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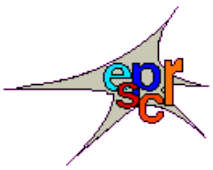
HAPPY NEW YEAR 2013

CONTENT



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

17th ESPCR Meeting, Geneva, 11-13 september 2012
Meeting Report

Session 6: Hyperpigmentation
Report prepared by the Chairs: Heather Etchevers and Dot Bennett

IS12 Jo Lambert (Gent, Belgium)
The melanocyte and its microenvironment : lessons from the clinic.
IS13 Alain Taïeb (Bordeaux, France)
Dermal influences on epidermal pigmentation.
IS14 Jose Carlos Garcia-Borron (Murcia, Spain)
Relationships of melanocortin 1 receptor signaling to the cAMP and mitogen-activated protein kinase ERK1 and ERK2 pathways in heterologous and human melanoma cells.
OP19 Andre Furger (London, UK)
MC1R poly(A) site and its role to regulate intergenic splicing and the expression of chimeric MC1R-Tubulin beta III receptors.
OP19bis Kasraee Behrooz (Geneva, Switzerland)
Evaluation of a novel colorimetric technology for discrimination and measurement of cutaneous pigmentation and erythema.

A unifying theme of this session was that hyperpigmentation phenotypes arise from interactions between the melanocyte and multiple cell types.
Jo Lambert (Ghent, Belgium) spoke first, with a clinical view of the melanocyte and its microenvironment. She presented an overview of intercellular signaling factors associated with human hyperpigmentation phenotypes, such as increases in dermal hepatocyte growth factor (HGF) after minor inflammatory injuries like insect bites. Melanocytes had been cultured from café-au-lait macules (CALMs) from heterozygous neurofibromatosis (NF1-mutant) patients, and, interestingly, commonly showed a second NF1 mutation. In addition, there was increased expression of stem cell factor/KIT ligand from the associated fibroblasts and of KIT in the melanocytes.

The group was also studying immune reactions to melanocytes. Autoimmune responses form a continuum from the halo nevus (a zone of depigmentation around a nevus) to severe vitiligo, whereas there is a deficient immune response to melanoma. In melanoma, indoleamine 2,3-dioxygenase (IDO) is a marker for low immune function and – in sentinel nodes of melanoma patients – for poor prognosis. Normally expressed in certain immune and endothelial cells, it impairs cytotoxic T-lymphocyte (CTL) responses and can function in tolerance. High IDO expression is associated with increased numbers of FOXP3+ regulatory T cells of the sentinel node, and with tumor cell escape from immune regulation. Altered IDO levels were not observed in halo nevi (without vitiligo), but CTLs reactive against gp100/PMEL and MART1 were detected. The mechanism of local targeting to a nevus (as indeed in vitiligo patches) remains to be explored.

Alain Taïeb (Bordeaux, France) proposed that the concept of the epidermal melanin unit should be extended to the "dermal-epidermal melanin unit", given the dermal influences on epidermal pigmentation. He described their work on human skin reconstructs xenografted into nude mice, in which graft pigmentation depended on the dermal component. Invested with human fibroblasts, they stayed light, but invested with fibroblasts from the host, they darkened. Cytokine effects of endothelins 1 and 3 and HGF were implicated in this species-specific distinction.
Prof Taïeb then reviewed other dermal effects. The Hearing laboratory has shown that the secreted WNT signaling inhibitor Dickkopf-1 is produced by dermal fibroblasts in palmoplantar skin, giving a coordinated effect on melanocytes (reduced MITF and melanogenesis) and keratinocytes (expression of keratin-9 and skin thickening). On the other hand, dermal neuregulin-1 can increase epidermal pigmentation and is produced more by people with darker phototypes. Citing preliminary evidence for upregulation of keratinocyte growth factor (FGF7 or KGF) in the dermis of people with the darkest phototypes, he then discussed work on the human condition, familial progressive hyper/hypopigmentation. Picardo's group demonstrated that affected skin shows increased dermal expression of KGF as well as HGF and KITL in the hyperpigmented zones, while the Vikkula group identified a gain-of-function mutation in the KITL gene in a family with this condition. Finally, he briefly discussed work from his own group on lentigo senilis ("liver/age spots"), which show an accumulation of melanosomes only at the tips of the rete ridges, and some similarity to the mottled pigmentation in certain forms of epidermiolysis bullosa simplex due to keratin-5 mutations. This could be another example of perturbed dermal-epidermal homeostasis.

José-Carlos García-Borrón (Murcia, Spain), spoke about melanocortin-1 receptor (MC1R) signaling to the cAMP and mitogen-activated protein kinase (MAPK)/ERK pathways. His group had previously shown that ERK1/2 were activated in response to MC1R stimulation in human melanocytes, and this was abolished by knockdown of KIT. They now used forskolin to stimulate cAMP in heterologous cells (rat adrenal PC12 cells), and show that this did not activate ERKs, and nor did ligand activation of transfected MC1R, unless KIT was also transfected. Loss-of-function "red hair colour" MC1R mutations such as V92M, which affect human pigmentation usually through decreased cAMP signal transduction, often retained good or even above-normal activation of the MAPK (proliferation) signaling pathway in response to MSH, showing the two pathways can become unbalanced, with possible implications for melanoma risk. The mechanism of KIT activation by MC1R remains unknown.

Lastly, crosstalk between these pathways was studied in human melanoma cells with normal MC1R. Separate ERK activation did not affect MC1R signaling to cAMP, nor did higher cAMP levels impair the phosphorylation of ERK. Interestingly, forskolin could block ERK activation by MC1R, but as a side-effect, independent of cAMP signalling. Different melanoma cell lines often (although not always) failed to respond to MSH through cAMP. This was independent of the presence of oncogenic BRAF or NRAS mutations and is another avenue for further elucidation.

Andre Furger (Oxford, UK), discussed the unusual splicing events that can occur after transcription of the single exon of MC1R. The polyadenylation site of MC1R is particularly inefficient, in the sense that it is not always cleaved and capped, so that read-through transcripts into the next 3' gene, TUBB3 (tubulin beta III) are produced. Splice products of MC1R and the second exon of TUBB3 are detectable receptor isoforms in human melanoma cells and immortalized melanocyte lines, but not in two mouse melanocyte lines unless transfected with the human locus. One of the MC1R-TUBB3 fusion transcripts could be translated into a receptor that could reach the cell membrane and transduce α-MSH signalling, though much less efficiently than normal MC1R. In response to α-MSH over time, human melanoma cells reduced transcription of MC1R but concomitantly increased production of the chimeric transcripts. This could potentially lead to desensitization of melanocytes in response to prolonged solar irradiation and α-MSH stimulation.

CURRENT LITERATURE

1. Chemistry of Melanins and other Pigments

(Pr A. Napolitano)

A number of very interesting papers related to melanin properties and applications have appeared in the last three months.
Solubilisation of synthetic melanins either by functionalization with sugar units (Adinolfi et al Eur J. Org. Chem) or by preparation in a non-aggregating conditions has allowed to discriminate intrinsic properties from aggregation and scattering effects. It was shown that glycosylation of DHI imparts monomer-like behavior to oligomers and polymers, due to steric effects hindering planar conformations and efficient interunit electron communication. (Corani et al J. Phys. Chem. B). The ability of small molecules with a high affinity for eumelanin to inihibit or promote the aggregation of melanin particles during polymer formation hints to new ways of control of melanin pigmentation in view of the critical association of color development with particle aggregation. (Belitsky et al. Bioorg. Med Chem. Lett) 1D-and 2D-NMR spectroscopic techniques were combined to highlight structural features and motional behavior of melanosomes isolated from black and red hair. It was thus shown for the first time the presence of a pigment fraction with a higher mobility with respect to the proteinaceous components that coexist in the melanosome, an effect particularly evident for the red pigment (Thureau et al. Chemistry A European Journal). Moreover, high quality 2D spectra in the solid phase allowed for an insight into the structural features of pheomelanin providing direct evidence for the presence of isoquinoline- like structures recently proposed as core structural units of pheomelanins. The classical chemical degradation approach was used to investigate the UVA induced photoxidation of red and black hair, a process associated to oxidative fission of 5,6-dihydroxyindole units to pyrrole carboxylic acids in eumelanin and ring contraction of benzothiazine units to benzothiazole in pheomelanins (Wakamatsu et al PCMR). Finally, in a paper appeared on Nature (Mitra et al, Nature) the concept that melanoma is not necessarily associated to UV exposure was supported by analysis of mice carrying an inactivating mutation of the mc1r gene and featuring a pheomelanic phenotype. These model animals showed DNA and lipid damages even in the absence of UV exposure suggesting that pheomelanin pigment pathway produces UV-radiation-independent carcinogenic contributions to melanomagenesis by a mechanism of oxidative damage. Application of esr spectroscopy to comparative analysis of melanoma nevi and non-melanoma tissues showed that eu/pheomelanin ratio was significantly different in melanomas "Low Breslow's" vs. melanomas "High Breslow's" depth and in nevi vs. melanomas "High Breslow's depth". (Cesareo et al. PLoS One)

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2. Biology of pigment cells and pigmentary disorders

(Dr M. Picardo)

Wnt/ β-catenin signal transduction plays an important role in the process of neural crest formation, migration, proliferation and differentiation as well as in adult melanogenesis. In a recent paper Kim et al., demonstrated that the expression of Wnt inhibitory factor-1 (WIF-1) gene, an antagonist of Wnt signaling, is implicated in hyperpigmentation process of melasma. WIF-1 downregulation, which may occur in epidermal keratinocytes and in dermal fibroblasts of melasma patientes stimulates melanogenesis and melanosome transfer through upregulation of the canonical and the noncanonical Wnt signaling pathway. WIF-1 expression, evaluated in a set of hyperpigmented and normally pigmented skin of melasma patients, is significantly reduced. The effect of WIF-1 overexpression induced the amelioration hyperpigmentation by reduced tyrosinase expression and melanosome transfer. The WIF-1 knockdown decreased glycogen synthase kinase-3 β (GSK-3 β), β -catenin, and NFATc2 (nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 2) phosphorylation and increased microphthalmia-associated transcription factor (MITF) expression.

The paper from **Gallagher and co-worker**, shows that unlike its positive role in stimulating migration and invasion of carcinoma cells, β-catenin signaling decreases the migration of melanocytes and melanoma cell lines. In vivo, b-catenin signaling in melanoblasts reduced the migration of these cells, causing a white belly-spot phenotype. Despite reducing migration, β-catenin signaling promoted lung metastasis in the NRAS-driven melanoma murine model. Thus, β-catenin may have conflicting roles in the metastatic spread of melanoma, repressing migration while promoting metastasis. One of the most interesting points discussed in this manuscript is the melanocyte-specific biological effect of β-catenin signaling. According with authors' idea the negative effect of β-catenin on migration is highlights critical differences in the biology of epithelial cells and melanocytes. In fact, epithelial cells are normally locked-in in the organized architecture of the epithelium and cell- matrix adhesion are mediated by β-catenin's structural role; thus, incipient carcinoma cells in addition to increased proliferation, reduced apoptosis must acquire properties of local invasiveness and increased migration to reach lymphatic and blood vessels for distant metastasis; β-catenin activation stimulates both properties in carcinoma cells. To the contrary, cells of the melanocytic lineage are not organized in a multicellular architecture requiring the structural function of β-catenin and in fact have intrinsic migratory properties from early development during colonization of the skin; here, we show that β-catenin activation remarkably reduces migration in cells of the melanocytic lineage.

The letter by **Mitra et al**., published on Nature presented interesting data concerning the association between inactivating polymorphisms in the melanocortin receptor (MC1R) gene and melanoma risk. These genetic variants, determining minimal receptor activity as in red hair/fair skin produce the red/yellow pheomelanin pigment, in place of black/brown eumelanin. Pheomelanin has weak shielding capacity against ultraviolet radiation relative to eumelanin, and has been shown to amplify ultraviolet-A-induced reactive oxygen species and cell damage. This study demonstrated that the pheomelanin pigment pathway also produces ultraviolet-radiation-independent carcinogenic by a mechanism of oxidative DNA and lipid damage. Author concluded that although protection from ultraviolet radiation remains important, additional strategies may be required for optimal melanoma prevention.

The paper of **Herraiz et al**., examined the crosstalk of the cAMP and ERK pathways downstream to the MC1R activation. Using several different natural and synthetic MC1R genetic variants they showed that MC1R mutants impair cAMP production much more often than ERK activation, confirming that ERK activation is cAMP-independent and suggesting less stringent requirements for functional coupling to the ERK pathway.

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Reduced WIF-1 expression stimulates skin hyperpigmentation in patients with melasma. J Invest Dermatol Epub ahead of print.

3. MSH, MCH, other hormones, differentiation

(Pr M. Böhm)

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4. Photobiology

(Pr M-D Galibert)

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  Coat color determination by miR-137 mediated down-regulation of microphthalmia-associated transcription factor in a mouse model. RNA. 2012 Sep;18(9):1679-86.
  Abstract : Coat color is a key economic trait in wool-producing species. Color development and pigmentation are controlled by complex mechanisms in animals. Here, we report the first production of an altered coat color by overexpression of miR-137 in transgenic mice. Transgenic mice overexpressing miR-137 developed a range of coat color changes from dark black to light color. Molecular analyses of the transgenic mice showed decreased expression of the major target gene termed MITF and its downstream genes, including TYR, TYRP1, and TYRP2. We also showed that melanogenesis altered by miR-137 is distinct from that affected by UV radiation in transgenic mice. Our study provides the first mouse model for the study of coat color controlled by miRNAs in animals and may have important applications in wool production.

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  Abstract : The current treatments for hyperpigmentation are often associated with a lack of efficacy and adverse side effects. We hypothesized that microRNA (miRNA)-based treatments may offer an attractive alternative by specifically targeting key genes in melanogenesis. The aim of this study was to identify miRNAs interfering with the pigmentary process and to assess their functional role. miRNA profiling was performed on mouse melanocytes after three consecutive treatments involving forskolin and solar-simulated UV (ssUV) irradiation. Sixteen miRNAs were identified as differentially expressed in treated melan-a cells versus untreated cells. Remarkably, a 15-fold downregulation of miR-145 was detected. Overexpression or downregulation of miR-145 in melan-a cells revealed reduced or increased expression of Sox9, Mitf, Tyr, Trp1, Myo5a, Rab27a, and Fscn1, respectively. Moreover, a luciferase reporter assay demonstrated direct targeting of Myo5a by miR-145 in mouse and human melanocytes. Immunofluorescence tagging of melanosomes in miR-145-transfected human melanocytes displayed perinuclear accumulation of melanosomes with additional hypopigmentation of harvested cell pellets. In conclusion, this study has established an miRNA signature associated with forskolin and ssUV treatment. The significant down- or upregulation of major pigmentation genes, after modulating miR-145 expression, suggests a key role for miR-145 in regulating melanogenesis.

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  Abstract : Melanomas resist conventional chemotherapeutics, in part, through intrinsic disrespect of apoptotic checkpoint activation. In this study, using an unbiased genome-wide RNA interference screen, we identified RhoJ and its effector PAK1, as key modulators of melanoma cell sensitivity to DNA damage. We find that RhoJ activates PAK1 in response to drug-induced DNA damage, which then uncouples ATR from its downstream effectors, ultimately resulting in a blunted DNA damage response (DDR). In addition, ATR suppression leads to the decreased phosphorylation of ATF2 and consequent increased expression of the melanocyte survival gene Sox10 resulting in a higher DDR threshold required to engage melanoma cell death. In the setting of normal melanocyte behavior, this regulatory relationship may facilitate appropriate epidermal melanization in response to UV-induced DNA damage. However, pathologic pathway activation during oncogenic transformation produces a tumor that is intrinsically resistant to chemotherapy and has the propensity to accumulate additional mutations. These findings identify DNA damage agents and pharmacologic inhibitors of RhoJ/PAK1 as novel synergistic agents that can be used to treat melanomas that are resistant to conventional chemotherapies. Cancer Res; 72(21); 5516-28.

- Jonathan Shoag1, 4, Rizwan Haq5, 2, Mingfeng Zhang3, Laura Liu1, Glenn C. Rowe1, Aihua Jiang1, Nicole Koulisis1, Caitlin Farrel1, Christopher I. Amos7, Qingyi Wei7, Jeffrey E. Lee8, Jiangwen Zhang6, Thomas S. Kupper3, Abrar A. Qureshi3, Rutao Cui9, Jiali Han3, 10, 12, David E. Fisher5, 2, 11, 12, Zoltan Arany.
  PGC-1 Coactivators Regulate MITF and the Tanning Response. Mol Cell. 2012 Nov 28.
  Abstract : The production of pigment by melanocytes tans the skin and protects against skin cancers. UV-exposed keratinocytes secrete α-MSH, which then activates melanin formation in melanocytes by inducing the microphthalmia-associated transcription factor (MITF). We show that PPAR-γ coactivator (PGC)-1α and PGC-1β are critical components of this melanogenic system in melanocytes. α-MSH signaling strongly induces PGC-1α expression and stabilizes both PGC-1α and PGC-1β proteins. The PGC-1s in turn activate the MITF promoter, and their expression correlates strongly with that of MITF in human melanoma cell lines and biopsy specimens. Inhibition of PGC-1α and PGC-1β blocks the α-MSH-mediated induction of MITF and melanogenic genes. Conversely, overexpression of PGC-1α induces pigment formation in cell culture and transgenic animals. Finally,

polymorphism studies reveal expression quantitative trait loci in the PGC-1β gene that correlate with tanning ability and protection from melanoma in humans. These data identify PGC-1 coactivators as regulators of human tanning.

- Kim JY, Lee TR, Lee AY.
  Reduced WIF-1 Expression Stimulates Skin Hyperpigmentation in Patients with Melasma. J Invest Dermatol. 2012 Sep 6.
  Abstract : The expression of Wnt inhibitory factor-1 (WIF-1) gene, which was detected by a microarray analysis of hyperpigmented and normally pigmented skin sets of melasma patients, was significantly reduced in the hyperpigmented skin from melasma patients, but not in healthy controls, regardless of UV irradiation. Wnt signals regulate skin pigmentation; however, WIF-1 is expressed in cultured skin keratinocytes and fibroblasts, but not in melanocytes. Therefore, we examined whether WIF-1 knockdown in neighboring keratinocytes and fibroblasts plays a role in melasma. Additionally, the effect of WIF-1 overexpression on the amelioration of hyperpigmentation was examined. WIF-1 knockdown, either in fibroblasts or in keratinocytes, significantly stimulated tyrosinase expression and melanosome transfer, whereas melanocytes with WIF-1 overexpression significantly reduced those parameters. The WIF-1 knockdown decreased glycogen synthase kinase-3β (GSK-3β), β-catenin, and NFATc2 (nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 2) phosphorylation and increased microphthalmia-associated transcription factor (MITF) expression as in melanocytes with Wnt-1 overexpression, whereas the WIF-1 overexpression reversed the results. Expression of Wnts, both canonical and noncanonical, was increased in the hyperpigmented skin of melasma patients. Collectively, WIF-1 downregulation, which may occur in epidermal keratinocytes and in dermal fibroblasts, is involved in melasma development because of the stimulation of melanogenesis and melanosome transfer through upregulation of the canonical and the noncanonical Wnt signaling pathway.

- Schäfer A, Hofmann L, Gratchev A, Laspe P, Schubert S, Schürer A, Ohlenbusch A, Tzvetkov M, Hallermann C, Reichrath J, Schön MP, Emmert S.
  Molecular genetic analysis of 16 XP-C patients from Germany: environmental factors predominately contribute to phenotype variations. Exp Dermatol. 2012 Oct 20
  Abstract : Patients belonging to xeroderma pigmentosum (XP) complementation group C comprise one-third of all XP patients. Only four major reports compiled larger groups of XP-C patients from southern Europe (12 pts), North America (16 pts) and Africa (14 and 56 pts) as well as their genetic background (46 XPC mutations). We identified 16 XP-C patients from Germany. Interestingly, only five patients exhibited severe sun sensitivity. The mean age of XP diagnosis was 9.4 years, and the median age of the first skin cancer was 7 years. Neurological symptoms were absent in all but two patients. Primary fibroblasts from all 16 patients showed reduced post-UV cell survival (mean: 50% vs 93% in normal cells) and reduced reactivation of an UV-treated luciferase reporter gene (mean: 6.4% vs 30.7% in normal cells). XPC mRNA expression was also greatly reduced compared with normal cells (mean: 14.3%; range 8.3-25.7%) except in XP47MA (274.1%). All patients carried homozygous XPC mutations. Four mutations have been described previously: c.1747_1748delTG (found in 4/16), c.567 C>T (4/16), c.1839 C>T (1/16) and a complex insertion/deletion mutation in exon 9 (1/16). The novel frameshift mutations c.446_447delAG (2/16), c.1525insA (1/16) and c.2271delC (1/16) lead to truncated XPC proteins as does the novel nonsense mutation c.843C>T (1/16). XP47MA carries an interesting mutation (c.2538_2540delATC; p.Ile812del) resulting in an in-frame single amino acid deletion. This mutation results in a classical XP phenotype, a non-functional XPC protein, but elevated XPC mRNA expression. Our study indicates that extrinsic factors may contribute to XP-C symptom severity due to nonsense-mediated message decay.

- Tan G, Niu J, Shi Y, Ouyang H, Wu ZH.
  NF-κB-dependent microRNA-125b up-regulation promotes cell survival by targeting p38α upon ultraviolet radiation. J Biol Chem. 2012 Sep 21;287(39):33036-47.
  Abstract : UV-induced stress response involves expression change of a myriad of genes, which play critical roles in modulating cell cycle arrest, DNA repair, and cell survival. Alteration of microRNAs has been found in cells exposed to UV, yet their function in UV stress response remains elusive. Here, we show that UV radiation induces up-regulation of miR-125b, which negatively regulates p38α expression through targeting its 3'-UTR. Increase of miR-125b depends on UV-induced NF-κB activation, which enhances miR-125b gene transcription upon UV radiation. The DNA damage-responsive kinase ATM (ataxia telangiectasia mutated) is indispensable for UV-induced NF-κB activation, which may regulate p38α activation and IKKβ-dependent IκBα degradation in response to UV. Consequently, repression of p38α by miR-125b prohibits prolonged hyperactivation of p38α by UV radiation, which is required for protecting cells from UV-induced apoptosis. Altogether, our data support a critical role of NF-κB-dependent up-regulation of miR-125b, which forms a negative feedback loop to repress p38α activation and promote cell survival upon UV radiation.

5. Neuromelanins

(Pr M. d'Ischia)

Oxidation of dopamine in the presence of cysteine in variable amounts is believed to play a central role in the genesis of neuromelanin in human substantia nigra. In a model in vitro study, Ferrari et al. (2012) show that oxidation of dopamine in the presence of cysteine, iron (III) ions and bovine serum albumin (BSA) leads to iron-binding conjugates which display spectral properties of potential relevance to the genesis and structural organization of the human pigment. The occurrence of variable degrees of iron clustering as a function of the pheomelanin-like character of the pigment provides useful information as to the state of iron in neuromelanin.
Alpha-Synuclein (α-Syn) is a protein expressed in the brain, skin as well as in tumors, including melanoma. α-Syn can interact both with tyrosinase (TYR) and tyrosine hydroxylase (TH), the enzymes involved in the biosynthesis of melanin and dopamine (DA), respectively. Now Pan et al. (2012) provide evidence that α-Syn may have inhibitory effects on melanin synthesis in melanoma cells, and an opposite stimulating effect on melanin production in dopaminergic neuronal SH-SY5Y and PC12 cells. On this basis, they propose that α-Syn may be the missing point linking the high co-occurrence of Parkinson's disease (PD) and melanoma via its differential roles in melanin synthesis in melanoma cells and in dopaminergic neuronal cells.
A paper by Munoz et al. (2012) finally addresses the role of oxidative stress and dopamine conversion in Parkinson's disease. While the emphasis of the paper is largely on the aminochrome intermediate, the role of the main quinone precursor dopaminequinone seems worthy of attention as well.

- Ferrari Emanuele, Engelen Mireille, Monzani Enrico, Sturini Michela, Girotto Stefania, Bubacco Luigi, Zecca Luigi, Casella Luigi.
  Synthesis and structural characterization of soluble neuromelanin analogs provides important clues to its biosynthesis. Journal of Biological Inorganic Chemistry, Ahead of Print.
  Elucidating the structure and biosynthesis of neuromelanin (NM) would be an important step towards understanding its putative role in the pathogenesis of Parkinson's disease. A useful complement to studies aimed at unraveling the origin and properties of this essentially insol. natural substance is the prepn. of synthetic derivs. that resemble NM. With this aim in mind, water-sol. conjugates between dopamine-derived melanin and bovine serum albumin (BSA) were synthesized. Melanin-BSA adducts were prepd. with both eumelanic oligomers obtained through the oxidative polymn. of dopamine and pheomelanic oligomers obtained under the same conditions from dopamine and cysteine. Iron ions were added during the synthesis to understand the interaction between the pigment and this metal ion, as the NM in neurons in several human brain regions contains significant amts. of iron. The structures of the conjugates were analyzed by 1H NMR spectroscopy and controlled proteolysis/MS expts. The binding of iron(III) ions was evaluated by ICP anal. and EPR spectroscopy. The EPR signal from bound iron(III) indicated high-spin octahedral sites and, as also seen for NM, the signal is coupled to a signal from a radical assocd. with the melanic components of the conjugates. However, the intensity of the EPR signal from iron suggested a reduced fraction of the total iron, indicating that most of the iron is strongly coupled in clusters within the matrix. The amt. of paramagnetic, mononuclear iron(III) was greater in the pheomelanin-BSA conjugates, suggesting that iron clustering is reduced in the sulfur-contg. pigment. Thus, the melanin-BSA conjugates appear to be good models for the natural pigment.

- Munoz Patricia, Huenchuguala Sandro, Paris Irmgard, Segura-Aguilar Juan.
  Dopamine oxidation and autophagy. Parkinson's Disease (2012), 920953, 13 pp.
  The mol. mechanisms involved in the neurodegenerative process of Parkinson's disease remain unclear. Currently, there is a general agreement that mitochondrial dysfunction, α-synuclein aggregation, oxidative stress, neuroinflammation, and impaired protein degrdn. are involved in the neurodegeneration of dopaminergic neurons contg. neuromelanin in Parkinson's disease. Aminochrome has been proposed to play an essential role in the degeneration of dopaminergic neurons contg. neuromelanin by inducing mitochondrial dysfunction, oxidative stress, the formation of neurotoxic α-synuclein protofibrils, and impaired protein degrdn. Here, we discuss the relationship between the oxidn. of dopamine to aminochrome, the precursor of neuromelanin, autophagy dysfunction in dopaminergic neurons contg. neuromelanin, and the role of dopamine oxidn. to aminochrome in autophagy dysfunction in dopaminergic neurons. Aminochrome induces the following: (i) the formation of α-synuclein protofibrils that inactivate chaperone-mediated autophagy; (ii) the formation of adducts with α- and β-tubulin, which induce the aggregation of the microtubules required for the fusion of autophagy vacuoles and lysosomes.

- Pan Tianhong, Zhu Julie, Hwu Wen-Jen, Jankovic Joseph.
  The role of alpha-Synuclein in melanin synthesis in melanoma and dopaminergic neuronal cells. PLoS One (2012), 7(9), e45183.
  The relatively high co-occurrence of Parkinson's disease (PD) and melanoma has been established by a large no. of epidemiol. studies. However, a clear biol. explanation for this finding is still lacking. Ultra-violet radiation

(UVR)-induced skin melanin synthesis is a defense mechanism against UVR-induced damage relevant to the initiation of melanoma, whereas, increased neuromelanin (NM), the melanin synthesized in dopaminergic neurons, may enhance the susceptibility to oxidative stress-induced neuronal injury relevant to PD. SNCA is a PD-causing gene coding for alpha-Synuclein (α-Syn) that expresses not only in brain, but also in skin as well as in tumors, such as melanoma. The findings that α-Syn can interact with tyrosinase (TYR) and inhibit tyrosine hydroxylase (TH), both of which are enzymes involved in the biosynthesis of melanin and dopamine (DA), led us to propose that α-Syn may participate in the regulation of melanin synthesis. In this study, by applying UV B (UVB) light, a physiol. relevant stimulus of melanogenesis, we detected melanin synthesis in A375 and SK-MEL-28 melanoma cells and in SH-SY5Y and PC12 dopaminergic neuronal cells and detd. effects of α-Syn on melanin synthesis. Our results showed that UVB light exposure increased melanin synthesis in all 4 cell lines. However, we found that α-Syn expression reduced UVB light-induced increase of melanin synthesis and that melanin content was lower when melanoma cells were expressed with α-Syn, indicating that α-Syn may have inhibitory effects on melanin synthesis in melanoma cells. Different from melanoma cells, the melanin content was higher in α-Syn-over-expressed dopaminergic neuronal SH-SY5Y and PC12 cells, cellular models of PD, than that in non-α-Syn-expressed control cells. We concluded that α-Syn could be one of the points responsible for the pos. assocn. between PD and melanoma via its differential roles in melanin synthesis in melanoma cells and in dopaminergic neuronal cells.

6. Genetics, molecular and developmental biology

(Dr. L. Montoliu)

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Abstract
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7. Tyrosinase, TRPs, other enzymes

(Pr. J.C. Garcia-Borron)

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  Colorimetric paper bioassay for the detection of phenolic compounds. Anal Chem. 2012 Nov 20;84(22):9729-37.
  A new type of paper based bioassay for the colorimetric detection of phenolic compounds including phenol, bisphenol A, catechol and cresols is reported. The sensor is based on a layer-by-layer (LbL) assembly approach formed by alternatively depositing layers of chitosan and alginate polyelectrolytes onto filter paper and physically entrapping the tyrosinase enzyme in between these layers. The sensor response is quantified as a color change resulting from the specific binding of the enzymatically generated quinone to the multilayers of immobilized chitosan on the paper. The color change can be quantified with the naked eye but a digitalized picture can also be used to provide more sensitive comparison to a calibrated color scheme. The sensor was optimized with respect to the number of layers, pH, enzyme, chitosan and alginate amounts. The colorimetric response was concentration dependent, with a detection limit of 0.86 (±0.1) μg/L for each of the phenolic compounds tested. The response time required for the sensor to reach steady-state color varied between 6 and 17 min depending on the phenolic substrate. The sensor showed excellent storage stability at room temperature for several months (92% residual activity after 260 days storage) and demonstrated good functionality in real environmental samples. A procedure to mass-produce the bioactive sensors by inkjet printing the LbL layers of polyelectrolyte and enzyme on paper is demonstrated.

- Bae SJ, Ha YM, Park YJ, Park JY, Song YM, Ha TK, Chun P, Moon HR, Chung HY.
  Design, synthesis, and evaluation of (E)-N-substituted benzylidene-aniline derivatives as tyrosinase inhibitors. Eur J Med Chem. 2012 Nov;57:383-90.
  We attempted to design and synthesize (E)-N-substituted benzylidene-hydroxy or methoxy-aniline derivatives and to evaluate their inhibitory effect on tyrosinase activity and anti-melanogenesis activity in murine B16F10 melanoma cells. Derivatives with a 4-methoxy- or 4-hydroxy-anilino group exerted more potent inhibition against mushroom tyrosinase than those with a 2-hydroxyanilino group. (E)-4-((4-Hydroxyphenylimino)methyl)benzene-1,2-diol exhibited the most potent and non-competitive inhibition on mushroom tyrosinase showing an IC(50) of 17.22 ± 0.38 μM and being more effective than kojic acid (51.11 ± 1.42 μM). This compound decreased melanin production stimulated by the alpha-melanocyte-stimulating hormone and inhibited murine tyrosinase activity in a dose-dependent manner. Therefore, we propose (E)-4-((4-hydroxyphenylimino)methyl)benzene-1,2-diol as a new candidate of potent tyrosinase inhibitors that could be used as therapeutic agent with safe skin-whitening efficiency.

- Bae-Harboe YS, Park HY.
  Tyrosinase: a central regulatory protein for cutaneous pigmentation. J Invest Dermatol. 2012 Dec;132(12):2678-80.
  Cutaneous pigmentation or skin color is the body's natural protection against sun-induced damage. Skin color is determined primarily by melanin, a biopolymer that is synthesized within epidermal melanocytes, packaged in cellular organelles called melanosomes, and then dispersed to neighboring keratinocytes. The process of melanogenesis involves numerous molecules and intracellular pathways that are subject to regulation by endogenous and exogenous factors. Tyrosinase is the central and rate-limiting enzyme in melanin biosynthesis. Therefore, elucidation of the molecules and pathways that regulate tyrosinase levels and activity could identify target areas for the development of compounds to decrease excessive pigmentation on one hand or induce pigmentation on the other. The following commentary will summarize the key regulatory molecules and pathways involved in tyrosinase function.

- Chang H, Choi H, Joo KM, Kim D, Lee TR.
  Manassantin B inhibits melanosome transport in melanocytes by disrupting the melanophilin-myosin Va interaction. Pigment Cell Melanoma Res. 2012 Nov;25(6):765-72.
  Human skin hyperpigmentation disorders occur when the synthesis and/or distribution of melanin increases. The distribution of melanin in the skin is achieved by melanosome transport and transfer. The transport of melanosomes, the organelles where melanin is made, in a melanocyte precedes the transfer of the melanosomes to a keratinocyte. Therefore, hyperpigmentation can be regulated by decreasing melanosome transport. In this study, we found that an extract of Saururus chinensis Baill (ESCB) and one of its components, manassantin B, inhibited melanosome transport in Melan-a melanocytes and normal human melanocytes (NHMs). Manassantin B disturbed melanosome transport by disrupting the interaction between melanophilin and myosin Va. Manassantin B is neither a direct nor an indirect inhibitor of tyrosinase. The total melanin content was not reduced when melanosome transport was inhibited in a Melan-a melanocyte monoculture by manassantin B. Manassantin B decreased melanin content only when Melan-a melanocytes were co-cultured with SP-1 keratinocytes or stimulated by α-MSH. Therefore, we propose that specific inhibitors of melanosome transport, such as

manassantin B, are potential candidate or lead compounds for the development of agents to treat undesirable hyperpigmentation of the skin.

- Choi YJ, Uehara Y, Park JY, Chung KW, Ha YM, Kim JM, Song YM, Chun P, Park JW, Moon HR, Chung HY.
  Suppression of melanogenesis by a newly synthesized compound, MHY966 via the nitric oxide/protein kinase G signaling pathway in murine skin. J Dermatol Sci. 2012 Dec;68(3):164-71.
  BACKGROUND: Ultraviolet B (UVB) radiation is the main physiological stimulus for skin pigmentation. Nitric oxide (NO) and the NO/PKG signaling pathway play an important role in UVB-induced melanogenesis, which is related to the induction of expression of tyrosinase. In an attempt to find a novel anti-melanogenic agent, we synthesized a new compound, 2-bromo-4-(5-chloro-benzo[d]thiazol-2-yl) phenol (MHY966).
  OBJECTIVE: The purpose of this study was to investigate the action of MHY966 on NO and the NO-mediated signaling pathway using in vitro and in vivo models of melanogenesis.
  METHODS: NO generation, melanin synthesis, and the expression of tyrosinase and PKG were measured in B16F10 melanoma cells to verify the anti-melanogenic effect of MHY966 in vitro. Next, melanin-possessing hairless mice were pre-treated with MHY966 and then irradiated with UVB repeatedly. Morphological, histological, and biochemical analyses including the expressions of PKG, tryosinase and nuclear MITF, and productions of nitric oxide, peroxynitrite and ROS were conducted.
  RESULTS: MHY966 effectively inhibited NO generation and subsequent melanin synthesis induced by sodium nitroprusside, an NO donor, and suppressed the expression of tyrosinase and PKG. Topical application of MHY966 dose-dependently attenuated UVB-induced pigmentation in a mouse model. This hypopigmentation effect induced by MHY966 treatment was mediated by the down-regulation of tyrosinase, PKG, and nuclear MITF, which was accompanied by decreased NO and NO-related oxidative stress.
  CONCLUSION: The novel compound, MHY966 had an inhibitory effect on NO generation and the NO-mediated signaling pathway leading to the down-regulation of tyrosinase. The significance of the present study is the finding of a promising anti-melanogenic agent targeting the NO/PKG signaling pathway.

- Kawaguchi M, Valencia JC, Namiki T, Suzuki T, Hearing VJ.
  Diacylglycerol kinase regulates tyrosinase expression and function in human melanocytes. J Invest Dermatol. 2012 Dec;132(12):2791-9.
  Diacylglycerol (DAG) increases the melanin content of human melanocytes in vitro and increases the pigmentation of guinea pig skin in vivo, but the mechanism(s) underlying those effects remain unknown. In this study, we characterized the role of diacylglycerol kinase (DGK), which phosphorylates DAG to generate phosphatidic acid, in the regulation of pigmentation. Ten isoforms of DGK have been identified, and we show that DGKζ is the most abundant isoform expressed by human melanocytic cells. Melanin content, tyrosinase activity, and tyrosinase protein levels were significantly reduced by a DGK inhibitor, but tyrosinase and microphthalmia-associated transcription factor messenger RNA (mRNA) levels were not changed by that inhibition, and there were no effects on the expression of other melanogenesis-related proteins. Isoform-specific small interfering RNAs showed that knockdown of DGKζ decreased melanin content and tyrosinase expression in melanocytic cells. Overexpression of DGKζ increased tyrosinase protein levels, but did not increase tyrosinase mRNA levels. Glycosidase digestion revealed that inhibition of DGK reduced only the mature form of tyrosinase, and the decrease of tyrosinase resulting from DGK inhibition could be blocked partially by protease inhibitors. These results suggest that DGK regulates melanogenesis via modulation of the posttranslational processing of tyrosinase, which may be related with the protein degradation machinery.

- Kim JY, Lee TR, Lee AY.
  Reduced WIF-1 Expression Stimulates Skin Hyperpigmentation in Patients with Melasma. J Invest Dermatol. 2012 Sep 6.
  The expression of Wnt inhibitory factor-1 (WIF-1) gene, which was detected by a microarray analysis of hyperpigmented and normally pigmented skin sets of melasma patients, was significantly reduced in the hyperpigmented skin from melasma patients, but not in healthy controls, regardless of UV irradiation. Wnt signals regulate skin pigmentation; however, WIF-1 is expressed in cultured skin keratinocytes and fibroblasts, but not in melanocytes. Therefore, we examined whether WIF-1 knockdown in neighboring keratinocytes and fibroblasts plays a role in melasma. Additionally, the effect of WIF-1 overexpression on the amelioration of hyperpigmentation was examined. WIF-1 knockdown, either in fibroblasts or in keratinocytes, significantly stimulated tyrosinase expression and melanosome transfer, whereas melanocytes with WIF-1 overexpression significantly reduced those parameters. The WIF-1 knockdown decreased glycogen synthase kinase-3β (GSK-3β), β-catenin, and NFATc2 (nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 2) phosphorylation and increased microphthalmia-associated transcription factor (MITF) expression as in melanocytes with Wnt-1 overexpression, whereas the WIF-1 overexpression reversed the results. Expression of Wnts, both canonical and noncanonical, was increased in the hyperpigmented skin of melasma patients. Collectively, WIF-1 downregulation, which may occur in epidermal keratinocytes and in dermal fibroblasts, is involved in melasma development because of the stimulation of melanogenesis and melanosome transfer through upregulation of the canonical and the noncanonical Wnt signaling pathway.

- Laura Dántola M, Gojanovich AD, Thomas AH.
  Inactivation of tyrosinase photoinduced by pterin. Biochem Biophys Res Commun. 2012 Aug 3;424(3):568-72.
  Tyrosinase catalyzes in mammals the first and rate-limiting step in the biosynthesis of the melanin, the main pigment of the skin. Pterins, heterocyclic compounds able to photoinduce oxidation of DNA and its components, accumulate in the skin of patients suffering from vitiligo, a chronic depigmentation disorder in which the protection against UV radiation fails due to the lack of melanin. Aqueous solutions of tyrosinase were exposed to UV-A irradiation (350 nm) in the presence of pterin, the parent compound of oxidized pterins, under different experimental conditions. The enzyme activity in the irradiated solutions was determined by spectrophotometry and HPLC. In this work, we present data that demonstrate unequivocally that the enzyme is photoinactivated by pterin. The mechanism of the photosensitized process involves an electron transfer from tyrosinase to the triplet excited state of pterin, formed after UV-A excitation of pterin. The biological implications of the results are discussed.

- Lee HJ, Park MK, Lee EJ, Kim YL, Kim HJ, Kang JH, Kim HM, Lee AY, Lee CH.
  Histamine receptor 2-mediated growth-differentiation factor-15 expression is involved in histamine-induced melanogenesis. Int J Biochem Cell Biol. 2012 Dec;44(12):2124-8.
  Vitiligo is a progressive depigmenting disorder. Histamine has been shown to induce melanogenesis via histamine receptor 2, suggesting the possibility of histamine as a repigmenting agent for the treatment of vitiligo. However, the role and signaling mechanism of histamine are still unclear in melanogenesis, especially in relation to growth-differentiation factor-15, which is a protein belonging to transforming growth factor beta and found to be overexpressed in metastatic or malignant melanoma. We found that histamine induces growth-differentiation factor-15 in melanoma cell lines such as SK-MEL-2, B16F10, and melan-a cells. Therefore, in the present study, the role of growth-differentiation factor-15 in histamine-induced melanogenesis was investigated using gene silencing or overexpression of growth-differentiation factor-15 and histamine related compounds such as histamine, amthamine, and cimetidine. Gene silencing of growth-differentiation factor-15 suppressed histamine-induced proliferation, melanin production, tyrosinase activity, and chemotactic migration of SK-MEL-2 cells. Histamine-induced expression of tyrosinase, tyrosinase-related protein 1, and tyrosinase-related protein 2 was also suppressed by growth-differentiation factor-15 gene silencing. On the other hand, overexpression of growth-differentiation factor-15 using a plasmid containing growth-differentiation factor-15 in SK-MEL-2 cells increased melanin production and chemotactic migration. Amthamine induced expression of growth-differentiation factor-15 in a time and concentration dependent manner. Amthamine-induced expression of growth-differentiation factor-15 was suppressed by cimetidine. Our results suggest that growth-differentiation factor-15 is a new player in histamine-induced melanogenesis, which can help researchers to extend the knowledge of the role of the transforming growth factor beta family in melanogenesis and in skin pigment disorders such as vitiligo.

- Long MJ, Hedstrom L.
  Mushroom tyrosinase oxidizes tyrosine-rich sequences to allow selective protein functionalization. Chembiochem. 2012 Aug 13;13(12):1818-25.
  We show that mushroom tyrosinase catalyzes the formation of reactive o-quinones on unstructured, tyrosine-rich sequences such as hemagglutinin (HA) tags (YPYDVPDYA). In the absence of exogenous nucleophiles and at low protein concentrations, the o-quinone decomposes with fragmentation of the HA tag. At higher protein concentrations (>5 mg mL^{-1}), crosslinking is observed. Besthorn's reagent intercepts the o-quinone to give a characteristic pink complex that can be observed directly on a denaturing SDS-PAGE gel. Similar labeled species can be formed by using other nucleophiles such as Cy5-hydrazide. These reactions are selective for proteins bearing HA and other unstructured poly-tyrosine-containing tags and can be performed in lysates to create specifically tagged proteins.

- Marin MB, Ghenea S, Spiridon LN, Chiritoiu GN, Petrescu AJ, Petrescu SM.
  Tyrosinase degradation is prevented when EDEM1 lacks the intrinsically disordered region. PLoS One. 2012;7(8):e42998.
  EDEM1 is a mannosidase-like protein that recruits misfolded glycoproteins from the calnexin/calreticulin folding cycle to downstream endoplasmic reticulum associated degradation (ERAD) pathway. Here, we investigate the role of EDEM1 in the processing of tyrosinase, a tumour antigen overexpressed in melanoma cells. First, we analyzed and modeled EDEM1 major domains. The homology model raised on the crystal structures of human and Saccharomyces cerevisiae ER class I α1,2-mannosidases reveals that the major mannosidase domain located between aminoacids 121-598 fits with high accuracy. We have further identified an N-terminal region located between aminoacids 40-119, predicted to be intrinsically disordered (ID) and susceptible to adopt multiple conformations, hence facilitating protein-protein interactions. To investigate these two domains we have constructed an EDEM1 deletion mutant lacking the ID region and a triple mutant disrupting the glycan-binding domain and analyzed their association with tyrosinase. Tyrosinase is a glycoprotein partly degraded endogenously by ERAD and the ubiquitin proteasomal system. We found that the degradation of wild type and

misfolded tyrosinase was enhanced when EDEM1 was overexpressed. Glycosylated and non-glycosylated mutants co-immunoprecipitated with EDEM1 even in the absence of its intact mannosidase-like domain, but not when the ID region was deleted. In contrast, calnexin and SEL 1L associated with the deletion mutant. Our data suggest that the ID region identified in the N-terminal end of EDEM1 is involved in the binding of glycosylated and non-glycosylated misfolded proteins. Accelerating tyrosinase degradation by EDEM1 overexpression may lead to an efficient antigen presentation and enhanced elimination of melanoma cells.

– Pan T, Zhu J, Hwu WJ, Jankovic J.
The role of alpha-synuclein in melanin synthesis in melanoma and dopaminergic neuronal cells. PLoS One. 2012;7(9):e45183.
The relatively high co-occurrence of Parkinson's disease (PD) and melanoma has been established by a large number of epidemiological studies. However, a clear biological explanation for this finding is still lacking. Ultraviolet radiation (UVR)-induced skin melanin synthesis is a defense mechanism against UVR-induced damage relevant to the initiation of melanoma, whereas, increased neuromelanin (NM), the melanin synthesized in dopaminergic neurons, may enhance the susceptibility to oxidative stress-induced neuronal injury relevant to PD. SNCA is a PD-causing gene coding for alpha-Synuclein (α-Syn) that expresses not only in brain, but also in skin as well as in tumors, such as melanoma. The findings that α-Syn can interact with tyrosinase (TYR) and inhibit tyrosine hydroxylase (TH), both of which are enzymes involved in the biosynthesis of melanin and dopamine (DA), led us to propose that α-Syn may participate in the regulation of melanin synthesis. In this study, by applying ultraviolet B (UVB) light, a physiologically relevant stimulus of melanogenesis, we detected melanin synthesis in A375 and SK-MEL-28 melanoma cells and in SH-SY5Y and PC12 dopaminergic neuronal cells and determined effects of α-Syn on melanin synthesis. Our results showed that UVB light exposure increased melanin synthesis in all 4 cell lines. However, we found that α-Syn expression reduced UVB light-induced increase of melanin synthesis and that melanin content was lower when melanoma cells were expressed with α-Syn, indicating that α-Syn may have inhibitory effects on melanin synthesis in melanoma cells. Different from melanoma cells, the melanin content was higher in α-Syn-over-expressed dopaminergic neuronal SH-SY5Y and PC12 cells, cellular models of PD, than that in non-α-Syn-expressed control cells. We concluded that α-Syn could be one of the points responsible for the positive association between PD and melanoma via its differential roles in melanin synthesis in melanoma cells and in dopaminergic neuronal cells.

– Ping F, Shang J, Zhou J, Song J, Zhang L.
Activation of neurokinin-1 receptor by substance P inhibits melanogenesis in B16-F10 melanoma cells. Int J Biochem Cell Biol. 2012 Dec;44(12):2342-8.
Skin pigmentation plays a number of valuable roles and its regulation is a complex process that is controlled by different factors. Substance P (SP) regulates many biological functions, including neurogenic inflammation, pain, and stress. However, to date, the regulatory role of SP in the control of melanogenesis has not been elucidated. The present study was designed to investigate the effects of SP on melanogenesis and to elucidate its underlying mechanism(s). After treatment for 48h in mouse B16-F10 melanoma cells, SP (1 and 10nM) significantly down-regulated tyrosinase activity and melanin content. Importantly, western blot analysis revealed the presence of neurokinin-1 receptor (NK-1 R) in B16-F10 cells and the activation of it after SP treatment. It was also found that preincubation with NK-1 receptor antagonist Spantide I could partially reversed SP-induced down-regulations of tyrosinase activity, melanin content and the expression of tyrosinase and tyrosinase-related protein 1. Furthermore, SP could remarkably inhibit the expressions of microphtalmia-associated transcription factor (MITF) and p-p38 MAPK and stimulated p-p70 S6K1. These effects could also be partially reversed by the pretreatment with Spantide I. These results collectively suggested that SP inhibited melanogenesis in B16-F10 cells, which might be attributed to the fact that SP induces the activation of NK-1 receptor, stimulates the phosphorylation of p70 S6K1 and inhibits that of p38 MAPK, decreases the tyrosinase and tyrosinase-related protein 1 expression through MITF, finally resulting in the suppression of melanogenesis. These observations in vitro indicated that the regulation of the SP/NK-1 receptor system might be a useful novel management for skin pigmentation.

– K B, Purohit R.
Mutational analysis of TYR gene and its structural consequences in OCA1A. Gene. 2012 Oct 22. pii: S0378-1119(12)01273-5.
Oculocutaneous albinism type 1A (OCA1A) is the most severe form of albinism characterized by a complete lack of melanin production throughout life and is caused by mutations in the TYR gene. TYR gene codes tyrosinase protein to its relation with melanin formation by knowing the function of these SNPs. Based on the computational approaches, we have analyzed the genetic variations that could change the functional behaviour by altering the structural arrangement in TYR protein which is responsible for OCA1A. Consequences of mutation on TYR structure were observed by analyzing the flexibility behaviour of native and mutant tyrosinase protein. Mutations T373K, N371Y, M370T and P313R were suggested as high deleterious effect on TYR protein and it is responsible for OCA1A which were also endorsed with previous in vivo experimental studies. Based on the quantitative assessment and flexibility analysis of OCA1A variants, T373K showed the most deleterious effect.

Our analysis determines that certain mutations can affect the dynamic properties of protein and can lead to disease conditions. This study provides a significant insight into the underlying molecular mechanism involved in albinism associated with OCA1A.

- Shimoda H, Shan SJ, Tanaka J, Maoka T.
  β-Cryptoxanthin suppresses UVB-induced melanogenesis in mouse: involvement of the inhibition of prostaglandin E2 and melanocyte-stimulating hormone pathways. J Pharm Pharmacol. 2012 Aug;64(8):1165-76.
  OBJECTIVE: β-cryptoxanthin (β-CPX) is a carotenoid that is widely contained in the fruits of citrus plants. We evaluated the effect of β-CPX on UVB-induced pigmentation and mRNA expression related to melanogenesis in mouse skin. In addition, changes in melanogenic molecules were evaluated in cultured melanocytes stimulated with prostaglandin (PG) E(2), melanocyte-stimulating hormone (MSH) and endothelin (ET)-1.
  METHODS: Mice were irradiated with UVB and were given β-CPX (0.1, 1 and 10 mg/kg) orally for 14 days. Pigmentation was evaluated by skin colour change and microscopic observation. Total RNA was obtained from the skin and the expression of melanogenic mRNA was evaluated by RT-PCR. In cell culture studies, human melanocytes were cultured with β-CPX and melanogenic stimulants (PGE(2), MSH and ET-1) for 6-10 days. Melanin contents, dendricity, melanogenic mRNA and phosphorylation of cyclic AMP response element-binding protein (CREB) were evaluated.
  KEY FINDINGS: β-CPX (10 mg/kg) significantly suppressed skin pigmentation and mRNA expression of cyclooxygenase-2, ET-1 receptors, low-affinity neurotrophin receptor, PGE(2) receptor (EP1), melanocortin 1 receptor (MC1R), tyrosinase (Tyr), tyrosinase-related protein (Tyrp) 1 and microphthalmia transcription factor. β-CPX (10 μg/ml) suppressed melanogenesis induced by PGE(2), MSH and ET-1. In the PGE(2)-stimulated melanocytes, mRNA expressions of EP-1, Tyr and Tyrp1 and phosphorylation of CREB protein were suppressed. In the ET-1-stimulated cells, only expression of CREB protein was suppressed. In the MSH-induced cells, mRNA expression of MC1R and Tyrp1 and protein expression of CREB were suppressed.
  CONCLUSION: Oral administration of β-CPX was found to suppress UVB-induced melanogenesis. Suppression of melanogenic enzymes, receptors of melanogenic stimulators, expression and phosphorylation of CREB are thought to be involved in the mechanism.

- Wakamatsu K, Murase T, Zucca FA, Zecca L, Ito S.
  Biosynthetic pathway to neuromelanin and its aging process. Pigment Cell Melanoma Res. 2012 Nov;25(6):792-803.
  Using model compounds of the melanic component of neuromelanin (NM) prepared by tyrosinase oxidation at various ratios of dopamine (DA) and cysteine (Cys) under physiological conditions, we examined a biosynthetic pathway to NM and its aging process by following the time course of oxidation to NM and the subsequent structural modification of NM under various heating conditions. Chemical degradation methods were applied to the synthetic NM. 4-Amino-3-hydroxyphenylethylamine (4-AHPEA) and thiazole-2,4,5-tricarboxylic acid (TTCA) were used as markers of benzothiazine and benzothiazole units, respectively. By following the time course of the biosynthetic pathway of synthetic NM, we found that neurotoxic molecules are trapped in NM. An aging simulation of synthetic NM showed that benzothiazine units in NM are gradually converted to benzothiazole during the aging process. Thus, natural NM was found to be similar to aged (heated) NM prepared from a 2:1 molar ratio of DA and Cys.

- Wang P, Li Y, Hong W, Zhen J, Ren J, Li Z, Xu A. **The changes of microRNA expression profiles and tyrosinase related proteins in MITF knocked down melanocytes.** Mol Biosyst. 2012 Oct 2;8(11):2924-31.
  Microphthalmia-associated transcription factor (MITF) is a master regulator in melanocyte proliferation, development, survival and melanoma formation. In melanocyte dysfunction disease, it is observed that the expressions of MITF, tyrosinase (TYR), tyrosinase related protein 1 (TYRP1) and tyrosinase related protein 2 (TYRP2)/dopachrome tautomerase (DCT) are changed, the consequence of which remains unclear. In this study, we focused on the change of microRNA (miRNA) profiles and Tyrosinase Related Proteins (TRPs) in MITF knocked down melanocytes. For the first time, we assayed the MITF-KD miRNA profiles using a miRNA microarray and found that hsa-miR-1225-3p, hsa-miR-634, hsa-miR-197, hsa-miR-766, hsa-miR-574-5p and hsa-miR-328 were upregulated, and hsa-miR-720 and hsa-miR-1308 were downregulated in MITF knocked down melanocytes. These miRNAs were validated by miRNA real time qPCR. These miRNA potential targets, especially the TRPs, were analyzed according to the miRNA database (Sanger Center). By TargetScan prediction, the hsa-miR-634 and hsa-miR-328 have poorly conserved sites on TYR and hsa-miR-197 have poorly conserved sites on TYR1. Through qPCR and western blotting we found that the expression of TYR and TYRP1 were dramatically decreased and the expression of TYRP2 was increased in MITF knocked down melanocytes (MITF-KD). These results suggested that the miRNAs may be involved in MITF regulation of TYR, TYRP1 and TYRP2, which provides a new clue for understanding the role of miRNAs in melanocyte dysfunctional disease.

- Yang J, Liu X, Zhang J, Qing B, Lu B.

Molecular cloning and biochemical analysis of tyrosinase from the crested ibis in china. Biochem Genet. 2012 Dec;50(11-12):936-45.
The crested ibis, one of the most endangered birds in the world, could benefit from research into its genetic diversity as a tool for conservation in the future. Tyrosinase is thought to play a major role in the production of common yellow to black melanins in birds. We have cloned and sequenced four exons of the crested ibis tyrosinase gene and discovered that the amino acid sequence has high similarity to zebra finch tyrosinase (93 %), followed by chicken (91 %) and quail (91 %). Some functional and structural domains in the crested ibis tyrosinase coding area were found to be conserved during evolution. Nine sequence variants were found in the partial coding sequence, one in exon 1 and eight in exon 4. Sequence variant 1 (SV1) shows intermediate polymorphism (0.25 < PIC < 0.5), and further study is needed to determine whether it can be used as a potential molecular marker in crested ibis artificial breeding programs.

- Yoshida-Amano Y, Hachiya A, Ohuchi A, Kobinger GP, Kitahara T, Takema Y, Fukuda M.
Essential role of RAB27A in determining constitutive human skin color. PLoS One. 2012;7(7):e41160.
Human skin color is predominantly determined by melanin produced in melanosomes within melanocytes and subsequently distributed to keratinocytes. There are many studies that have proposed mechanisms underlying ethnic skin color variations, whereas the processes involved from melanin synthesis in melanocytes to the transfer of melanosomes to keratinocytes are common among humans. Apart from the activities in the melanogenic rate-limiting enzyme, tyrosinase, in melanocytes and the amounts and distribution patterns of melanosomes in keratinocytes, the abilities of the actin-associated factors in charge of melanosome transport within melanocytes also regulate pigmentation. Mutations in genes encoding melanosome transport-related molecules, such as MYO5A, RAB27A and SLAC-2A, have been reported to cause a human pigmentary disease known as Griscelli syndrome, which is associated with diluted skin and hair color. Thus we hypothesized that process might play a role in modulating skin color variations. To address that hypothesis, the correlations of expression of RAB27A and its specific effector, SLAC2-A, to melanogenic ability were evaluated in comparison with tyrosinase, using human melanocytes derived from 19 individuals of varying skin types. Following the finding of the highest correlation in RAB27A expression to the melanogenic ability, darkly-pigmented melanocytes with significantly higher RAB27A expression were found to transfer significantly more melanosomes to keratinocytes than lightly-pigmented melanocytes in co-culture and in human skin substitutes (HSSs) in vivo, resulting in darker skin color in concert with the difference observed in African-descent and Caucasian skins. Additionally, RAB27A knockdown by a lentivirus-derived shRNA in melanocytes concomitantly demonstrated a significantly reduced number of transferred melanosomes to keratinocytes in co-culture and a significantly diminished epidermal melanin content skin color intensity ($\Delta L^*=4.4$) in the HSSs. These data reveal the intrinsically essential role of RAB27A in human ethnic skin color determination and provide new insights for the fundamental understanding of regulatory mechanisms underlying skin pigmentation.

- Zhang P, Liu W, Zhu C, Yuan X, Li D, Gu W, Ma H, Xie X, Gao T.
Silencing of GPNMB by siRNA inhibits the formation of melanosomes in melanocytes in a MITF-independent fashion. PLoS One. 2012;7(8):e42955.
BACKGROUND: Melanosomes are specialized membrane-surrounded organelles, which are involved in the synthesis, storage and transport of melanin. Glycoprotein (transmembrane) non-metastatic melanoma protein b (GPNMB), a melanosome-specific structural protein, shares significant amino acid sequence homology with Pmel-17. Proteomic analysis demonstrated that GPNMB is present in all stages (I-IV) of melanosomes. However, little is known about the role of GPNMB in melanosomes.
METHODOLOGY/PRINCIPAL FINDINGS: Using real-time quantitative PCR, Western blotting and immunofluorescence analysis, we demonstrated that the expression of GPNMB in PIG1 melanocytes was up-regulated by ultraviolet B (UVB) radiation. Transmission electron microscopy analysis showed that the total number of melanosomes in PIG1 melanocytes was sharply reduced by GPNMB-siRNA transfection. Simultaneously, the expression levels of tyrosinase (Tyr), tyrosinase related protein 1 (Trp1), Pmel17/gp100 and ocular albinism type 1 protein (OA1) were all significantly attenuated. But the expression of microphthalmia-associated transcription factor (MITF) was up-regulated. Intriguingly, in GPNMB silenced PIG1 melanocytes, UVB radiation sharply reduced MITF expression.
CONCLUSION: Our present work revealed that the GPNMB was critical for the formation of melanosomes. And GPNMB expression down-regulation attenuated melanosome formation in a MITF-independent fashion.

8. Melanosomes

(Pr J. Borovansky)

Reviews Two review articles deal with photodynamic therapy (PDT) in melanoma and both of them (*Baldea & Filip; Huang et al.*) conclude that melanin and melanosomes are responsible for melanoma resistance to the PDT.

Melanosome photothermolysis proved to be efficient to produce a significant fading of mucocutaneous melanosis in the Peutz-Jeghers syndrome (*Li et al.*). Melanosome regeneration after selective a laser photothermolysis was investigated in the adult zebrafish skin (*Kim et al.*).

Melanosome cation-exchange properties. Melanosomes were shown to retain a protective ability against oxidative stress even under conditions of elevated iron (*Kaczara et al.*). Elemental analyse, performed by means of energy dispersive X-ray analysis, excluded the hypothesis that Tycho Brahe had been poisoned by mercury because Hg was not found in his beard hair melanosomes (*Jonas et al.*).

Melanosome affinity to cyclic compounds was confirmed in studies using 18F-N-[2-(diethylaminoethyl]-6-fluoro-pyridine-3-carboxamide as a promising melanoma PET tracer (*Rbah-Vidal et al.*).

Melanosomal protein Pmel17 was tested as a target for antibody-conjugate therapy in melanoma (*Chen et al.*) and exploited in the quantitative measurement of melanosome transfer from melanocytes to keratinocytes (*Verdy et al.*).

Various aspects of melanosome transport were studied by *Bouzat et al.*, *Bruder et al.* and *Chang et a*l.
Functions of melanoregulin in organelle biogenesis and in melanosome transfer were characterized by *Rachel et al.* and *Wu et al.*, respectively.

In a proteomic study comparing the alterations between giant melanocytic naevi and normal skin samples the melanosome GO cellular component was detected among 46 proteins significantly enriched in naevi (*Kim et al*).

Supramolecular arrangement of eu- and phaeomelanin and the role of matrix structure in relation to different morphologies of the two types of melanosomes were studied by *Thureau et al.*

Melanosome degradation.The role of acid hydrolases has been again taken into account by *Ebanks et al.*

- Baldea I, Filip AG.
  Photodynamic therapy in melanoma – An update. J Physiol Pharmacol 63(2): 109-118, 2012.
  To increase the effectiveness of PDT in melanoma, the photodynamic therapy has to overcome the protective mechanisms like pigmentation and increased oxidative stress defense, possibly through an inhibition of melanogenesis and melanosome targeted photosensitizers. The combination of PDT with immune stimulation therapies might increase the efficiency.

- Bouzat S, Levi V, Bruno L.
  Transport Properties of Melanosomes along Microtubules Interpreted by a Tug-of-War Model with Loose Mechanical Coupling. PLoS ONE 7(8), 2012.
  A stochastic model to investigate the transport of cargoes along microtubules was presented which focused on reproducing and interpreting previous experimental results for Xenopus melanosomes transport in living cells.The model offers plausible explanations how the typical features observed in trajectories of cargoes in vivo are determined by the motors.

- Bruder JM, Pfeiffer ZA, Ciriello JM, Horrigan DM, Wicks NL, Flaherty B, Oancea E.
  Melanosomal Dynamics Assessed with a Live-Cell Fluorescent Melanosomal Marker. PLoS ONE 7(8): e43465. doi:10.1371, 2012.
  To monitor melanosome dynamics within melanocytes and their transport to keratinocytes in real time, the authors designed and tested a fluorescent melanosomal marker by fusing the green fluorescent protein to the ocular albinism 1 protein (OA1). The authors conclude that the OA1 fluorescently tagged at the carboxyterminus is a specific and stable tool to visualize and quantify melanosomal dynamics in the primary human cultured melanocytes. They observed that melanosomes can switch between two types of movement, which correspond to a restricted diffusion and an active transport. In addition, using OA1-GFP in co-cultures, they could monitor the melanosomal transfer to keratinocytes..

- Chang H, Choi H, Joo KM, Kim D, Lee TR

Manassantin B inhibits melanosome transport in melanocytes by disrupting the melanophilin-myosin Va interaction. Pigment Cell Melanoma Res. 25(6):765-772, 2012.
An extract of Saururus chinensis Baill and one of its components, manassantin B, inhibited the melanosome transport in Melan-a melanocytes and normal human melanocytes. Manassantin B disturbed melanosome transport by disrupting the interaction between melanophilin and myosin Va. Manassantin B is neither a direct nor an indirect inhibitor of tyrosinase. The total melanin content was not reduced when the melanosome transport was inhibited in a Melan-a melanocyte monoculture by manassantin B.

- Chen Y, Chalouni C, Tan C, Clark R, Venook R, Ohri R, Raab H, Firestein R, Mallet W, Polakis P.
The Melanosomal Protein PMEL17 as a Target for Antibody Drug Conjugate Therapy in Melanoma. J Biol Chem 287(29): 24082-24091, 2012.
An antibody drug conjugate (ADC) specific to PMEL17 was shown to specifically target melanoma cells. Although a newly synthesized PMEL17 is ultimately routed to the melanosome, substantial PMEL17 amounts are accessible to ADC at the cell surface that undergo internalization and routing to a LAMP1-enriched, lysosome-related organelle. Accordingly, an ADC reactive with PMEL17 exhibits target-dependent tumour cell killing in vitro and in vivo.

- Ebanks JP, Koshoffer A, Wickett RR, Hakozaki T, Boissy RE.
Hydrolytic enzymes of the interfollicular epidermis differ in expression and correlate with the phenotypic difference observed between light and dark skin. J Dermatol. 39: 1-7, 2012.
Different expression of six hydrolytic enzymes was identified by microassay analyses of the suprabasal epidermis from light and dark skin. An immunoblotting technique demonstrated that prostatic acid phosphatase and cathepsin L2 were upregulated in dark skin and light skin, respectively. Further analyses confirmed a differential expression of the two enzymes both at gene and protein levels. The authors reconsider the participation of acid hydrolases in the degradation of melanosomes.

- Huang YY, Vecchio D, Avci P, Yin R, Garcia-Diaz M, Hamblin MR.
Melanoma resistence to photodynamic therapy: New insights. Biol Chem. doi:10.1515/hsz-2012-0228, 2012.
Approaches to overcoming melanoma resistance to PDT include:1. the discovery of highly active photosensitizers absorbing in the 700-800-nm spectral region; 2. interventions that can temporarily reduce the amount of melanin and melanosomes; 3. compounds that can reverse apoptotic defects or inhibit drug-efflux of photosensitizers; and 4. immunotherapy approaches that can take advantage of the ability of PDT to activate the host immune system to the treated tumour.

- Jonas L, Jaksch H, Zellmann E, Kerstin I. Klemm KI, Ande PH.
Detection of Mercury in the 411-year-old Beard Hairs of the Astronomer Tycho Brahe by Elemental Analysis in Electron Microscopy. Ultrastructural Pathology, 36(5): 312–319, 2012.
The TEM study of more than 400-year-old well preserved hairs of Tycho Brahe revealed typical stage II melanosomes of red hair. The elemental analysis performed by means of energy dispersive X-ray analysis in a field cathode SEM revealed mercury containing granules only in the outer hair scales but neither in the hair roots nor in hair axis.

- Kaczara P, Zareba M, Herrnreiter A, Skumatz CMB, Andrzej Zadło A, Sarna T Burke JM.
Melanosome–iron interactions within retinal pigment epithelium-derived cells. Pigment Cell Melanoma Res. 25(6): 804–814, 2012.
Melanosomes can protect cells against oxidative stress. Using ARPE-19 cells, a human retinal pigment epithelium (RPE) cell line, the authors confirmed the iron-binding property
of melanosomes within living RPE cells. Melanosomes with different iron content exhibited a similar ability to protect cells against H2O2 treatment thus suggesting that melanosomes may retain the capacity to protect against oxidative stress even under conditions of elevated iron.

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Recovery of Pigmentation Following Selective Photothermolysis in Adult Zebrafish Skin: Clinical Implications for Laser Toning. Treatment of Melasma. J Cosmetic Laser Surgery 14(6): 277-285, 2012.
Melanosomes in the adult zebrafish skin can be utilized to study the melanosome regeneration response to laser irradiation (often used in melasma treatment) and to develop a system to assess the comparative efficacy of melanogenic regulatory compounds. Melanosomes regenerated after a selective photothermolysis. Furthermore, a tyrosinase inhibitor, 1-phenyl-2-thiourea, completely blocked the melanosome regeneration after a laser irradiation.

- Kim HK, Kim YK, Song IS, Lee SR, Jeong SH, Kim MH, Seo DY, Kim N, Rhee BD, Ko KS, Tark KC, Park CG, Cho JY, Han J.

Human giant congenital melanocytic nevus exhibits potential proteomic alterations leading to melanotumorigenesis. Proteome Sci.;10(1):50, 2012.
Proteomic differences between giant congenital melanocytic nevi (GCMN) and normal skin samples were analyzed by one-dimensional-liquid chromatography-tandem mass spectrometry and by established bioinformatic tools to identify the proteins that may play a key role in the malignant transformation of GCMN. Among the specific 46 proteins identified as significantly enriched in GCMN was melanosome GO_cellular component.

- Li Y, Tong X, Yang J, Yang L, Tao J, Tu Y.
Q-switched alexandrite laser treatment of facial and labial lentigines associated with Peutz-Jeghers syndrome. Photodermatol Photoimmunol Photomed. 28(4):196-199, 2012.
The Q-switched alexandrite laser used at 752 nm, a wavelength well absorbed by melanin relative to other optically absorbing structures in the skin, caused a highly selective destruction of pigment-laden cells. In addition, the 75-nanosecond pulse duration produced by this laser approximates the thermal relaxation time for melanosomes, thereby confining the energy to the target. The Q-switched alexandrite laser produces clinically significant fading of mucocutaneous melanosis in association with the Peutz-Jeghers syndrome.

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Early detection and longitudinal monitoring of experimental primary and disseminated melanoma using [^{10} F]ICF01006, a highly promising melanoma PET tracer. Eur J Nucl Med Mol Imaging 39(9):1449-1461, 2012.
A new and rapid radiosynthesis of (18)F-N-[2-(diethylamino)ethyl]-6-fluoro-pyridine-3-carboxamide ,a molecule with a high specificity for melanotic tissue, melanosomes and melanin and its evaluation in a murine model for an early specific detection of the pigmented primary and disseminated melanoma were reported.

- Thureau P, Ziarelli, F, Thévand A, Martin RW, Farmer PJ, Viel,S, Mollica G.
Probing the Motional Behavior of Eumelanin and Pheomelanin with Solid-State NMR Spectroscopy: New Insights into the Pigment Properties. Chemistry 18(34), 10689 – 10700, 2012.
This study aims at highlighting the differences in the actual supramolecular arrangement
and the mobility of the two forms of melanin, thus trying to mimic the conditions in vivo. Its results reveal a significantly higher mobility in the red pheomelanin and the presence of two dynamically distinguishable melanin fractions in both black eumelanin and red pheomelanin, in agreement with the different morphologies reported for the two types of melanosome. The authors conclude that not only the structural features inherent in the pure pigment, but also the role of the matrix structure in defining the overall melanin supramolecular arrangement and the resulting dynamic behavior of the two melanin compounds, should be taken into account to explain their functions.

- Verdy C, Branka JE, Mekideche N.
Melanosome transfer evaluation by quantitative measurement of Pmel 17 in human normal melanocyte-keratinocyte co-cultures effect of an Alaria esculenta extract. J Cosmet Sci. 63(3):197-203, 2012.
Melanosome-specific membrane-bound glycoprotein, Pmel 17 is released from the melanosome membrane by ectodomain shedding. The authors demonstrated that it was possible to evaluate the melanosome transfer by quantifying this "soluble" Pmel 17. The Pmel 17 developed ELISA assay permits a detection of 10 to 1000 ng/ml of this glycoprotein in human normal melanocyte-keratinocyte co-culture media. A whitening cosmetic - Alaria esculenta extract, was shown to induce a significant decrease in the melanosome transfer to produce a lightening effect without affecting the melanin production.

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Melanoregulin regulates a shedding mechanism that drives melanosome transfer from melanocytes to keratinocytes. Proc Natl Acad Sci U S A. 109(31):E2101-2109, 2012.
A report showing that dilute/dsu melanocytes, but not dilute melanocytes, readily transfer the melanosomes concentrated in their center to surrounding keratinocytes in situ. Using time-lapse imaging of wild type melanocyte/keratinocyte cocultures in which the plasma membranes of the two cells were marked with different colours, the authors define an intercellular melanosome transfer pathway that involves the shedding by the melanocyte of melanosome-rich packages, that subsequently are phagocytosed by the keratinocyte. Shedding,

which occurs primarily at dendritic tips but also in more central regions, involves adhesion to the keratinocyte, thinning behind the forming package, and apparent self-abscission.

9. Melanoma experimental, cell culture

(Dr R. Morandini)

Okoci *et al.* presented a study demonstrating the importance of fibroblast interaction in relation with the invasive capacity of melanoma in 3D cells culture. The three-dimensional multicellular tumor spheroid culture array has been fabricated using a magnetic force-based cell patterning method. The expression of IL-8 and MMP-2 increased by 24-fold and 2-fold, respectively, in real time RT-PCR compared to the absence of fibroblasts.
In an other type of co-culture : melanoma-endothelial cell co-culture, Ghislin *et al*. show the importance of LFA-1 and ICAM-1 expression in favour of the transendothelial migration of melanoma cell lines in vitro.

A lot of research has been placed on the identification, functional characterization, and therapeutic potential of somatic variants in tumor genomes. However, the majority of somatic variants lie outside coding regions and their role in cancer progression is not well understood.
It is then unclear if and how noncoding variants might contribute to cancer progression.
In order to establish a system to test the functional importance of non-coding somatic variants in cancer, Parker et al. has performed a whole-genome sequencing and analysis of a low passage melanoma cell culture and make the comparison with the patient-matched normal genomes. These results show that mutation accumulation in metastatic melanoma is non-random across the genome and that a de-differentiated regulatory architecture is common process. Such information can help to establish a broader mechanistic understanding the linkage between non-coding genomic variations and the cellular evolution of cancer.

A. Signal transduction and cell culture

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C. 3D cell culture and/or skin reconstitution

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D. Other tools and cell culture

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E. Melanoma Experimental

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ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

2013 Melanoma 2013: 23rd Annual Cutaneous Malignancy Update
January 26-27, 2013, San Diego, California

2013 Pigment Cell Development Workshop
May 6-8, Edinburgh, UK
Contact: Liz Patton: e.patton@igmm.ed.ac.uk
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2013 International Investigative Dermatology
May 8-11, Edinburgh, Scotland
Contact: Web: www.iid2013.org

2013 Asian Society for Pigment Cell Research (ASPCR)
May 17-19 Sydney, Australia
Contact: Organizer(s): Prasad Kumarasinghe, Pritinder Kaur
Web: http://aspcr-asdr2013.org/
E-mail: prasadkumarasinghe@yahoo.com

2013 8th World Congress of Melanoma
July 18-20, Hamburg, Germany
Contact: E-mail: congress@worldmelanoma2013.com
Web: www.worldmelanoma2013.com

2013 XVIIIth Meeting of the ESPCR
September 9-12, Lisbon, Portugal
Contact: Web site: http://www.espcr.org/ESPCR2013
E-mail address: espcr2013@espcr.org

2013 Japanese Society for Pigment Cell Research (JSPCR),
November 16-17, Osaka, Japan
Contact: Organizer: Ichiro Katayama
Web: http://jspcr.jp/english/index.html
E-mail: katayama@derma.med.osaka-u.ac.jp

2013 PanAmerican Society for Pigment Cell Research (PASPCR)
September 8-11, Madison, WI, USA
Contact: Organizer: Vijayasaradhi Setaluri
Web (Society's web page): http://paspcr.med.umn.edu/
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2014 XXII[nd] IPCC Meeting

September 4-7, Singapore

Contact: Web: www.ipcc2014.org

Organizer/Chair: Boon-Kee Goh

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2014 44th Annual ESDR Meeting

September 10-13, Copenhagen, Denmark

2015 45[th] Annual ESDR Meeting

September 9-12, Rotterdam, The Netherlands

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