wnt-3a protein also transactivates the MITF-M promoter via the LEF-1-binding site. These results suggest that Wnt-3a signaling recruits beta-catenin and LEF-1 to the LEF-1-binding site of the MITF-M promoter. Therefore, the present study identifies Mitf-M/MITF-M as a direct target of Wnt signaling.

- Takeuchi S, Takeuchi T, Yamamoto H.
  A possible mechanism for feedback regulation of the mouse tyrosinase gene by its 3 ' non-coding RNA fragments. Pigment Cell Research 13(2):109-115, 2000.

- Udono T, Yasumoto K, Takeda K, Amae S, Watanabe K, Saito H, Fuse N, Tachibana M, Takahashi K, Tamai M, Shibahara S.
  Structural organization of the human microphthalmia-associated transcription factor gene containing four alternative promoters. Biochimica et Biophysica Acta - Gene Structure & Expression 1491(1-3):205-219, 2000.

- Wilson SM, Yip R, Swing DA, O'Sullivan TN, Zhang Y, Novak EK, Swank RT, Russell LB, Copeland NG, Jenkins NA.
  A mutation in Rab27a causes the vesicle transport defects observed in ashen mice. Proceedings of the National Academy of Sciences of the United States of America 97(14):7933-7938, 2000.
  Abstract: The dilute (d), leaden (ln), and ashen (ash) mutations provide a unique model system for studying vesicle transport in mammals. All three mutations produce a lightened coat color because of defects in pigment granule transport. In addition, all three mutations are suppressed by the semidominant dilute-suppressor (dsu), providing genetic evidence that these mutations function in the same or overlapping transport pathways, Previous studies showed that d encodes a major vesicle transport motor, myosin-VA, which is mutated in Griscelli syndrome patients. Here, using positional cloning and bacterial artificial chromosome rescue, we show that ash encodes Rab27a, Rab GTPases represent the largest branch of the p21 Ras superfamily and are recognized as key players in vesicular transport and organelle dynamics in eukaryotic cells. We also show that ash mice have platelet defects resulting in increased bleeding times and a reduction in the number of platelet dense granules. These defects have not been reported for d and In mice. Collectively, our studies identify Rab27a as a critical gene for organelle-specific protein trafficking in melanocytes and platelets and suggest that Rab27a functions in both MyoVa dependent and independent pathways.

7. Tyrosinase, TRP1, TRP2 and other enzymes

(Prof. J.C. Garcia-Borron)

Five of the papers referenced in this issue deal with the post-translational events associated to the processing of tyrosinase and the tyrps. This certainly reflects the increasing interest of this area, which, I think, is due at least to two factors: the biomedical relevance of the process, and the realization that, at least as far as tyrosinase and the tyrps are concerned, the regulation of pigmentation is much more than translational control. Indeed, it is becoming evident that defective processing has important pathological and biomedical implications, including certain forms of albinism and antigen processing in melanocytes. For instance, Halaban et al (Proc Natl Acad Sci U S A. 2000 May 23;97(11):5889-94) demonstrate that several loss-of-function mutations of tyrosinase, associated with albinism, produce a retention of misfolded protein in the endoplasmic reticulum (ER). They go on to conclude that albinism can be at least partially considered an "ER retention disease". According to the results presented by Wang and Androlewicz (Biochem Biophys Res Commun. 2000 Apr 29;271(1):22-7), and to previous work from Ruth Halaban's laboratory already commented in this Bulletin, this retention could result in retrograde transport of tyrosinase from the ER to the cytosol, followed by proteasome-dependent degradation and presentation of antigenic epitopes to the inmune system. On the other hand, the romanian group lead by S. Petrescu continues to provide a wealth of information on the mechanism of processing of tyrosinase and the tyrps (J Biol Chem 2000 Mar 17;275(11):8169-75; Biochemistry. 2000 May 9;39(18):5229-37; J Biol Chem. 2000 Jul 27), in keeping with their outstanding recent scientific production. Thus, the complex pathways

of post-translational processing of the melanogenic enzymes have been already reasonably well delineated, and their details may be definitively solved soon.
On the other hand, several papers describe new forms of regulation of melanogenesis at different levels. Takeuchi et al (Pigment Cell Res. 2000 Apr;13(2):109-15) describe a novel mechanism of tyrosinase gene expression regulation based on the interaction of 3' non coding mRNA sequences with repetitive sequences in the 5' upstream regulatory region of the gene. It will be interesting to assess the relevance "in vivo" of this mechanism. Yoshida et al (J Invest Dermatol 2000 Feb;114(2):334-42) describe the regulation of tyrosinase activity via H2 histamine receptors. Since these receptors are coupled to adenylate ciclase and their activation increases intracellular cAMP levels, it is not surprising that the effects of histamine on melanocytes are reminiscent of those of alphaMSH, and, apparently, mediated by protein kinase A. In a very interesting and puzzling paper, Fuller et al (J Invest Dermatol. 2000 Jul;115(1):130-1) demonstrate that yohimbine reversibly decreases tyrosinase activity in cultured melanocytes by a still uncharacterized and probably novel mechanism. The compound has no effect on cAMP levels, but blocks the activatory effect of cAMP elevating agents. It has no effect on either substrate availability or tyrosinase abundance, and, therefore, its mode of action is as yet unknown. As the authors point out, it will be interesting to see whether the drug finds clinical applications for the treatment of hyperpigmentary disorders, but, from a basic point of view, it will also be extremely interesting to unravel its probably novel mechanism of action. Finally, Ancans and Thody (FEBS Lett. 2000 Jul 28;478(1-2):57-60) and Hornyak et al (J Invest Dermatol. 2000 Jul;115(1):106-12) deal with two well known regulatory factors, namely, intracellular pH and cell density, and provide new interesting information and , which is also important, a reminder to the pigment cell community of two simple and often forgotten factors influencing melanogenesis, whose accurate control is critical for many experimental setups.
The new series of reviews published by Pigment Cell Research deserves a special comment. These extremely well documented reviews on the hotest topics, written by leading experts, will be extremely useful not only for the pigment cell community, but also for scientists from other fields willing to get a clear and updated picture of pigment cell biology. Let's hope that the reviews published thus far will set up a standard of quality and a new tradition for the journal.

- Ancans J, Thody AJ.
  Activation of melanogenesis by vacuolar type H(+)-ATPase inhibitors in amelanotic, tyrosinase positive human and mouse melanoma cells. FEBS Lett. 478(1-2):57-60, 2000.

- Aigner B, Besenfelder U, Muller M, Brem G.
  Tyrosinase gene variants in different rabbit strains. Mamm Genome. 11(8):700-2, 2000.

- Amae S, Yasumoto K, Takeda K, Udono T, Takahashi K, Shibahara S.
  Identification of a composite enhancer of the human tyrosinase-related protein 2/DOPAchrome tautomerase gene(1). Biochim Biophys Acta. 1492(2-3):505-508, 2000.

- Berson JF, Frank DW, Calvo PA, Bieler BM, Marks MS.
  A common temperature-sensitive allelic form of human tyrosinase is retained in the endoplasmic reticulum at the nonpermissive temperature. J Biol Chem. 275(16):12281-9, 2000.

- Boersma MG, Vervoort J, Szymusiak H, Lemanska K, Tyrakowska B, Cenas N, Segura-Aguilar J, Rietjens IM.
  Regioselectivity and reversibility of the glutathione conjugation of quercetin quinone methide. Chem Res Toxicol 13(3):185-91, 2000.

- Branza-Nichita N, Negroiu G, Petrescu AJ, Garman EF, Platt FM, Wormald MR, Dwek RA, Petrescu SM.
  Mutations at critical N-glycosylation sites reduce tyrosinase activity by altering folding and quality control. J Biol Chem 275(11):8169-75, 2000.

- Busca R, Ballotti R.
  Cyclic AMP a key messenger in the regulation of skin pigmentation. Pigment Cell Res. 13(2):60-9, 2000.

- Decker H, Tuczek F.
  Tyrosinase/catecholoxidase activity of hemocyanins: structural basis and molecular mechanism. Trends Biochem Sci. 25(8):392-397, 2000.

- Fenoll LG, Rodriguez-Lopez JN, Varon R, Garcia-Ruiz PA, Garcia-Canovas F, Tudela J.
  Action mechanism of tyrosinase on meta- and para-hydroxylated monophenols. Biol Chem. 381(4):313-20, 2000.

- Fuller BB, Drake MA, Spaulding DT, Chaudhry F.
  Downregulation of tyrosinase activity in human melanocyte cell cultures by yohimbine. J Invest Dermatol. 115(1):130-1, 2000.

- Halaban R, Svedine S, Cheng E, Smicun Y, Aron R, Hebert DN.
  Endoplasmic reticulum retention is a common defect associated with tyrosinase-negative albinism. Proc Natl

Acad Sci U S A. 97(11):5889-94, 2000.

- Hornyak TJ, Hayes DJ, Ziff EB.
Cell-density-dependent regulation of expression and glycosylation of dopachrome Tautomerase/Tyrosinase-related protein-2. J Invest Dermatol. 115(1):106-12, 2000.

- Kong KH, Hong MP, Choi SS, Kim YT, Cho SH.
Purification and characterization of a highly stable tyrosinase from Thermomicrobium roseum. Biotechnol Appl Biochem 31 (Pt 2):113-8, 2000.

- Kong KH, Park SY, Hong MP, Cho SH.
Expression and characterization of human tyrosinase from a bacterial expression system. Comp Biochem Physiol B Biochem Mol Biol. 125(4):563-9, 2000.

- Matsunaga N, Virador V, Santis C, Vieira WD, Furumura M, Matsunaga J, Kobayashi N, Hearing VJ.
In situ localization of agouti signal protein in murine skin using immunohistochemistry with an ASP-specific antibody. Biochem Biophys Res Commun 270(1):176-82, 2000.

- Negroiu G, Dwek RA, Petrescu SM.
Folding and maturation of tyrosinase related protein-1 are regulated by the post-translational formation of disulfide bonds and by N-Glycan processing. J Biol Chem. 2000.

- Petrescu SM, Branza-Nichita N, Negroiu G, Petrescu AJ, Dwek RA.
Tyrosinase and glycoprotein folding: roles of chaperones that recognize glycans. Biochemistry. 9;39(18):5229-37, 2000.

- Pisarra P, Lupetti R, Palumbo A, Napolitano A, Prota G, Parmiani G, Anichini A, Sensi M.
Human melanocytes and melanomas express novel mRNA isoforms of the tyrosinase-related protein-2/DOPAchrome tautomerase gene: molecular and functional characterization. J Invest Dermatol. 115(1):48-56, 2000.

- Rees JL.
The melanocortin 1 receptor (MC1R): more than just red hair. Pigment Cell Res. 13(3):135-40, 2000.

- Rosei MA, Coccia R, Foppoli C, Blarzino C, Cini C, Schinina ME.
Cysteinyldopaenkephalins: synthesis, characterization and binding to bovine brain opioid receptors. Biochim Biophys Acta 1478(1):19-29, 2000.

- Santagostini L, Gullotti M, Monzani E, Casella L, Dillinger R, Tuczek F.
Reversible dioxygen binding and phenol oxygenation in a tyrosinase model system. Chemistry 6(3):519-22, 2000.

- Setaluri V.
Sorting and targeting of melanosomal membrane proteins: signals, pathways, and mechanisms. Pigment Cell Res. 13(3):128-34, 2000.

- Solano F, Lucas-Elio P, Fernandez E, Sanchez-Amat A.
Marinomonas mediterranea MMB-1 transposon mutagenesis: isolation of a multipotent polyphenol oxidase mutant. J Bacteriol. 182(13):3754-60, 2000.

- Sugumaran M, Nellaiappan K.
Characterization of a new phenoloxidase inhibitor from the cuticle of Manduca sexta. Biochem Biophys Res Commun 268(2):379-83, 2000.

- Takeuchi S, Takeuchi T, Yamamoto H.
A possible mechanism for feedback regulation of the mouse tyrosinase gene by its 3' non-coding RNA fragments. Pigment Cell Res. 13(2):109-15, 2000.

- Thorneby-Andersson K, Sterner O, Hansson C.
Tyrosinase-mediated formation of a reactive quinone from the depigmenting agents, 4-tert-butylphenol and 4-tert-butylcatechol. Pigment Cell Res 13(1):33-8, 2000.

- van Gastel M, Bubacco L, Groenen EJ, Vijgenboom E, Canters GW.
EPR study of the dinuclear active copper site of tyrosinase from Streptomyces antibioticus. FEBS Lett. 474(2-3):228-32, 2000.

- Wang G, Aazaz A, Peng Z, Shen P.
Cloning and overexpression of a tyrosinase gene mel from Pseudomonas maltophila. FEMS Microbiol Lett 185(1):23-7, 2000.

- Wang Y, Androlewicz MJ.
Oligosaccharide trimming plays a role in the endoplasmic reticulum-associated degradation of tyrosinase. Biochem Biophys Res Commun. 271(1):22-7, 2000.

- Yoshida M, Takahashi Y, Inoue S.
Histamine induces melanogenesis and morphologic changes by protein kinase A activation via H2 receptors in human normal melanocytes. J Invest Dermatol 114(2):334-42, 2000.

8. Melanosomes

(Dr. J. Borovansky)

Papers investigating the role of microtubule- and actin-based motor proteins in melanosome transport have recently flooded the literature. Another large group of reports focused on the characterization of melanosomes and pigment granules in tumours. A special attention should be paid to papers by Peters et al. and by Salceda & Sanchez.

- Akeo K, Amaki S, Suzuki T, Hiramitsu T.
Melanin granules prevent the cytotoxic effects of L-DOPA on retinal pigment epithelial cells in vitro by regulation of NO and superoxide radicals. Pigment Cell Res 13(2): 80-88, 2000.
Comments: An indirect evidence suggesting that RPE melanosomes might have a role in preventing the cytotoxicity derived from L-DOPA and in regulating the generation of NO.

- Hara M, Yaar M, Byers HR, Goukassian D, Fine RE, Gonsalves J, Gilchrest BA.
Kinesin participates in melanosomal movement along melanocyte dendrites. J Invest Dermatol 114(3): 438-443, 2000.
Comments: Study supporting a major role for kinesin in microtubule-associated anterograde melanosomal transport in human melanocyte dendrites. Ultrastructurally, kinesin molecules were closely associated with melanosomes.

- Kameyama K, Takami H.
Pigmented granules in functional black adenoma of thyroid gland: A histochemical and ultrastructural study. Endocrine Pathology 10(4): 353-357, 1999.
Comments: Adrenal black adenoma (ABA) cells contain numerous pigment granules but the nature of these granules has remained controversial. Electron microscopic study of a ABA case revealed two types of pigmented granules - typical lipofuscin granules and structures resembling stage IV melanosomes. According to histochemical reactions the pigment had characteristics of lipofuscin. Table of histochemical reactions distinguishing between lipofuscin, melanin and neuromelanin.

- Koren R, Bernheim J, Schachter P, Schwartz A, Siegal A, Gal R.
Black thyroid adenoma. Clinical, histochemical and ultrastructural features. Applied Immunohistochem & Molecular Morphol 8(1): 80-84, 2000.
Comments: Black thyroid adenoma in woman treated with minocycline. The pigment had histochemical characteristics of melanin, was osmiophilic and was deposited within lysosomes of follicular cells.

- Marszalek JR, Goldstein LSB.
Understanding the functions of kinesin-II. Biochim Biophys Acta 1496(1): 142-150, 2000.
Comments: Evidence has been summarized for possible roles of kinesin-II in neuronal transport, melanosome transport (in melanophores), the secretory pathway and during mitosis. Molecular anatomy of kinesin-II molecule.

- Misawa H, Yanagita N, Iwagaki T, Asahi Y, Yokoi H, Kato K, Qian B, Shamoto M.
Primary malignant melanoma arising from the base of the tongue. ORL 62(3): 134-139, 2000.
Comments: EM characterization of melanosomes in tongue melanoma. Lamellar melanosomes with uneven deposition of melanin and often missing limiting membranes were present in the primary tumour, whereas metastatic lesion contained immature abnormal melanosomes frequently fusing together.

- Peters EMJ, Tobin D, Seidah NG, Schallreuter KU.
Pro-opiomelanocortin-related peptides, prohormone convertases 1 and 2 and the regulatory peptide 7B2 are present in melanosomes of human melanocytes. J Invest Dermatol 114(3): 430-437, 2000.
Comments: By means of immunohistochemistry, immunogold electron microscopy and western blotting the presence of the entire system for pro-opiomelanocortin processing was demonstrated in the melanosome.

- Reck-Peterson SL, Provance Jr DW, Mooseker MS, Mercer JA.

Class V myosins. Biochim Biophys Acta 1496(1): 36-51, 2000.
Comments: Review discussing the emerging evidence that myosin V is a processive actin-based motor that has multiple functions in the cell. Detailed description of myosin V domains and function. Special paragraphs devoted to melanosome movement and to Griscelli syndrome.

- Ribalta T, Lloreta J, Munne A, Serrano S, Cardesa A.
Malignant pigmented clear cell epitheloid tumor of the kidney: Clear cell ("sugar") tumor versus malignant melanoma. Human Pathology 31(4): 516-519, 2000.
Comments: The presence of classic or aberrant melanosomes belongs to the most frequent findings in angiomyolipomas; clear cell ("sugar") tumour, regarded by some authors as a clear cell epitheloid variant of angiomyolipoma, also habitually contains melanosomes. A case of such tumour in kidney consisting of S1000 and HMB45 positive cells with Fontana-Masson positive pigment and melanosomes demonstrated by EM is presented.

- Salceda R, Sanchez-Chavez G.
Calcium uptake, release and ryanodine binding in melanosomes from retinal pigment epithelium. Cell Calcium 27(4): 223-229, 2000.
Comments: Characterization of ^{45}Ca uptake to and release from melanosomes in the absence and presence of ionophore A23187, nigericin and inhibitors of plasma membrane channels. Demonstration of ryanodine binding sites in melanosomes. Description of isolation method to obtain pure melanosome fractions with intact membranes. Demonstration of the enrichment of acid phosphatase activity within the melanosomal fraction.

- Tuxworth RI, Titus MA.
Unconventional myosins: Anchors in the membrane traffic. Traffic1(1): 11-18, 2000.
Comments: An excellent review concentrating on the fuctions of myosin classes I, V, VI and VII in membrane trafficking processes and also on the switching between microtubule and actin networks. Genetic disorders mapped to the myosin V locus (Griscelli syndrome, dilute lethal mouse mutation) and mutations in myosin VIIa (shaker mice) are associated with altered distribution of melanosomes.

- Vancoille G, Lambert J, Mulder A, Koerten HK, Mommaas AM, Van Oostveldt P, Naeyaert JM.
Kinesin and kinectin can associate with the melanosomal surface and form a link with microtubules in normal human melanocytes. J Invest Dermatol 114(3): 421-429, 2000.
Comments: Data suggesting that kinesins and their receptor kinectin have an important role in microtubuli-based melanosome transport in human melanocytes.

9. Melanoma_experimental, Cell culture

A. Melanoma cytotoxicity, experimental

- Albino AP, Juan G, Traganos F, Reinhart L, Connolly J, Rose DP, Darzynkiewicz Z.
Cell cycle arrest and apoptosis of melanoma cells by docosahexaenoic acid: association with decreased pRb phosphorylation. Cancer Res. 60(15):4139-45, 2000.

- Caltagirone S, Rossi C, Poggi A, Ranelletti FO, Natali PG, Brunetti M, Aiello FB, Piantelli M.
Flavonoids apigenin and quercetin inhibit melanoma growth and metastatic potential. Int J Cancer. 87(4):595-600, 2000.

- Cho D, Kim TG, Lee W, Hwang YI, Cho HI, Han H, Kwon O, Kim D, Park H, Houh D.
Interleukin-18 and the costimulatory molecule B7-1 have a synergistic anti-tumor effect on murine melanoma; implication of combined immunotherapy for poorly immunogenic malignancy. J Invest Dermatol. 114(5):928-34, 2000.

- Della Morte R, Squillacioti C, Garbi C, Derkinderen P, Belisario MA, Girault JA, Di Natale P, Nitsch L, Staiano N.
Echistatin inhibits pp125FAK autophosphorylation, paxillin phosphorylation and pp125FAK-paxillin interaction in fibronectin-adherent melanoma cells. Eur J Biochem. 267(16):5047-5054, 2000.

- Franchi J, Coutadeur MC, Marteau C, Mersel M, Kupferberg A.
Depigmenting effects of calcium D-pantetheine-S-sulfonate on human melanocytes. Pigment Cell Res. 13(3):165-71, 2000.

- Gembitsky DS, De Angelis PM, Reichelt KL, Elgjo K.
An endogenous melanocyte-inhibiting tripeptide pyroGlu-Phe-GlyNH2 delays in vivo growth of monoclonal experimental melanoma. Cell Prolif. 33(2):91-9, 2000.

- Hiratsuka J, Kondoh H, Tsuboi T, Yoshino K, Imajo Y, Mishima Y.
Selective uptake of para-boronophenylalanine increases in amelanotic melanoma cells transfected by the tyrosinase gene. Melanoma Res. 10(3):297-302, 2000.

- Huang Q, Hu JK, Lohr F, Zhang L, Braun R, Lanzen J, Little JB, Dewhirst MW, Li CY.
Heat-induced gene expression as a novel targeted cancer gene therapy strategy. Cancer Res. 60(13):3435-9, 2000.

- Kalechman Y, Longo DL, Catane R, Shani A, Albeck M, Sredni B.
Synergistic anti-tumoral effect of paclitaxel (Taxol) + AS101 in a murine model of B16 melanoma: association with ras-dependent signal-transduction pathways. Int J Cancer. 86(2):281-8, 2000.

- Kanazawa J, Ohta S, Shitara K, Fujita F, Fujita M, Hanai N, Akinaga S, Okabe M.
Therapeutic potential of chimeric anti-(ganglioside GD3) antibody KM871: antitumor activity in xenograft model of melanoma and effector function analysis. Cancer Immunol Immunother. 49(4-5):253-8, 2000.

- Kang IC, Kim DS, Jang Y, Chung KH.
Suppressive mechanism of salmosin, a novel disintegrin in B16 melanoma cell metastasis. Biochem Biophys Res Commun. 275(1):169-73, 2000.

- Koshkina NV, Kleinerman ES, Waidrep C, Jia SF, Worth LL, Gilbert BE, Knight V.
9-Nitrocamptothecin liposome aerosol treatment of melanoma and osteosarcoma lung metastases in mice. Clin Cancer Res. 6(7):2876-80, 2000.

- Laird AD, Vajkoczy P, Shawver LK, Thurnher A, Liang C, Mohammadi M, Schlessinger J, Ullrich A, Hubbard SR, Blake RA, Fong TA, Strawn LM, Sun L, Tang C, Hawtin R, Tang F, Shenoy N, Hirth KP, McMahon G, Cherrington.
SU6668 is a potent antiangiogenic and antitumor agent that induces regression of established tumors. Cancer Res. 60(15):4152-60, 2000.

- Panov V, Salomon Y, Kabalka GW, Bendel P.
Uptake and washout of borocaptate sodium and borono-phenylalanine in cultured melanoma cells: a multi-nuclear NMR study. Radiat Res. 154(1):104-12, 2000.

- Shiose S, Sakamoto T, Yoshikawa H, Hata Y, Kawano Y, Ishibashi T, Inomata H, Takayama K, Ueno H.
Gene transfer of a soluble receptor of VEGF inhibits the growth of experimental eyelid malignant melanoma. Invest Ophthalmol Vis Sci. 41(9):2395-403, 2000.

- Tanaka T, Kohno H, Murakami M, Kagami S, El-Bayoumy K.
Suppressing effects of dietary supplementation of the organoselenium 1,4-phenylenebis(methylene)selenocyanate and the Citrus antioxidant auraptene on lung metastasis of melanoma cells in mice. Cancer Res. 60(14):3713-6, 2000.

- Tsurifune T, Ito T, Li XJ, Yamashiro S, Okada M, Kanematsu T, Shiku H, Furukawa K.
Alteration of tumor phenotypes of B16 melanoma after genetic remodeling of the ganglioside profile. Int J Oncol. 17(1):159-65, 2000.

- Villa R, Folini M, Lualdi S, Veronese S, Daidone MG, Zaffaroni N.
Inhibition of telomerase activity by a cell-penetrating peptide nucleic acid construct in human melanoma cells. FEBS Lett. 473(2):241-8, 2000.

- Yamamura S, Hakomori S, Wada A, Igarashi Y.
Sphingosine-1-phosphate inhibits haptotactic motility by overproduction of focal adhesion sites in B16 melanoma cells through EDG-induced activation of Rho. Ann N Y Acad Sci. 905:301-7, 2000.

B. Culture systems to study melanocytes

- Castel S, Pagan R, Garcia R, Casaroli-Marano RP, Reina M, Mitjans F, Piulats J, Vilaro S.
Alpha v integrin antagonists induce the disassembly of focal contacts in melanoma cells. Eur J Cell Biol. 79(7):502-12, 2000.

- Dekker SK, van Doorn R, Kempenaar J, Gruis NA, Vermeer BJ, Ponec M.
Skin equivalent: an attractive model to evaluate early melanoma metastasis. Melanoma Res. 10(2):127-40, 2000.

- Desai SH, Boskovic G, Eastham L, Dawson M, Niles RM.

Effect of receptor-selective retinoids on growth and differentiation pathways in mouse melanoma cells. Biochem Pharmacol. 59(10):1265-75, 2000.

- Graeven U, Rodeck U, Karpinski S, Jost M, Andre N, Schmiegel W.
Expression patterns of placenta growth factor in human melanocytic cell lines. J Invest Dermatol. 115(1):118-23, 2000.

- Hsu MY, Meier FE, Nesbit M, Hsu JY, Van Belle P, Elder DE, Herlyn M.
E-cadherin expression in melanoma cells restores keratinocyte-mediated growth control and down-regulates expression of invasion-related adhesion receptors. Am J Pathol. 156(5):1515-25, 2000.

- La Porta CA, Di Dio A, Porro D, Comolli R.
Overexpression of novel protein kinase C delta in BL6 murine melanoma cells inhibits the proliferative capacity in vitro but enhances the metastatic potential in vivo. Melanoma Res. 10(2):93-102, 2000.

- Okamoto-Inoue M, Nakayama J, Hori Y, Taniguchi S.
Human malignant melanoma cells release a factor that inhibits the expression of smooth muscle alpha-actin. J Dermatol Sci. 23(3):170-177, 2000.

- Straten P, Kirkin AF, Siim E, Dahlstrom K, Drzewiecki KT, Seremet T, Zeuthen J, Becker JC, Guldberg P.
Tumor infiltrating lymphocytes in melanoma comprise high numbers of T-cell clonotypes that are lost during in vitro culture. Clin Immunol. 96(2):94-9, 2000.

ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

Also available from address: http://www.ulb.ac.be/medecine/loce/espcr.htm

2000 **9th ESPCR Meeting: Ulm, Germany**

Sept 28 - Oct 1

Contact: Prof. R.U. PETER
University of Ulm (BWK)
Dept of Dermatology
Oberer Eselsberg 40
D - 89081 ULM
Tel: 49-731 502-3770 Fax: 49-731 502-3772
E-mail: ralf.peter@medizin.uni-ulm.de

2001 **5th World Conference on Melanoma: Venice**

Feb 28- Mar 3

Contact: Dr. M. SANTINAMI
Secretary General
5th World Conference on Melanoma
Dept. of Surgery - Casa di Cura S. Pio X
Via F. Nava 31
I- 20159 Milano
Phone/Fax: 39-02-69516449
E-Mail: info@melanoma2001.org or marsant@tin.it
Website: www.melanoma2001.org

2001 **VIth International Conference on Solar Energy and Applied Photochemistry: Cairo, Egypt**

April 3-8

Contact: Prof. M.S.A. ABDEL-MOTTALEB
Photoenergy Center
Faculty of Science, Ain Shams Unversity
Abbassia, Cairo, Egypt
Tel: 002012 216 9584 (cellular)
Faxes: 00202 244 7683 or 00202 484 5941
E-mail: solar@phoenergy.org
solar@link.com.eg
Website: http://www.photoenergy.org/solar2001.html

2001 **Xth Annual Meeting of the PASPCR, Minneapolis, MN**

June 14-17

Contact: Dr. R. KING
University of Minnesota
Depts of Medecine and Pediatrics
Box 485 UMHC
420 Delaware Street
USA - Minneapolis, MN 55455
E-Mail: king@mail.ahc.umn.edu

2001 **Xth Annual Meeting of the ESPCR, Rome, Italy**

Sept 27-29 **Contact**: Dr. M. Picardo
Lab. Cutaneous Physiopathology
San Gallican Dermatological Institute
I - 0053 Rome
Tel: 39-0658 543 662
Fax: 39-0658 543 740
E-Mail: picardo@crs.ifo.it

2002 **2002 XVIIIth International Pigment Cell Conference: The Hague, NL**

Contact: Dr. S. PAVEL
University Hospital Leiden
Dept of Dermatology
PO Box 9600
NL - 2300 RC LEIDEN
Tel: 31-(71) 526 1952
Fax: 31-(71) 524 8106
E-mail: SPavel@algemeen.azl.nl

Dear Colleagues,

Following a suggestion by Dr. W. Westerhof and the advise of the International Editors of the Bulletin, we thought that it was a good idea to publish summeries of PhD theses presented by ESPCR members or done in an ESPCR members' laboratory.

The aim is to inform ESPCR members on: research activities that can remain unpublished, the expertise field of the author,... and also to acknowledge the work of ESPCR members.

This should trigger even more scientific exchange and encourage collaborations that are also the goals of our Society.

Should you have such a material or any other that you think it deserves to be reported, please do not hesitate to send it to the Editorial office.
The first is reported below.

In advance, thank you.
The Bulletin Editor