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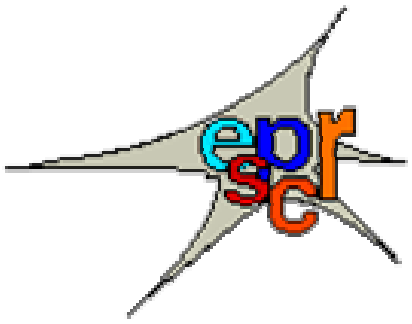

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CONTENTS

DISCUSSION

GENETICS OF SENESCENCE IN MELANOCYTES

Adapted and summarized by Prof. DC Bennett from a section of:
Bennett DC and Medrano EE (2002).
Molecular regulation of melanocyte senescence.
***Pigment Cell Res.*, 15, 242-250**

Introduction: Cell senescence is the process whereby normal mammalian somatic cells become unable to divide after a finite number of divisions, a process often disrupted in cancer cells. This may have a special significance in melanocytes, as the three genes so far associated with familial melanoma susceptibility – *INK4A, CDK4* and *ARF,* are all implicated in the molecular pathways controlling cell senescence. These pathways are reviewed in the above article, with a discussion of the possible roles of cell senescence in the development and molecular genetics of melanoma and its precursor lesions.
INK4A* and *ARF: The *INK4A and ARF* genes are unusual in sharing some coding sequence in different reading frames, within a common locus (*INK4A-ARF*). Both encode powerful cellular growth inhibitors, which act through key tumour suppressor genes RB1 and p53. INK4A protein, also known as $p16^{INK4A}$ or p16, is an activator of RB1 (by inhibiting kinase CDK4), while ARF is an activator of p53 and its downstream growth inhibitor p21. Some mutations associated with familial melanoma susceptibility affect both *INK4A* and *ARF*; others affect *INK4A* only, and in one case *ARF* only (see article for literature references).

Genetically engineered inbred mice were used to analyze the effect of an *Ink4a-Arf* deletion on cell senescence. This deletion abolishes the function of both p16 and Arf. Mouse fibroblasts homozygous for this deletion show very little senescence, and melanocytes of this genotype behaved similarly. However a difference was seen between fibroblasts and melanocytes with only one copy of the deletion (hemizygous, as in most familial melanoma cases). The hemizygous fibroblasts senesced normally, whereas hemizygous melanocytes showed only partial senescence. Another interesting aspect was pigmentation. Normal wild-type mouse melanocytes showed heavy pigmentation and increased cell size and protein content at the time of senescence. These rises did not occur in *Ink4a-Arf* null melanocytes, and only partially in *Ink4a-Arf* hemizygous melanocytes. Thus, in mouse melanocytes, both normal copies of the *Ink4a-Arf* locus are required for normal senescence, and the associated rises in pigmentation and cell size.

To analyze the relative roles of p16 and Arf, wild-type *Ink4a* and *Arf* sequences were separately replaced in the *Ink4a-Arf*-/- melanocytes. p16 expression led to growth arrest, with increased pigmentation and cell size. The cells also expressed acidic □-galactosidase, a partial marker of senescence.. Conversely, the cells expressing Arf without p16 had a high rate of cell death, again with apparent high pigmentation but no size increase and no detectable □-galactosidase. Moreover, spontaneously immortalized lines of mouse melanocytes and melanoblasts from *Ink4a-Arf*+/+ mice often expressed Arf protein, but never p16 protein. These findings indicated a key role for the p16/Rb1 pathway in control of mouse melanocyte senescence, with loss of p16 (but not Arf) expression apparently mandatory for immortalization.

Genetic analysis of p16 in melanocyte senescence has also been possible in human melanocytes (work submitted for publication). Two strains of melanocytes from humans with deficiencies in both

p16 alleles were cultured. Both showed high rates of apoptosis in a standard melanocyte medium. Addition of either keratinocyte feeder cells or keratinocyte-derived growth factors enabled the cells of both strains to proliferate well and both then achieved a greatly extended lifespan. Thus, p16/RB1 deficiency in melanocytes allows an extended lifespan, but promotes cell death in the absence of keratinocyte products. Blockade of p53 using the HPV16-E6 oncogene showed that the cell death was partially independent of p53. Both strains showed partial upregulation of p53 while growing, with eventual p21 accumulation and senescence. In comparison, normal melanocytes senesced with low p53 and no detectable p21. This with other evidence (see review) supports the view that senescence of human melanocytes is controlled primarily by the p16/RB1 pathway. The p53/p21 pathway can effect only a delayed arrest, when the p16/RB1 pathway is deficient.

p53: Evidence from transgenic mice overexpressing a stable, hyperactive mutant p53, $p53^{m}$, supported the hypothesis that p53 has little part in normal melanocyte senescence. Although these animals showed accelerated ageing in several tissues, pigmentation in hair and skin did not show appreciably early reduction. Thus, the $p53^{+/m}$ hair bulb melanocytes retained proliferative capacity for a normal time, through repeated hair cycles – further evidence that mouse melanocyte senescence is normally independent of p53.

Extension of melanocyte lifespan by genetic manipulations: One group described the immortalization of two neonatal human melanocyte strains by expression of HPV16 oncogenes E6 and E7, interfering with both p53 and RB. This was interesting but surprising, because no manipulation was performed to restore telomerase activity, which does appear to limit lifespan in cultured melanocytes (see below). It is possible that telomerase became spontaneously reactivated; this was not checked.

Conversely, expression of exogenous hTERT (human telomerase reverse transcriptase) alone, by retroviral transduction, was also followed by marked lifespan extension in human melanocytes, by more than 70 additional doublings. The cells retained normal appearance. The melanocytes did not however reach immortality, because hTERT expression, mediated by a viral promoter, was extinguished at ~ passage 80. These melanocytes showed some intriguing changes in gene expression, including reduced levels of p16 and another growth inhibitor $p27^{Kip\text{-}1}$. It is unknown whether such changes contributed to the extended lifespan, and whether they arose as a result of hTERT expression or spontaneously. The reduction in p16 level is especially interesting.

In summary, most or all the genetic evidence suggests that downregulation of the p16/RB1 pathway may be required, in addition to telomerase activation, for immortalization of human melanocytes. Accordingly, both these changes are predicted to be necessary for the development of a human melanoma, since neoplastic cells are generally immortal.

CURRENT LITERATURE

1. Biology of pigment cells and pigmentary disorders

(Dr. M. Picardo)

Several factors are involved in the control of melanogenesis and its significance is due even to protective role against sun-induced DNA damage and carcinogenesis. **MC Scott** evaluates the role of melanocortin receptor 1 (MC1R) in the modulating the melanocyte response to UV radiation. It is know that the eumelanin synthesis is induced by activation of the α-MSH specific receptor, MC1R, and that eumelanin is able to protect the skin by UVR-mediated damage through a direct scavenger action and an enhanced resistance to photodegradation. The author shows that melanocytes with MC1R allelic variants (i.e.Val92Met) show a low affinity for α-MSH, reduced α-MSH-induced tyrosinase activity and proliferation, high sensitivity to UVR (cell death), and are associated with red hair phenotype and increased incidence of melanoma. The *in vitro* study of pigmentation makes use of large methods, among which recently **TC Lei** proposed a new melanocytes-keratinocyte coculture model with the aim to test the action of pro or anti-melanogenic factors. Also a mathematic model has been proposed, by **L Oyehaug**, to understand the melanogenic switching between eu- and pheo-melanin synthesis. The author proposes that the switch can be due to a jump between two stable production pattern when tyrosinase activity changes between two levels suggesting that small changes in external regulatory factors may cause an accentuated change in the proportion of the pigment produced. **EV Sviderskaya** studied in melanocyte culture the role of p16Ink4a in the regulation of senescence. She demonstrated that normal senescence and pigmentation require both copies of Ink4a-Arf and depend more on p16 function than Arf function. Ink4a-Arf mutation favors tumorigenesis by impairing senescence process and cell death. **DC Bennett** proposed an attractive review about the regulatory mechanism of melanocyte senescence. The cellular senescence is characterized by loss ability to divide and then by stop growing. On the other hand, the cells must overcome the barrier of senescence in order to become neoplastic (and immortal). The lifespan and the senescence in vitro depend on culture condition (medium supplementation): cholera toxin, IBMX, MSH, TPA are all able to stimulate the proliferation but also differentiation and pigmentation. Thus, the balance between these different factors supports the proliferation (TPA) or the differentiation (CT, IBMX). There is then a correlation between differentiation and senescence but the association is not a direct one. Also the age of the donor affects the culture lifespan of the melanocytes. However, the genetic aspects of senescence must be examined closely, considering the observed association of the mutations of three genes (INK4A, CDK4, and ARF), involved in pathways controlling cell senescence, with familial melanoma susceptibility. Senescence is accompanied by down-regulation of cyclin E protein level, up-regulation of $p16^{INK4a}$, dephosphorylation of RB1. p16/RB1 shows a key role in in control of melanocyte senescence, with loss of p16 mandatory for immortalization. Arf expression not leads to senescence in absence of p16. Moreover, the cell death pathway is partially independent on p53, which appears to act only when p16/RB1 is deficient. The molecular factors involving in the so-called M2 phase (mortality phase 2) are even considered. **R Han** and co-workers reassess cutaneous melanogenesis using tyramine-based tyrosinase assay (TTA). TTA serves as indicator of skin and eye pigment cell distribution and status, with relevant possible benefit in diagnosis of pigmentary disorders (vitiligo or melanocytic naevi). The role of fibronectin on migration and differentiation of melanocytes during embryogenesis was evaluated by **N Takano** using cultured mouse neural crest cells. **FL Meyskens** evaluated the role of the alterated redox-sensitive transcriptional factors, with a consequent enhancement of anti-apoptotic phenotype, in melanomagenesis.

TC Lei, Vieira WD and VJ Hearing provided proof (through WB and RT-PCR) for an involvement of matrix metalloproteinase 2 (MMP2) in melanoblast migration even in response to PUVA therapy used for vitiligo treatment. Moreover, MMP2 appears appears to be induced by 8MPO and/or MSH.

Scott MC and co-workers investigated the control of MC1R expression in melanocytes by endocrine factors and UVR. They suggest a regulation by paracrine factors, including its own ligands, and by UVR. Among the different factors, MSH, ET-1, bFGF, PKC, cAMP are positive regulators whereas testosterone and UVR inhibit it.

Hirobe T suggests that the increased proliferative response and differentiation of mouse epidermal melanocytes UVB radiated are regulated by keratinocytes rather than melanocytes.

G Scott reviews the structure, hormonal regulation and molecular mediators of melanocyte dendrite formation with a particular attention to Rac and Rho function.

A crucial role in the control of melanogenesis is carried out by the microphthalmia-associated transcription factor (MITF), consisting at least of seven isoforms. A novel isoform of Mitf was identified by **CM Takemoto**: Mitf-mc, present in mast cells. Mitf-mc acts only on mast cells promoter whereas fails to activate the melanocyte promoter even if is capable of binding its E-box element. The molecular study, based on transfection of different isoform with subsequent RT-PCR and EMSA, shows that the mechanism of selectivity for gene target activation is independent of DNA binding preferences and thus is probably due to differential recruitment of protein complexes to Mitf, without a true gene repression. Mitf mutations

have been reported in the pathogenesis of several diseases, such as the Waardenburg syndrome 2 (WS2), characterized by deafness and hypopigmentation due to lack of melanocytes from inner ear and skin. MITF-M is essential for melanocyte differentiation and is transcriptionally induced by Wnt signaling mediated by β-catenin and LEF1. **H Saito** demonstrates that MITF-M activates its own M promoter by interacting with LEF1. MITF-M acts as a self regulator to maintain a threshold level of MITF-M required for melanocyte development. The author suggests that the haploinsuffinciency of MITF-M in WS2 may impair the dosage-sensitive role of MITF-M or the correct assembly of multiple transcription factors. The synergism between MITF-M and LEF1 regulates also the DCT gene even if through a different mechanism from that of the M promoter. Moreover, DCT, detoxificating melanin precursors, is involved in the survival of the melanocytes. The finding that *vit* mutation impairs the synergism with LEF1 on DCT promoter but not on M promoter could account for Mitf ^{vit} mice, which exhibit age-depending melanocyte loss. Vit affects the postnatal viability of melanocytes because of the differential effects on the synergism with LEF1 on DCT and M promoter. The group of **KI Watanabe** identified a distal enhancer for the promoter M of MITF gene, regulated by SOX10 in a development stage-specific manner. SOX10 mutation is involved in another form of WS, WS4 (or Waardenburg-Hirschsprung syndrome). **HT Khong and SA Rosenberg** have identified SOX10 as able to encode a melanoma/melanocyte differentiation antigen recognized by CTLs. The study was performed by using cDNA library screening, RT-PCR and DNA sequencing. Interestingly, in Autoimmune Polyendocrine Syndrome I vitiligo is common (8-15% vs 1% of prevalence in general population) and more than half of the vitiligo with APS I had autoantibody against SOX10. Moreover, considering that tumor infiltrating lymphocytes are capable of recognizing SOX10, this protein could be the target of the melanoma immunotherapy. The cause of hypopigmentation observed in Hermanansky-Pudlak (HPS) and Griscelli (GS) syndromes was investigated in animal models. In particular, the ashen (ash) mouse, a model for HPS and a subset of GS, is characterized by hypopigmentation, prolonged bleeding time, platelet storage pool deficiency due to a mutation of Rab27a, without other defect of the secretion of the lysosomal enzymes of several other tissue. In this model **EK Novak** emphasizes the role of the genetic background as regard the effect of Rab27a mutation on the platelet dense granules, offering a possible explanation for the normal bleeding time in GS with Rab27a mutation. Moreover, in GS (hair pigment dilution, uncontrolled T lymphocyte and macrophage activation) a redundancy of Rab27 proteins (Rab27a and Rab27b) could clarify the pathogenesis of GS, which may depend by the relative esxpression of Rab27a and rab27b, as suggested by **DC Barral**. Further studies on melanosome transport, performed by **K Nagashima**, indicate that melanophilin binds Rab27a and Myo5a through its N-terminal and C-terminal, respectively. The evaluation of cytokine pattern in non-lesional, peri-lesional and involved areas by immunohystochemestry assay allows **S Moretti** to underline the involvement of epidermal cytokine production in the vitiligo pathogenesis. EH Kemp identified a novel autoantigen in vitiligo: the MCHR1 by using a melanocyte cDNA phage-display library and radiobinding assay.

A further hypopigmentary disease is oculocutaneous albinism 2 (OCA2), due to a mutation in the *pink-eyed dilution* locus (*p*). In *vitro* data from **K Chen** and co-workers show that in melan-p1 melanocytes (null at the *p* locus) p regulates posttranslational processing and trafficking of tyrosinase. Moreover, **T Hirobe** demonstrates that the proliferation of the epidermal cells from wild type mouse at p locus was inhibited by adding L-Tyrosine to culture medium whereas that of cells from mutant mouse was induced. On the other hand, L-Tyrosine stimulates (P/P) or induces (p/p) the differentiation of melanocytes. Eumelanin precursors in p/p melanocytes were increased as well as the number of stage II, III, IV melanosomes. Taken together, these results suggest that p/p melanocytes are induced to synthesize eumelanin but are not able to accumulate them in melanosomes. Similar data are presented also by **K Toyofuku,** which demonstrated an impaired trasport of tyrosinase but not of Dct or Pmel17. **B Roth** presented a case of acquired dermal melanocytosis associated with leptomeningeal melanosis. Melanocytes, because of disorder neural crest migration, remain in the dermis and are subsequently reactivated. **A Slominski** group presented evidences for a skin and skin-derived cells intrinsic capability to metabolize tryptophan in serotonin and serotonin in melatonin. Among the wide spectrum of skin lightening compounds, **T Hakozaki** investigated the activity of niacinamide, physiologically active form of vitamin B3, in cultured melanocytes, reconstructed epidermis model and in clinical trial. He reported that niacinamide has not effect on the tyrosinase activity or on keratinocytes proliferation, but was able to inhibit melanosome transfer (35-68% of inhibition), giving rise to a significant depigmentation in vivo.

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2. MSH, MCH, other hormones, differentiation

(Dr. B. Loir)

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Summary: The authors identified MCHR1 as a novel autoantigen related to vitiligo, using IgG from vitiligo patients to screen a melanocyte cDNA phage-display library. They demonstrated a high disease specificity for Abs against the receptor by using radiobinding assays and comparison with sera from healthy individuals and from other patients with autoimmune disease. Inhibition of MCH binding to its receptor by IgG from vitiligo patients was also shown.

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Summary: "The microphthalmia transcription factor MITF plays a pivotal role in the development and differentiation of melanocytes." In this study, the authors propose a role for the MITF-M isoform in the in vivo growth control and histopathological appearance of human melanoma.

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4. Neuromelanins

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5. Genetics, molecular and developmental biology

(Dr. F. Beermann)

Melanocyte stem cells: In the April 25 issue of Nature. the group of Nishikawa has published their work which provides evidence for the presence of melanocyte stem cells within the bulge area (not bulb!) of the hair follicle (Nishimura et al., 2002). The presence of stem-cell like cells in the bulge had already been anticipated by work of others, when they followed pigmentation gene expression, in dependence of SCF/c-kit signalling during the hair cycle (Botchkareva et al., 2001, FASEB J 15, 645) or by the presence of non-pigmented c-kit negative melanoblasts in the bulge (Peters et al., 2002). In addition, the new work demonstrated that stem cell progeny can migrate out of occupied sites (niches) and repopulate vacant ones, where they again can behave as stem cells.

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Circling, deafness, and yellow coat displayed by yellow submarine (ysb) and light coat and circling (lcc) mice with mutations on chromosome 3. Genomics 79(6):777-784., 2002.

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Artificial chromosome transgenesis in pigmentary research. Pigment Cell Res 15(4):258-264., 2002.

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Expression of Cre recombinase in pigment cells. Pigment Cell Res 15(4):305-309., 2002.
Comment: Transgenic mice expressing Cre recombinase under control of the Dct/Tyrp2 promoter.

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Bcl2 regulation by the melanocyte master regulator mitf modulates lineage survival and melanoma cell viability. Cell 109(6):707-718., 2002.
Abstract: Kit/SCF signaling and Mitf-dependent transcription are both essential for melanocyte development and pigmentation. To identify Mitf-dependent Kit transcriptional targets in primary melanocytes, microarray studies were undertaken. Among identified targets was BCL2, whose germline deletion produces melanocyte loss and which exhibited phenotypic synergy with Mitf in mice. BCL2's regulation by Mitf was verified in melanocytes and melanoma cells and by chromatin immunoprecipitation of the BCL2 promoter. Mitf also regulates BCL2 in osteoclasts, and both Mitf(mi/mi) and

Bcl2(-/-) mice exhibit severe osteopetrosis. Disruption of Mitf in melanocytes or melanoma triggered profound apoptosis susceptible to rescue by BCL2 overexpression. Clinically, primary human melanoma expression microarrays revealed tight nearest neighbor linkage for MITF and BCL2. This linkage helps explain the vital roles of both Mitf and Bcl2 in the melanocyte lineage and the well-known treatment resistance of melanoma.

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Site-specific somatic mutagenesis in the retinal pigment epithelium. Invest Ophthalmol Vis Sci 43(5):1384-1388., 2002.
Comment: Transgenic mice expressing Cre recombinase under control of the Tyrp1 promoter

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Dominant role of the niche in melanocyte stem-cell fate determination. Nature 416(6883):854-860., 2002.
Abstract: Stem cells which have the capacity to self-renew and generate differentiated progeny are thought to be maintained in a specific environment known as a niche. The localization of the niche, however, remains largely obscure for most stem-cell systems. Melanocytes (pigment cells) in hair follicles proliferate and differentiate closely coupled to the hair regeneration cycle. Here we report that stem cells of the melanocyte lineage can be identified, using Dct-lacZ transgenic mice, in the lower permanent portion of mouse hair follicles throughout the hair cycle. It is only the population in this region that fulfils the criteria for stem cells, being immature, slow cycling, self-maintaining and fully competent in regenerating progeny on activation at early anagen (the growing phase of hair follicles). Induction of the re-pigmentation process in K14-steel factor transgenic mice demonstrates that a portion of amplifying stem-cell progeny can migrate out from the niche and retain sufficient self-renewing capability to function as stem cells after repopulation into vacant niches. Our data indicate that the niche has a dominant role in the fate determination of melanocyte stem-cell progeny.

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The identification and functional characterization of a novel mast cell isoform of the microphthalmia-associated transcription factor (Mitf). J Biol Chem 30:30, 2002.

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Identification by cDNA microarray technology of genes modulated by artificial ultraviolet radiation in normal human melanocytes: relation to melanocarcinogenesis. J Invest Dermatol 117(6):1471-1482., 2001.

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Neural crest progenitors of the melanocyte lineage: coat colour patterns revisited. Development 129(14):3349-3357., 2002.
Abstract: Neural crest-derived melanoblasts are the progenitors of melanocytes, the pigment cells of the skin, hair and choroid. Previous studies of adult chimaeric mice carrying different coat colour markers have suggested that the total melanocyte population is derived from a small number of melanoblast progenitors, each of which generates a discrete unilateral transverse band of colour. This work also suggested minimal mixing of cells between clones. We have used two complementary approaches to assess the behaviour of migrating clones of melanoblasts directly in the developing embryo. First, we made aggregation chimaeras between transgenic Dct-lacZ and non-transgenic embryos, in which lacZ is a marker for melanoblasts. Second, we generated transgenic mice carrying a modified lacZ reporter construct containing a 289 base pair duplication (laacZ) under the control of the Dct promoter. The laacZ transgene is normally inactive, but reverts to wild-type lacZ at low frequency, labelling a cell and all of its progeny at random. Mosaic embryos containing labelled melanoblast clones were generated. In contrast to previous data, chimaeric and mosaic embryonic melanoblast patterns suggest that: (1) there is a large number of melanoblast progenitors; (2) there is a pool of melanoblasts in the cervical region; (3) different cell dispersion mechanisms may operate in the head and trunk regions; and (4) there is extensive axial mixing between clones.

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Microphthalmia-associated transcription factor interacts with LEF-1, a mediator of Wnt signaling. Embo J 21(11):2703-2714., 2002.
Abstract: Wnt signals regulate differentiation of neural crest cells through the beta-catenin associated with a nuclear mediator of the lymphoid-enhancing factor 1 (LEF-1)/T-cell factors (TCFs) family. Here we show the interaction between the basic helix-loop-helix and leucine-zipper region of microphthalmia-associated transcription factor (MITF) and LEF-1. MITF is essential for melanocyte differentiation and its heterozygous mutations cause auditory-pigmentary syndromes. Functional cooperation of MITF with LEF-1 results in synergistic transactivation of the dopachrome tautomerase (DCT) gene promoter, an early melanoblast marker. This activation depends on the separate cis-acting elements, which are also responsible for the induction of the DCT promoter by lithium chloride that mimics Wnt signaling. beta-catenin is required for efficient transactivation, but dispensable for the interaction between MITF and LEF-1. The interaction with MITF is unique to LEF-1 and not detectable with TCF-1. LEF-1 also cooperates with the MITF-related proteins, such as TFE3, to transactivate the DCT promoter. This study therefore suggests that the MITF/TFE3 family is a new class of nuclear modulators for LEF-1, which may ensure efficient propagation of Wnt signals in many types of cells.

6. Tyrosinase, TRPs, other enzymes

(Prof. J.C. Garcia-Borron)

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Identification of o-quinone/quinone methide metabolites of quercetin in a cellular in vitro system. FEBS Lett 520(1-3):30-4 , 2002.

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Abnormal acidification of melanoma cells induces tyrosinase retention in the early secretory pathway. J Biol Chem 277(17):14821-8, 2002.

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The Etiology of Oculocutaneous Albinism (OCA) Type II: The Pink Protein Modulates the Processing and Transport of Tyrosinase. Pigment Cell Res 15(3):217-24 , 2002.

7. Melanosomes

(Dr. J. Borovansky)

Flood of articles dealing with melanosome trafficking (with an emphasis to molecular mechanisms) has culminated (*Bahadoran et al, Bizario et al , Fukuda et al, Goud, Nagashima et al, Shiflett et al, Wu et al.*). Three articles have focused to melanosome biogenesis (*Falcón-Pérez & Dell´Angelica, Loftus et al, Raposo & Marks*). Another interesting articles concern the roles of melanosomal proteins (*Sharma et al*) and the role of filopodia in transfer of melanosomes to keratinocytes (*Scott et al*).

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Ethnic variation in melanin content and composition in photoexposed and photoprotected human skin. Pigment Cell Res 15(2): 112-118, 2002.

Comment: Study on ethnic variation in melanin content and composition including also analysis of melanosomes extracted from the epidermis from a range of different ethnic skin types: The analysis revealed a significant and progressive variation in melanosome size with ethnicity: African skin having the largest melanosomes followed in turn by Indian, Mexican, Chinese and European. Shape of melanosomes (an obsolete and non-reliable criterion) was used to detect phaeomelanosomes.

- Bahadoran P, Ortonne JP, Ballotti R.
Melanosome trafficking? MS-Med Sci 18(2):205-209, 2002.
Comments: Brief review with instructive schemes describing a model of transport and accumulation of melanosomes at the cell periphery. Rab 27a colocalizes with melanosomes and regulates peripheral distribution of melanosomes in melanocytes. Rab 27a can act as a direct receptor of myosin Va at the surface of melanosomes or can recruite an effector which binds myosin Va (see also *Fukuda et al and Wu et al*). Defects in pigment granule transport due to mutations of Rab27a and myosin Va are discussed.

- Bizario JCD, Nascimento AAD, Casaletti L, Patussi EV, Chociay MF, Larson RE, Espreafico EM.
Expression of constructs of the neuronal isoform of myosin-Va interferes with the distribution of melanosomes and other vesicles in melanoma cells. Cell Motility and the Cytoskeleton 51(2): 57-75, 2002.
Comments: The authors attempted to interphere with myosin-Va function by transfection of melanocytes with cDNA constructs encoding the full-length of the neuronal isoform of myosin-Va heavy chain and different domains of this molecular motor. Expression of the full-length myosin-Va in S91 melanoma cells partially rescues the *dilute* phenotype. Overexpression of myosin-Va tail induces a striking phenotype characterized by aggregation and/or fusion of melanosomes and other vesicles, which colocalize with microtubules. This finding supports previous evidence suggesting the involvement of myosin-Va in multiple pathways of vesicular trafficking.

- Falcón-Pérez JM, Dell´Angelica EC.
The *Pallidin* (*Pldn*) gene and the role of SNARE proteins in melanosome biogenesis. Pigment Cell Res. 15(2): 82-86, 2002.
Comments: Pigment Gene Focus Review devoted to the *pallidin (Pldn, pa,p2)* gene. *Pldn* encodes 20kDa protein which was found to bind to syntaxin 13 , a member of the syntaxin family of soluble N-ethylmaleimide–sensitive factor attachment protein receptors (SNAREs). As SNARE proteins mediate fusion of intracellular membranes, pallidin may play a role in membrane fusion events required for melanosome biogenesis.

- Fukuda M, Kuroda TS, Mikoshiba K.
Slac2-a/melanophilin, the missing link between Rab27 and myosin Va. Implication of a tripartite protein complex for melanosome transport. J Biol Chem 277(14): 12432-12436, 2002.
Comments: How myosin Va recognizes its cargo (i.e. melanosomes) has until now remained undetermined. This study demonstrated that Slac2-a (=synaptotagmin-like protein homologue lacking C2 domains)/melanophilin is the "missing" link between myosin Va and GTP-Rab 27a present in the melanosome. Deletion analysis and site-directed mutagenesis showed that the N-terminal synaptotagmin-like protein homology domain of Slac2-a specifically binds the Rab27A/B isoforms and that the C-terminal half directly binds the globular tail of myosin Va.

- Goud B.
How Rab proteins link motors to membranes. Nature Celll Biol. 4(4): E77-E78, 2002.
Comments: A short review (with superb illustrations). on the role of Rab27a in the formation of a receptor complex that allows the recruitment of the actin-based motor myosin Va. Molecular basis for several pathologies that result in pigmentation defects in both mouse and human, is explained.

- Loftus SK, Larson DM, Baxter LL, Antonellis A, Chen Y, Wu X, Jiang Y, Bittner M, Hammer III JA, Pavan WJ.
Mutation of melanosome protein RAB38 in *chocolate* mice. Proc Natl Acad Sci USA 99(7): 4471-4476, 2002.
Comments: Comparative genomic analysis localized human RAB38, a small GTP-binding protein, to the mouse *chocolate* (*cht*) locus. Further analysis confirmed that RAB38 is a melanosomal protein, mutated (G146T) in the *cht* mouse. RAB38 was demonstrated to regulate traffic of vesicular intermediates that move TYRP1 from the trans-Golgi network to end-stage melanosomes. The *cht/cht* melanosomes are similar in morphology to *Tyrp1*^{b} melanosomes. The authors propose RAB38 as a candidate gene for patients with OCA where a molecular defect in TYR, P, TYRP1 or AIM1 has not been identified.

- Nagashima K, Torii S, Yi Z, Igarashi M, Okamoto K, Takeuchi T, Izumi T.
Melanophilin directly links Rab27a and myosin Va through its distinct coiled-coil regions. FEBS Letters 517(1-3): 233-238, 2002.
Comments: Structural features of the rabphilin3/granulophylin-like Rab effector proteins, termed exophylins, were characterized. They have a highly conserved N-terminal domain that is capable of forming coiled-coils to directly bind to Rabs. A human homologue of melanophilin (member of the exophylin family), which is defective in

leaden, was shown to bind directly to both Rab27a and myosinVa through its N-terminal and its first C-terminal coiled coil region, respectively.

- Raposo G, Marks MS.
The dark side of lysosome-related organelles: Specialization of the endocytic pathway for melanosomes biogenesis. Traffic 3(4): 237-248, 2002.
Comments: An interesting review: By studying the fate of melanosomal and endosomal cargo in pigment cells , the effects of disease-related mutations on melanosome morphology, and genes affected by these mutations, novel insights into the biogenesis of the complex organelles and their relationship to the endocytic pathway can be gained. These insights demonstrate how specialized cells integrate unique and ubiquitous molecular mechanisms in subverting the endosomal system to generate cell-type specific structures and their associated functions.

- Scott G, Leopardi S, Printup S, Madden BC.
Filopodia are conduits for melanosome transfer to keratinocytes. J Cell Sci 115(7): 1441-1451, 2002.
Comments: Melanosome enriched fractions isolated from human melanocytes expressed the Cdc42 effector proteins PAKI and N-WASP. Expression of constitutively active Cdc42, known to mediate filopodia formation, in melanocytes co-cultured with keratinocytes induced a highly dendritic phenotype with extensive contacts between melanocytes and keratinocytes through filopodia that served as conduits for melanosome transfer to keratinocytes.

- Sharma S, Wagh S, Govindarajan R.
Melanosomal proteins – role in melanin polymerization. Pigment Cell Res. 15(2): 127-133, 2002.
Comments: Purified melanosomal proteins differ in their ability both to polymerize melanin and to bind to melanin. Conclusion has been drawn that polymerization and binding abilities of melanosomal proteins are specific to each protein and that melanin-protein interactions is not nonspecific.

- Shiflett SL, Kaplan J, McVey Ward D.
Chediak-Higashi syndrome: A rare disorder of lysosomes and lysosome related organelles. Pigment Cell Res. 15(4): 251-257, 2002.
Comments: Review from the Series Pigment Gene Focus. Molecular basis of Chediak-Higashi syndrome, autosomal recessive disorder, is mutation(s) of the *CHS1/LYST* gene on chromosome1 in humans and the *beige* gene on chromosome 13 in mice. Although the structure of CHS1/LYST and beige proteins has been characterized, the function of the proteins in vesicular trafficking affecting lysosome-related organelles, has remained unclear.

- Wu XFS, Rao K, Zhang H, Wang F, Sellers JR, Matesic LE, Copeland NG, Jenkins NA, Hammer JA.
Identification of an organelle receptor for myosin-Va. Nature Cell Biology 4(4): 271-278, 2002.
Comments: Description of organelle receptor for an actin-based motor: Rab 27a binds to the melanosome first and then recruits melanophilin, which in turn recruits myosin-Va. Melanophilin creates this link by binding to Rab27a in a GTP-dependent fashion through its amino terminus, and to myosin-Va through its carboxyl terminus (the interaction is absolutely dependent on the presence of nexon-F, an alternatively spliced exon in the myosin-Va tail.

8. Melanoma experimental, Cell culture

(Dr. N. Smit)

Melanocyte and other culture models

- Bennett DC, Medrano EE.
Molecular regulation of melanocyte senescence. Pigment Cell Res. 15:242-250, 2002.

- Borges CR, Martin SD, Meyer LJ, Wilkins DG, Rollins DE.
Influx and efflux of amphetamine and N-acetylamphetamine in keratinocytes, pigmented melanocytes, and nonpigmented melanocytes. J.Pharm.Sci. 91:1523-1535, 2002.

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An NAD(P)H oxidase regulates growth and transcription in melanoma cells. Am.J.Physiol Cell Physiol 2002, 282:C1212-C1224, 2002.

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Rab27b association with melanosomes: dominant negative mutants disrupt melanosomal movement. J.Invest Dermatol. 118:933-940, 2002.

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Inducible nitric oxide synthase is expressed in normal human melanocytes but not in melanoma cells in response to tumor necrosis factor-alpha, interferon-gamma, and lipopolysaccharide. J.Invest Dermatol. 118:1019-1025, 2002.

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Activated MAPK/ERK Kinase (MEK-1) Induces Transdifferentiation of Pigmented Epithelium into Neural Retina. Dev.Biol. 248:251, 2002.

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Autocrine stimulation by osteopontin contributes to antiapoptotic signalling of melanocytes in dermal collagen. Cancer Res. 62:4820-4828, 2002.

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Efficient transfection method for primary cells. Tissue Eng 8:235-245, 2002.

- Hirobe T, Wakamatsu K, Ito S, Abe H, Kawa Y, Mizoguchi M.
Stimulation of the proliferation and differentiation of mouse pink-eyed dilution epidermal melanocytes by excess tyrosine in serum-free primary culture. J.Cell Physiol 191:162-172, 2002.

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Role of leukemia inhibitory factor in the regulation of the proliferation and differentiation of neonatal mouse epidermal melanocytes in culture. J.Cell Physiol 192:315-326, 2002.

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Melanin-concentrating hormone and its receptor are expressed and functional in human skin. Biochem.Biophys.Res.Commun. 296:698, 2001.

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Delayed ERK activation by ceramide reduces melanin synthesis in human melanocytes. Cell Signal. 14:779-785, 2002.

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A melanocyte-keratinocyte coculture model to assess regulators of pigmentation in vitro. Anal.Biochem. 305:260-268, 2002.

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Specific induction of gadd45 in human melanocytes and melanoma cells after UVB irradiation. Int.J.Cancer 98:811-816, 2002.

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Melanophilin, the product of the leaden locus, is required for targeting of myosin-Va to melanosomes. Traffic. 3:124-132, 2002.

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mRNA expression of multiple cytochrome p450 isozymes in four types of cultured skin cells. Int.Arch.Allergy Immunol. 127:333-33, 2002.

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Human melanocortin 1 receptor variants, receptor function and melanocyte response to UV radiation. J.Cell Sci. 115:2349-2355, 2002.

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Protein kinase C isoforms in normal and transformed cells of the melanocytic lineage. Melanoma Res. 12:201-209, 2002.

- Takano N, Kawakami T, Kawa Y, Asano M, Watabe H, Ito M, Soma Y, Kubota Y, Mizoguchi M. **Fibronectin combined with stem cell factor plays an important role in melanocyte proliferation, differentiation and migration in cultured mouse neural crest cells**. Pigment Cell Res. 15:192-200, 2002.

ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

2002 XVIIIth International Pigment Cell Conference

Egmond aan Zee, Holland 9 - 13 September 2002

Contact: Dr. Stan PAVEL
E-mail: SPavel@algemeen.azl.nl
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Web-site: http://users.raketnet.nl/ipcc/

2002 European Immunodermatology Society, Satellite Meeting

Geneva, Switzerland September 18 –19

Contact: Ms. A. Kuehn
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Fax:+49/761-2706655
E-mail: A_Kuehn@haut.ukl.uni-freiburg.de
Web-site: http://www.esdr.ch/ESDR_meeting_2002/Symposia/eis.htm

2002 5th International Congress on Cutaneous Adverse Drug Reactions Satellite congress of the 32nd ESDR annual meeting

PALEXPO Geneva, Switzerland September 18 –19

Contact: Luigi Naldi
Clinica Dermatologica – Ospedali Riuniti
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Tel:+0039-035-400625
Fax:+0039-035-253070
E-mail: gised@uninetcom.it

2002 32nd ESDR Annual Meeting

Geneva, Switzerland September 19 – 21

Tel:+(41) 22 839 84 84
Fax:+(41) 22 839 84 85
E-mail: esdr@symporg.ch
Web-site: http://www.esdr.org

2002 11th European Academy of Dermatology and Venereology Congress (EADV)

Prague, Czech Republic October 2-6

Tel:+(42) 0 284 00 1493
Fax:+(42) 0 284 00 1448
E-mail: eadv2002@guarant.cz
Web-site: http://www.eadv2002.cz

2002 Annual Meeting of the New Zealand Dermatological Society 2002

Wellington, New Zealand October 9-11

Tel:+(64) 04 5667 445
Fax:+(64) 04 5668 262
E-mail: btaylor@paradise.net.nz

2002 3rd European Symposium on Teledermatology

Graz, Austria November 8-9

Tel:+(43) 316 385 2423
Fax:+(43) 316 385 2466
E-mail: telederm.uni-graz.at

2002 7th Congress of the European Society for Paediatric Dermatology (ESPD)

Barcelona, Spain November 21-23

Tel:+(34) 322 75400 (ext 2422)
Fax:+(34) 322 75438
E-mail: rgmalt@medicina.ub.es
Web-site: http:www.espd2002.org/

2003 XIth The 7th International Conference on Solar Energy and Applied Photochemistry [SOLAR '03] Combined with the 4th International Training Workshop on Environmental Photochemistry, [ENPHO '03]

Luxor, Egypt, 23-28 February 2003

Contact: Professor M. S. A. Abdel-Mottaleb
Professor of Chemistry, Director of Photoenergy Center
Faculty of Science, Ain Shams University, 11566 Abbassia, Cairo, Egypt
E-mail: solar@photoenergy.org
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Fax: 00202 634 7683 or 00202 484 5941
Tel.: 002012 216 9584 (cellular)
Web-site: http://www.photoenergy.org

2003 International Investigative Dermatology Meeting

South Miami Beach, Florida USA , April 30 - May 4

Joint Meeting of the ESDR, JSID, and SID

2003 XIth Meeting of the ESPCR

Gent, Belgium

Contact: Prof. JM NAEYAERT
E-mail: JeanMarie.Naeyaert@rug.ac.be

2003 XIth Annual Meeting of the PASPCR

Wood's Hole, MA, September 3-7
Contact: Dr. Jean BOLOGNIA
E-mail: jean_bolognia@qm.yale.edu

2004 14th International Congress on Photobiology

Jungmoon, Jeju (Cheju), Korea June 10-15

2004 XIIth Meeting of the ESPCR

Paris, France

Contact: Dr. Lionel LARUE
E-mail: Lionel.Larue@curie.fr

2005 XIVth International Pigment Cell Conference (IPCC)

Bethesda, USA

Contact: Dr. V. HEARING
E-mail: hearingv@nih.gov

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.

Dr. FAAS L.
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UK – BERKSHIRE SL6 8XY

Dr. VAN SCHANKE A.
Leiden University
medical Center
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NL - 2333 AL LEIDEN

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 2003, instead of December 2002? 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

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

ESPCR COUNCIL ELECTIONS

Dear ESPCR members,

The election process to cover four vacancies in the ESPCR Council was completed in July. The elected candidates are:

- Dr. Friedo Beermann, from the ISREC, Lausanne.
- Dr. Mauro Picardo, from the Dermatological Institute San Gallicano, Rome.
- Dr. Nico Smit, from the University of Leiden, Leiden
- Prof. Alain Taïeb, from the University of Bordeaux, Bordeaux.

The new composition of the Council will be presented for approval to the next General Assembly, to be hekd in Egmond aan Zee, on the occasion of the XVIIIth IPCC.

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)
N. Smit (Leiden)
A. Taïeb (Bordeaux)

José Carlos García-Borrón
Secretary