PIGMENT CELL RESEARCH BULLETIN

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LETTER TO THE EDITOR OF

PIGMENT CELL BULLETIN

Commentary

CD11c-POSITIVE CELLS INFILTRATING MELANOMA

Primary cutaneous melanoma (PCM) is commonly associated with a dermal infiltrate, possibly suggesting a defense mechanism of the host towards abnormal melanocytes. In fact, such a dermal infiltrate, mainly comprised of Langerhans cells (LC), macrophages and T cells, may presumably cause, according to some suggestions, even the regression of PMC. However, the exact mechanism of defense yielded by the dermal infiltrate against the abnormal melanocytes is up to date not completely clear.

Recently, a heterodimeric protein, composed of an alpha subunit of 150kD noncovalently associated to a beta subunit of 95kD, named gp150,95 (CD11c/CD18), was detected on the membrane of monocytes, macrophages, NK cells (reviewed by 1), a minor part of cytotoxic T lymphocytes (CTL) (2), and on LC (3,4). Such gp 150,95 molecule is involved in cell-mediated cytolysis by CTL (2). Further, it was shown to be able to uniquely trigger the adhesion of mononuclear cells expressing it to monolayers of melanoma cells (5). In fact, antibodies directed to the alpha chain of gp150,95 (anti-CD11c antibodies) inhibited adhesion : thus, the monocyte adhesion to melanoma monolayers is caused by the CD11c moiety (5).

We intended therefore to investigate the expression of the CD11c molecule on the cells infiltrating the PCM, using a series of "in situ" immunostaining procedures, both in light microscopy and in immunoelectron microscopy, developped in our laboratory (6,7,8,9), on "early invasive" melanomas. Our results showed a consistent proportion of dermal CD11c-positive cells, including macrophages, LC and lymphocytes, infiltrating the "early invasive" PCM.

The presence of macrophages and especially LC in the dermal infiltrate of PCM has been associated with the hypothesis that such antigen-presenting cells, pulsed by melanoma antigens, could be essential for initiation and maintenance of a cutaneous immune response against early transformed melanocytes (10,11). This hypothesis seems to be extended by the results of the present study. We indeed

observed that a vast proportion of mononuclear cells infiltrating PCM was CD11c-positive, including LC, macrophages and lymphocytes. Such CD11c expressions might suggest at least three different hypothetical roles for the CD11c-positive mononuclear cells infiltrating PCM.

(1) The CD11c adhesive moiety could subserve, at least partly, the contact of both LC and macrophages with abnormal melanocytes, as demonstrated "in vitro" (5), possibly to capture and then "process" the melanocytic neoantigens.

(2) Subsequently, the presence on the membrane of antigen-presenting cells of adhesive proteins could facilitate the interaction with T lymphocytes for clustering (12), thought to be necessary for an efficient antigen-presentation.

(3) It seems conceivable that, in a further phase, the CD11-positive lymphocytes, and perhaps also the CD11c-positive macrophages, could play a cytolytic role against melanoma cells, acting, as demonstrated "in vitro" for human CTL clones (2), at the level of conjugate formation between effector and target cells.

In conclusion, our findings demonstrate the occurence of a quantity of CD11c-positive cells infiltrating the "early invasive" PCM, possibly involved in (1) neoantigen recruitment, (2) neoantigen presentation and even (3) cytolytic activity against tranformed melanocytes, thus playing a key role in the host resistance, and possibly favouring the regression of PCM.

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Short communication

EXPERIMENTAL APPROACH TO THE SWITCH FROM THE NORMAL TO THE NEOPLASTIC STATE OF THE PIGMENT CELLS IN XIPHOPHORUS

Certain genotypes of Xiphophorus harbour an accessory Mendelian gene which, following loss, impairment or insufficiency of its regulatory genes in the germ line, mediates the hereditary capacity to develop neoplasia spontaneously or following induction with initiating and promoting carcinogens. Together with its linked regulatory genes it forms a "tumor gene-complex" (Tu-complexes that are responsible for sex chromosome-linked melanoma formation.

Southern analyses of the xiphophorine genome with 15 authentic oncogene probes have revealed that only three v-erbB related Eco RI fragments comprising 4.9 kb of a certain X-, 11.5 kb of another X-, and 6.7 kb of both a Y- and Z-chromosome are inherited in parallel with the Tu-complex and melanoma formation. They are accessory in the genome, and are highly homologous with each other. The sequence of the X-chromosomal 4.9 kb fragment shows minor but significant differences from that of the invariably present autosomal xiphophorine erbB (x-erbB) fragment of 5.5 kb, indicating that at least two different x-erbB genes coding for different EGF receptors can exist in the fish.

Northern analyses showed expression of both genes in a fibroblast cell line, and overexpression of the sex chromosomal x-erbB in a melanoma cell line.

The co-segregation of the hereditary trait of melanoma with the sex chromosomal x-erbB fragments, suggests that the accessory x-erbB gene may be responsible for the switch from the normal to the neoplastic state of the pigment cells.

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CURRENT LITERATURE IN

We acknowledge the valuable assistance of Ms Linda ALBRECHT and the financial support of Lawrence M. Gelb Research Foundation.

ESPCR

PIGMENT CELL RESEARCH

We are pleased to offer you an improved classification of literature references. Since melanins represent a large item, it has been splitted into :

1) melanins and other pigments chemistry
2) biology of pigment cells and pigmentary disorders
3) MSH, other hormones, differentiation
4) photobiology and photochemistry
5) neuromelanins
6) genetics
7) tyrosinase and other enzymes
8) melanoma
9) eye

The title "Genetics" will cover the genetic control of pigment cells, oncogenes and genetic engeneering.

1. MELANINS, AND OTHER PIGMENTS CHEMISTRY

- Allegri G, Biasiolo M, Frison G, Pelli B, Traldi P
Collisional spectroscopy in structural characterization of melanins. 2--Laser desorption experiments on bio- and synthetic tryptophan melanins. Biomed Environ Mass Spectrom 15:353-355, 1988.
Abstract : Melanins are naturally occurring macromolecules whose structural complexity appeared evident from the first researches of Quilico. Their structural characterization remains a difficult problem, mainly due to the physico-chemical properties of such compounds. Melanins are insoluble in organic solvents as well as aqueous solutions and are infusible. Consequently the traditional chemical degradation and physicochemical methods such as ultraviolet, infrared, 1H and 13C nuclear magnetic resonance, ESR (electron spin resonance), XPS (X-rays photoelectron spectroscopy) and X-ray diffraction have led, until now, to limited information on melanin chemical structure.

- Bilinska B, Kolczynska U, Wilczok T
Infrared studies of melanin-iron complexes. 1988.
Abstract : IR spectra of modified and unmodified melanin and melanin-Fe3+ complexes show differences suggesting that COOH

and phenol OH groups are involved in complex formation. Dark and red hair melanins showed differences in their interaction with Fe3+.

- Bilinska B, Wilczok T, Vucelic V, Hranisavljevic J, Simonovic B, Vucelic D
Microcalorimetric studies of natural and synthetic melanins 1988.
Abstract : Differential scanning calorimetry measurements of synthetic and natural melanins were performed and the results compared with IR spectroscopy, thermogravimetric, and elemental anal. data. Endothermal effects in the temp. region 315-356 K were ascribed to structural changes in melanin mols.

- Bilinska B, Stepien K, Wilczok T
Infrared spectroscopy of melanins and melanoproteins. 1988
Abstract : Model melanoproteins were synthesized. IR spectroscopy of synthetic and natural melanins and model melanin-human serum albumin (HSA) complexes were analyzed before and after removal of protein moieties. The disappearance of IR bands characteristic of melanins in samples of natural melanins and model melanin-HSA complexes is due only to the presence of proteins. The hydrolysis of the protein component gives melanin samples again showing bands typical of purified melanins.

- Buszman E, Dzierzewicz Z, Kwasniak B, Wilczok T
The effect of cobalt(II) and nickel(II) ions on dopa-melanin properties. 1988
Abstract : Differences in drug binding ability and free radical content in melanins were found when Co2+ and Ni2+ were bound to DOPA used for in vitro melanin synthesis or to intact DOPA-melanin. The Co2+ and Ni2+ ion concn. in melanins depends on their addn. prior to or after the melanin synthesis.

- Buszman E, Kwasniak B, Dzierzewicz Z, Wilczok T
Dynamics of metal ion-melanin complex formation. ESR and radiochemical studies. 1988.
Abstract : Dynamics of metal ion-DOPA-melanin complex formation was analyzed. Radiochem. methods showed that metal ion affinity to melanin strongly depends on the nature of the metal, the physicochem. properties. of melanin, and stoichiometric molar ratios. Nine types of dia- and paramagnetic ion-melanin complexes were prepd. and the effect of metals on the free radical state in melanins was detd. by the use of ESR spectroscopy.

- Coelho R, Linhares LF, Martin JP
Sugars in hydrolyzates of fungal melanins and soil humic acids. Plant Soil 106:127-133, 1988.
Abstract : Humic acids from 4 Brazilian topsoils of different origin and 4 melanins formed by soil fungi under 2 cultural conditions were subjected to a 2-step hydrolysis procedure, and the monosaccharides released were detd. qual. and quant. by gas-liq. chromatog. The neutral sugars glucose,

galactose, mannose, arabinose, xylose, fucose, and rhamnose and the alc. sugar inositol were detected in most of the soil humic acid samples. The fungal melanins showed the presence of glucose, galactose, mannose, and arabinose. Ribose was present in melanin hydrolyzates for 2 of the fungi. Some quant. differences in the 2 types of humic polymers were noted and expected considering their origins. However, similarities were more apparent than differences and give further indication that melanic fungi may play a significant role in the formation of soil humic acids.

- Dayhaw-Barker P, Truscott TG,
Direct detection of singlet oxygen sensitized by nalidixic acid: the effect of pH and melanin. Photochem. Photobiol. 47:765-767, 1988.
Abstract : Singlet O yields (.vphi..DELTA.) are reported for the antibiotic nalidixic acid in D2O at pH values above and below its pKa in water. The .vphi..DELTA. increases on lowering the pH. The effect of eumelanin on the .vphi..DELTA. values is shown to be substantial at pH 4.4, but virtually zero above the pKa value. Human serum albumin seems to have little effect on the singlet O yield at high pH in the presence of melanin. The results are correlated with the exptl. and clin. observations relating to the photosensitizing activity of the drug.

- Debing I, Ijzerman AP, Vauquelin G
Melanosome binding and oxidation-reduction properties of synthetic L-dopa-melanin as in vitro tests for drug toxicity. Mol Pharmacol 33:470-476, 1988.
Abstract : Fifteen drugs were assessed for their ability to interact with calf eye melanosomes and to inhibit synthetic L-DOPA-melanin-catalyzed oxidation-reduction reactions. All drugs were able to bind to calf eye melanosomes. The Scatchard plots of the saturation binding data were curvilinear. At a free drug concentration of 0.1 mM, binding ranged between 0.8 nmol/mg for pirenzepine and 71 nmol/mg for chloroquine, a compound which has been described as provoking toxic side-effects in melanin-containing tissues and adjacent structures. As a result of its electron transfer properties, synthetic L-DOPA melanin catalyzes the NADH oxidation/ferricyanide reduction reaction. Except for (-)-norepinephrine, which underwent rapid oxidation in the presence of ferricyanide, all of the investigated drugs were also able to inhibit this catalytic activity of L-DOPA-melanin. The degree of inhibition is dictated by the extent of binding rather than by the chemical nature of the drug itself. Chlorpromazine itself was able to catalyze the oxidation-reduction reaction and has been proposed to shunt normal electron transport sequences in vivo. The implications of melanin binding with respect to drug toxicity are discussed in the light of the present observations.

- D'Ischia M, Napolitano A, Prota G
Sulfhydryl compounds in melanogenesis. Part II. Reactions of cysteine and glutathione with dopachrome. Tetrahedron

43:5357-5362, 1987.
Abstract : Under biomimetic conditions dopachrome (I, R = R1 = H), a key intermediate in the biosynthesis of melanins, is shown to react with glutathione to give a colorless adduct identified as 4-S-glutahionyl-5,6-dihydroxyindole (II, R2 = S-glutathionyl). In the case of cysteine, the reaction leads to a non-aminoacidic condensation product (.lambda.max 422 nm) which was too unstable to be characterized. The analogous adduct derived by reaction of dopachrome Me ester (I, R = H, R1 = Me) with cysteine Et ester (IV) could be isolated and formulated as II (R = R3 = H, R4 = Et), contg. the new 1,2-dihydro-3H,8H-pyrrolo[2,3-h][1,4]benzothiazine ring system. Likewise, 2-methyldopachrome Me ester (I, R = R1 = Me) reacts with IV and penicillamine Me ester to give the corresponding adducts III (R = Me, R3 = H, R4 = Et; R = R3 = R4 = Me, resp.). For diagram(s), see printed CA Issue.

- Laub R, Stiller KJ, Wohlrab W
Computer-assisted quantification of epidermal pigment changes. Dermatol Monatsschr 173:585-590, 1987.

- Palumbo A
Structural modifications in biosynthetic melanins induced by metal ions. Biochim Biophys Acta 964:193-199, 1988.
Abstract : A number of transition metal ions with a wide distribution in biological systems, e.g., Cu2+, Co2+ and Zn2+, are shown to affect markedly the chemical properties of melanins formed by the tyrosinase-catalysed oxidation of dopa. Acid decarboxylation and permanganate degradation provide evidence that melanins prepared in the presence of metal ions contain a high content of carboxyl groups arising from the incorporation of 5,6-dihydroxyindole-2-carboxylic acid (DICA) into the pigment polymer. Naturally occurring melanins from cephalopod ink and B16 mouse melanoma were found to be much more similar to melanins prepared in the presence of metal ions than to standard melanins prepared in the absence of metal ions. These results suggest that the presence of carboxylated indole units in natural melanins is probably due to the intervention in the biochemical pathway of metal ions which, as recently shown, catalyse the formation of DICA versus 5,6-dihydroxyindole in the rearrangement of dopachrome.

- Papaspyrides CD, Protopapas SA
ESR approach on hydroquinone-melanin possible interaction. Int. J. Biol. Macromol. 10:62-63, 1988.
Abstract : Melanin comprises a phys. surface pigment polymer while hydroquinone is a well known and established depigmenting agent. The possibility of free radical interaction between synthetic melanin and hydroquinone in soln. has been examd. by ESR spectroscopy. The results obtained further prove this interaction which seems responsible for the skin depigmentary ability of hydroquinones.

- Pilas B, Sarna T, Kalyanaraman B, Swartz HM

The effect of melanin on iron associated decomposition of hydrogen peroxide. Free Radic Biol Med 4:285-293, 1988.
Abstract : The effects of melanin on the iron-catalyzed decomposition of hydrogen peroxide to hydroxyl radicals and hydroxyl ions have been studied using electron spin resonance, spin trapping and visible light spectrophotometry. Melanin altered these reactions by several different mechanisms and consequently, depending on conditions, can significantly increase or decrease the yield of reactive products, including hydroxyl radicals. For low concentrations of ferrous ions, melanin decreased the yield of hydroxyl radicals due to binding of ferrous ions by melanin; ferrous ions bound to melanin did not decompose H2O2 efficiently. Melanins increased the rate of hydroxyl radical production if the predominant form of iron was ferric, due to the ability of melanin to reduce ferric to ferrous iron. Hydroxyl radical production in the presence of a strong chelator (e.g. EDTA) and melanin was greater than in the presence of a weak chelator (e.g. ADP) and melanin. Melanin also increased the rate of destruction of the DMPO-OH adduct.

- Pileblad E, Slivka A, Bratvold D, Cohen G
Studies on the autoxidation of dopamine: interaction with ascorbate. Arch Biochem Biophys 263:447-452, 1988.
Abstract : An oxygen electrode was used to monitor the reaction between dopamine (DA, 1-20 mM) and oxygen at pH 7.4 and 37 degrees C, in both the presence and absence of ascorbate (10 mM). The selected concentrations approximate levels within DA neurons. Diethylenetriaminepentaacetic acid (DTPA, 0.1 mM) was used to suppress catalysis by trace metals in the reagents. Separate experiments with catalase showed that oxygen consumption could be equated with the formation of hydrogen peroxide. Depending upon the experimental conditions, ascorbate acted either as an antioxidant, suppressing oxygen consumption (H2O2 production) to 6-8% of the expected rate, or as a prooxidant, amplifying oxygen consumption by 640%. The antioxidant action is consistent with the scavenging of superoxide radicals by ascorbate. The prooxidant action is probably the result of redox cycling of a pre-melanin oxidation product derived from DA. Analyses conducted by high-performance liquid chromatography with electrochemical detection revealed formation of a product with a very low oxidation potential; the product was not 6-hydroxydopamine. These observations may be relevant to concepts of toxicity mediated by DA within neuronal systems.

- Polacheck I, Kwon-Chung KJ
Melanogenesis in Cryptococcus neoformans. J. Gen. Microbiol. 134:1037-1041, 1988.
Abstract : Melanogenesis in C. neoformans begins with the oxidn. of dihydroxyphenylalanine by the enzyme phenol oxidase. The succeeding steps are very rapid. Two intermediates, dopachrome and 5,6-dihydroxyindole, were isolated and characterized by HPLC. A pathway of melanin

formation in C. neoformans is proposed, based on the presence of these intermediates.

- Polewski K, Slawinska D
Fluorescence and phosphorescence of adrenolutin. Physiol Chem Phys Med NMR 19:117-124, 1987.
Abstract : Adrenolutin 3,5,6-trihydroxy-1-methylindole is an intermediate in the metabolism of adrenaline and in the formation of adrenochromo-melanins. Excitation and emission spectra, quantum yield of the adrenolutin fluorescence in water, D2O, ethanol, methanol, acetone and aqueous phosphate buffer at different pH at 293K temperature are reported. Dependence of the quantum yield of adrenolutin on its concentration are measured. Lifetimes of 0.1 mM adrenolutin in water and ethanol are 32.0 +/- 0.2 ns and 9.2 +/- 0.2 ns respectively. Also fluorescence and phosphorescence spectra of adrenolutin in methanol at 110K are obtained. Degrees of polarization and angles between the dipoles for the three main bands absorption of adrenolutin from measurements at 103K are calculated. Adrenolutin may be classified as one of the most strongly fluorescing metabolites. Broad excitation spectrum and high quantum yields make this compound a potential effective acceptor of excitation energy.

- Prota G
Some new aspects of eumelanin chemistry. Prog Clin Biol Res 256:101-124, 1988.

- Senba M, Toda Y, Yamashita H
Black thyroid associated with minocycline therapy: histochemical and ultrastructural studies on the brown pigment. Isr J Med Sci 24:51-53, 1988.
Abstract : The brown pigment found in the black thyroid, associated with minocycline therapy, was studied histochemically and ultrastructurally. The brown pigment was Fontana-Masson silver-positive, and was negative for iron, for autofluorescence under uv illumination, for periodic acid Schiff (PAS) and for acid-fast iodine peroxidase(AFIP) lipofuscin, and was bleached with potassium permanganate. The light and electron microscopic studies suggested that the pigment resembled melanin. Although the mechanism of the pigment deposition is not clear, a possible explanation may be that the pigment is related to direct oxidative degradation products of minocycline.

- Senesi N, Miano TM, Martin JP
Elemental, functional infrared and free radical characterization of humid acid-type fungal polymers (melanins). Biol. Fertil. Soils 5:120-125, 1987.
Abstract : Humic acid-type polymers (melanins) synthesized in culture media by the fungi Aspergillus glaucus, Eurotium echinulatum, Hendersonula toruloidea, Stachybotrys atra, and Aspergillus sydowi were analyzed for elemental compn., functional group content, IR, and ESR. Results were discussed in comparison with range values referred for soil humic acids. The fungal polymers showed significant

differences in carboxyl and N content and C/H at. ratios, reflecting a different degree of condensation (aromaticity) among the various samples. IR anal. gave evidence of the following: (1) the predominant arom. character of melanins from A. glaucus, E. echinulatum, and H. toruloidea; (2) the high content of aliph. and olefinic components of S. atra melanin; (3) the typical presence of amide bonds in the N-richest melanins from A. sydowi and H. toruloidea; and (4) the generally low amt. of free carboxyl groups, which often appeared involved in H bonds. ESR spectra showed that all the melanins studied contained appreciable concns. of org. free radicals of prevailing semiquinonic nature and of the same order of magnitude commonly measured in humic acids from soil and other sources. The free electron concn. was shown to be directly related to the C/H at. ratio and to the degree of aromaticity shown by IR anal. This indicated that the highest free radical content in the melanins from E. echinulatum and A. glaucus was assocd. with the highest presence of condensed arom. structures. Humic acid-type polymers synthesized by soil fungi may, therefore, contribute to the total free radical content of soil humic substances and play important roles in all reactions involving free radicals in soils and related environments.

- Stepien K, Wilczok J, Wilczok T
Model rheomelanins. I. The effect of copper ions on adrenaline, adrenochrome and adrenolutin oxidation. 1988.
Abstract : The oxidative polymn. of adrenaline to model rheomelanins was investigated by dynamics anal. of the reactions involved in this polymer formation in the presence of Cu2+. The transformation of adrenaline to adrenochrome was enhanced by Cu2+. The transformation rate of adrenochrome to adrenolutin was not affected under the exptl. conditions. The disappearance of adrenolutin is faster in the presence of Cu2+.

- Stepien K, Bilinska B, Wilczok T
Model rheomelanins. II. Conversion of adrenaline-copper complexes to melanin polymers. 1988.
Abstract : The products of adrenaline-Cu complex oxidn. were found to be similar in nature to adrenochrome melanin. Using IR and ESR spectroscopy it was demonstrated that polymers formed from these complexes contain Cu ions bound to o-semiquinone groups. The presence of Cu considerably modifies the sorptive properties of the melanins.

- Toda K
Melanin biosynthesis. Nippon Koshohin Kagakkaishi 11:322-326, 1987.
Abstract : A review, with 6 refs., on subcellular organizations and synthetic pathways for biosynthesis of melanin in epidermal melanin-forming cells (e.g., melanocytes) of humans and other mammalians or nonmammalians.

- Tomaselli M
Minor components of hides and skins : the melanins. 1987.

Abstract : The compn. of melanins (eumelanin and feomelanin) as natural org. pigments detg. the color of hides and skins is given. The melanins can be removed from hides during their processing in tanneries by mech. and chem. treatment. The hides contg. dark and black eumelanin can be treated with oxidizing agents, e.g. H2O2 or permanganates, for decreasing the color intensity or removal of the pigment.

- Vsevolodov EB, Zubriyanov AV, Kuchina I, Latypov IF
Determination of pheomelanin in animal wool by ESR. 1987
Abstract : Pheomelanin in animal wool is detd. by recording the EPR spectrum of the wool specimen and detecting and measuring an addnl. peak on the spectrogram with a g-factor of 2.015-2.018. The reliability of the detn. is increased by treating the wool specimen with a strong acid prior to recording of the EPR spectrum.

- Wilczok T, Stepien K, Buszman E, Dworzanski J, Bilinska B, Dzierzewicz Z, Vucelic D, Vucelic V, Simonovic B, Hranisavljevic J
Modern trends in the analysis of melanin structure and function. 1988.

2. BIOLOGY OF PIGMENT CELLS AND PIGMENTARY DISORDERS

- Almendros G, Martin F, Gonzalez-Vila FJ, Martinez AT
Melanins and lipids in Lycoperdon perlatum fruit bodies. Trans. Br. Mycol. Soc. 88:533-537, 1987.
Abstract : After sequential degrdn. with Na2S2O8 and KMnO4, the characteristics of the dark pigments from the soil gastromycete L. perlatum were described. Several arom. acids (phenolic and benzenecarboxylic) were detected by gas chromatog.-mass spectrometry of the degrdn. products, but the aliph. content of these polymer fractions was predominant, contg. a high proportion of protein and showing fatty acids similar to those previously found in the lipid fraction. An acid sol. fraction of melanin, of a highly aliph. nature, was also present in Lycoperdon fruit bodies.

- Boissy RE
The melanocyte. Its structure, function, and subpopulations in skin, eyes, and hair. Dermatol Clin 6:161-173, 1988.
Abstract : I would like to stress that there seem to be three subpopulations of neural crest-derived melanocytes in the body that can be functionally and morphologically distinguished : the cutaneous melanocytes, which continuously synthesize small melanosomes to be transferred to keratinocytes; the uveal melanocytes, which synthesize larger melanosomes for only a short while to be retained by this melanogenically dormant cell; and the hair melanocyte, which intermittently produces melanin either in a cyclic manner or as a periodic supply from a stem population. These three types of melanocytes synthesize melanin granules by an

identical bipartite system. However, the control mechanism regulating the specific differentiation and postmelanin synthesis function of these cell types needs to be addressed in future research.

- Chakraborty DP, Roy S, Chakraborty AK, Rakshit R, Chakravarty A
Profile of stress conditions during induced depigmentation: tryptophan participation in melanogenesis and a composite hypothesis of vitiligo. Med. Sci. Res. 16:21-22, 1988.
Abstract : Hydroquinone inhibited tyrosinase and increased tyrosine aminotransferase and tryptophan pyrrolase in skin and liver of Bufo melanostictus in a model of stress-induced vitiligo. Hydroquinone also elevated the levels of 17-hydroxycorticosterone concomitant with the depigmentation. During the recovery of pigmentation after psoralen treatment, all of the changes except the increased tyrosine aminotransferase were reversed. This may explain why psoralen is not an ideal therapeutic agent in vitiligo. The composite hypothesis of vitiligo, that the disorder is caused by ingestion of foreign inhibitory compds., is discussed.

- Cline DJ
Changes in hair color. Dermatol Clin 6:295-303, 1988.
Abstract : Hair color changes result not only from alterations of melanin production but also from changes in the hair structure itself, altering its optical properties. A variety of genetic, metabolic, nutritional, and acquired disorders result in hair color changes. When the underlying defect can be corrected, hair color usually returns to normal. The flag sign can occur as a result of nutritional insults or due to medications. Most drug-induced changes in hair color result in lighter hair color, although PABA and some chemotherapy regimens have darkened hair. Green hair due to exogenous copper may be associated with prior damage to the hair cuticle. Alopecia areata may selectively involve pigmented hairs. Regrowing white hairs have shown both keratinocyte and melanocyte abnormalities. Gray hair may temporarily darken after inflammatory processes, after electron-beam-induced alopecia, and after some chemotherapy regimens. Much remains to be learned about the physiology of human graying.

- De Simone G
Melanin spots, marbled grain, brine draw, asphalt spots, and metallic stains on leather. 1987.
Abstract : Spots were formed on the surface of raw hide and tanned leather in the presence of melanins, salts used in hide preservation, asphalt particles deposited on the hides during transportation and storage in open spaces, metals, and by contact with tannins during leather tanning. The removal of accidental metal spots (Fe, Pb, Cu, Ni, or Sn) from hides and tanned leather was described.

- Falabella R, Escobar CE, Carrascal E, Arroyave JA
Leukoderma punctata. J Am Acad Dermatol 18:485-494; 1988.

Abstract : Thirteen patients with vitiligo (1 segmental, 4 focal, 8 generalized) aged 7 to 38, most of them female children, developed numerous punctate hypopigmented and achromic spots. The spots measured 0.5 to 1.5 mm and were located primarily on the sun-exposed areas of the extremities; they appeared following treatment with PUVASOL. Two of these patients experienced a reduction of this leukodermic defect, whereas the remaining patients showed a stable clinical course. Dopa and Fontana stains disclosed, in most cases, decreased but not absent functional melanocytes and a marked reduction of melanin. Ultrastructural studies demonstrated slight to severe damage of keratinocytes and melanocytes similar to that previously reported in vitiligo patients. The phototoxic effect of PUVASOL therapy is suggested as a possible etiologic factor in these patients. A probable relationship among idiopathic guttate hypomelanosis, leukoderma punctata, and vitiligo is discussed.

- Hearing VJ, Jimenez M
Mammalian tyrosinase - the critical regulatory control point in melanocyte pigmentation. Int J Biochem 19:1141-1147, 1987.
Abstract : 1. Tyrosinase is a copper-containing enzyme responsible for the production of melanin pigment throughout the phylogenetic spectrum. 2. In mammals, tyrosinase is a glycosylated enzyme found specifically in melanocytes--cells functional in the production and secretion of pigment granules. 3. Although many factors determine the type, quantity and quality of the melanin produced, tyrosinase activity is the critical factor that ultimately regulates melanogenesis.

- Hori Y, Takayama O
Circumscribed dermal melanoses. Classification and histologic features. Dermatol Clin 6:315-326, 1988.
Abstract : Dermal melanosis is caused by deposition of melanin in melanophages or by free melanin in the dermis or in dermal melanocytes. Circumscribed dermal melanoses can be congenital or acquired and at times are nevoid in distribution. Bilateral nevus of Ota-like lesions and blue macules recently have been described in association with progressive systemic sclerosis. Macular amyloidosis and friction melanosis are also acquired dermal melanoses. It is important to distinguish dermal melanoses caused by the presence of melanocytes in the dermis from those produced by the presence of melanin free within the dermis. Clinically, the two different processes may have very similar appearances. Treatments for circumscribed dermal melanoses include cosmetics, cryotherapy, dermabrasion, or, rarely, skin grafts.

- Kermott LH, Timm RM
Scrotal melanins in bats (Chiroptera): description, distribution and function. J. Zool. 214:519-532, 1988.
Abstract : Seventy-two species of bats, representing 49

genera, were examd. for the presence of pigment granules within the scrotal skin, tunica vaginalis, or tunica albuginea surrounding the testis and(or) epididymis. Histol., chem., and spectrophotometric tests were performed, and these confirmed the pigment as melanin. Melanin was found only in the families Pteropidae, Megadermatidae, Myzopodidae, and Vespertilionidae. A strong correlation existed between scrotal pigmentation and roosting in locations where the bats are exposed to solar radiation. Melanin pigmentation in the scrotal region appears to be an adaptation protecting male germinal tissue from the harmful effects of UV radiation. In 1 species, Lavia frons, melanin deposited within the scrotal skin appears to have a social/reproductive communication function.

- King RA, Olds DP, Townsend D
Mechanisms of hypopigmentation in human oculocutaneous albinism. Prog Clin Biol Res 256:183-191, 1988.
Abstract : The synthesis of melanin is ubiquitous in the animal kingdom and is under complex genetic control. Inborn errors of melanin formation, as with other inborn errors of metabolism, provide models to explore this genetic control. Human OCA is a fascinating group of disorders of melanin formation, and careful analysis of each type allows the development of hypothesis on probable mechanisms of development. The broader category of mild to moderate hypopigmentation without all of the features of albinism may ultimately prove to be as important in understanding melanin metabolism.

- King RA, Summers CG
Albinism. Dermatol Clin 6:217-228, 1988.
Abstract : Genetic abnormalities of the melanin pigment system in which the synthesis of melanin is reduced or absent are called albinism. The reduction in melanin synthesis can involve the skin, hair follicle, and eye, resulting in oculocutaneous albinism, or can be localized primarily to the eye, resulting in ocular albinism. Approximately 1 in 17,000 individuals in the United States has oculocutaneous albinism, and more than 1 per cent of the population are heterozygous for a gene producing albinism.

- Mansur CP, Gordon PR, Ray S, Holick MF, Gilchrest BA
Vitamin D, its precursors, and metabolites do not affect melanization of cultured human melanocytes. J. Invest. Dermatol. 91:16-21, 1988.
Abstract : Human newborn foreskin-derived melanocytes were cultured in paired dishes in hormone-supplemented medium with 2% serum contg. no detectable vitamin D3 or in the same medium contg. 10-8 or 10-10M of either provitamin D3, lumisterol, previtamin D3, vitamin D3, 25-hydroxyvitamin D3, or 1,25-dihydroxyvitamin D3. After 10 days, cell no. in cultures contg. vitamin D compds. was 93-140% of unsupplemented controls and melanin content was 60-120% of control, with no significant difference in either parameter for any compd. tested. In sep. expts., human melanocytes and

Cloudman S91 melanoma cells were repeatedly irradiated with physiol. doses of simulated sunlight and incubated between irradiations with provitamin D3, previtamin D3, vitamin D3, or 1,25-dihydroxyvitamin D3. Irradiated cultures had a 90-95% inhibition of cell growth assocd. with a 200-800% increase in melanin content per cell relative to controls, but there was no effect of any vitamin D compd. on either cell type. Neither cultured human melanocytes nor S91 cells showed evidence of the cytosolic 1,25-dihydroxyvitamin D3 receptor binding by sucrose d. gradient anal. with radiolabeled 1,25-dihydroxyvitamin D3. Apparently, neither vitamin D3 nor its precursors or metabolites directly mediate melanogenesis in these cells.

- Negishi S, Kawazoe I, Kawauchi H
A sensitive bioassay for melanotropic hormones using isolated medaka melanophores. Gen Comp Endocrinol 70:127-132, 1988.
Abstract : Melanophore-stimulating hormones (MSHs) from chum salmon cause pigment dispersion in isolated melanophores of medaka, a teleost. The in vitro medaka melanophore bioassay that responded to light with pigment dispersion and to the dark with pigment aggregation was utilized for measuring the activity of melanotropic hormones. Alpha-MSH I was the most potent melanophore-dispersing agent tested. The minimal dose for the induction of pigment dispersion was 10(-15) M alpha-MSH I, 10(-13) M N-des-acetyl(Ac)-alpha-MSH, and 10(-11) M beta-MSH I, respectively. The melanosome-dispersing activity of beta-MSH I was enhanced about 40% by salmon N-acetyl-endorphin I (N-Ac-EP). The results suggest that N-Ac-EP may act as an enhancer for the activity of certain MSHs. The present bioassay provides a unique method for determining the biological activity of melanotropic peptides.

- Nimmo JE, Gawkrodger DJ, O'Docherty CS, Going SM, Percy-Robb IW, Hunter JA
Plasma 5-S-cysteinyldopa as an index of melanogenesis. Br J Dermatol 118:487-495, 1988.
Abstract : Plasma 5-S-cysteinyldopa (5-S-CD) concentration measured in healthy volunteers in Edinburgh, Scotland (latitude 56 degrees N) showed only minor changes during the day. However, when measurements were performed over a 12-month period a significant rise in 5-S-CD concentration was found. Skin pigmentation and hair colour were not related to plasma 5-S-CD levels. Patients with psoriasis treated with ultraviolet-B or photochemotherapy (PUVA) developed an almost two fold increase in their plasma 5-S-CD level within the first five treatments, before pigmentation developed, subsequent increments of up to four times the pretreatment level being found in the PUVA group. Dithranol treatment caused an increase in plasma 5-S-CD in some psoriatic patients, suggesting a possible association between skin erythema and elevated 5-S-CD levels. The value of plasma 5-S-CD in the follow-up of patients with malignant melanoma does not seem to be invalidated by unavoidable exposure of the subjects to sunlight in a temperate climate

such as that of South East Scotland.

- Ortonne JP
Piebaldism, Waardenburg's syndrome, and related disorders. "Neural crest depigmentation syndromes"? Dermatol Clin 6:205-216, 1988.
Abstract : The striking parallel between the melanin pigmentary abnormalities of the hair and skin in piebaldism, Waardenburg's syndrome, piebaldism with deafness, and piebaldism or Waardenburg's syndrome with aganglionosis of the gut suggests that all these disorders belong to the same category. At present, the most logical way to link these syndromes is to consider them the results of defective development of the neural crest. The reason that in certain circumstances only melanoblasts are affected whereas in other situations other neural crest derivatives also are involved is not yet clear. In addition, some features, such as the upper limb abnormalities observed in Klein's syndrome, are not explained by a neural crest defect. Our knowledge of the interaction between the neural crest and neighboring structures closely related to it during embryonic life is limited. Some clues allowing us to better understand these complex syndromes combining depigmentation of hair and skin will come from future research in this field.

- Ortonne JP
Chemical and drug induced hypermelanoses. Prog. Clin. Biol. Res. 256:247-259, 1988.
Abstract : A review and discussion with 17 refs. on drug- and chem.-induced melanotic and melanocytic hypermelanoses, drug- and chem.-induced mixed hyperpigmentation, and drug- and chem.-induced dermal hypermelanoses.

- Pawelek J, Bolognia J, McLane J, Murray M, Osber M, Slominski A
A possible role for melanin precursors in regulating both pigmentation and proliferation of melanocytes. Prog Clin Biol Res 256:143-154, 1988.

- Podymova NG, Kovalev IE, Zherebin YL, Andronati SA
Immunopharmacological study of enomelanin, a natural antioxidant. 1988
Abstract : Enomelanin possesses immunodepressive activity in mouse expts. at doses of 25-240 .mu.g/kg. Under the same conditions the drug increased the time of hexenal sleep of mice, probably inhibiting mouse R-450 cytochrome-dependent monooxygenase system. In vitro, the drug used in low doses enhanced the interaction of immune mouse spleen mononuclear cells with an antigen, while that given in high doses suppressed the interaction.

- Ranalli A
Effect of catechol melanin pigment on the pollution load of olive oil-mill wastewater. Inquinamento 29:40-43, 1987.
Abstract : The coloration of olive oil mill wastewaters is mainly due to a catechol melanin-type brown pigment.

Oxidative treatment with H2SO5 removed .ltoreq.38% and .ltoreq.93.6% of the COD and phenolic compds., resp.

- Riddiford LM, Hiruma K
Regulation of melanization in insect cuticle. Prog Clin Biol Res 256:423-436, 1988.
- Scalia M, Geremia E, Corsaro C, Santoro C, Sciuto S, Sichel G
The extracutaneous pigmentary system: evidence for the melanosynthesis in amphibia and reptilia liver. Comp. Biochem. Physiol., B: Comp. Biochem. 89B:715-717, 1988.
Abstract : In vitro incorporations of L-[14C]tyrosine and L-[14C]DOPA into purified melanin, extd. from frog and turtle liver after incubation of surviving tissue and purified melanosomes were measured. The results show an incorporation of labeled precursors in melanin both in incubating tissue slices and incubating isolated melanosomes and that the radioactivity detected in purified melanin was not due to an adsorption or binding phenomenon of labeled tyrosine. Thus, melanins occurring in the pigment cells of amphibian and reptile liver originate from the melanosynthetic activity of Kupffer cells and these pigment cells are to be considered as belonging to the extracutaneous pigmentary system.

- Sciuto S, Chillemi R, Patti A, Sichel G, Scalia M
Melanosomes from liver and skin of Rana esculenta L. a comparative chemical study. Comp. Biochem. Physiol., B: Comp. Biochem. 90B:397-400, 1988.
Abstract : Melanosomes from skin and liver of R. esculenta were isolated and some chem. properties of the relevant melanin and protein components were compared. In both cases the pigments show spectroscopic (ESR) and chem. characteristics similar to those of eumelanins. The melanin content in skin melanosomes is higher than in the liver counterparts. Amino acid patterns of the 2 protein components are different in their quant. compn. and both are characterized by high levels of glycine and proline. Thus, skin and liver melanosomes from the same animal markedly differ in their chem. compn.

- Shimizu T, Ando H, Hashimoto A, Makino T, Sakamura S
Skin-whitening cosmetics containing dioctyl phthalate. 1987.
Abstract : A skin-whitening cosmetic comprises 0.01-50% by wt. dioctyl phthalate (I). I inhibits the prodn. of melanins. The addn. of I at 5 .mu.g/mL in a melanoma cell-contg. culture bleached the melanins. A lotion contained EtOH 10.00, PVP 0.05, oleyl alc. 0.10, polyoxyethylene sorbitan monolaurate 1.20, propylene glycol 5.00, I 0.10% by wt., a perfume q.s., a preservative q.s., and water (balance).

- Slominski A, Moellmann G, Kuklinska E, Bomirski A, Pawelek J
Positive regulation of melanin pigmentation by two key substrates of the melanogenic pathway, L-tyrosine and L-dopa. J. Cell Sci. 89:287-296, 1988.
Abstract : L-Tyrosine and L-DOPA, the metabolic fates of

which are affected by the activity of the melanogenic pathway, can also act as its regulators. Supplementary Ham's F-10 medium with addnl. L-tyrosine or L-DOPA during the culture of amelanotic Bomirski hamster melanoma cells results in a rapid increase in melanin formation, which is not simply due to greater availablity of substrate. There is a rapid increase in tyrosinase (EC 1.14.18.1) activity and a large-scale synthesis of melanosomes. The effects of L-tyrosine and L-DOPA are prevented by the addn. of cycloheximide. The actions of L-tyrosine and L-DOPA are specific in that under similar conditions D-tyrosine, D-DOPA, N-acetyl-L-tyrosine, L-phenylalanine, L-tryptophan, and L-valine have little or no effect. The 2 substrates, L-tyrosine and L-DOPA, appear to act through related but distinct mechanisms. These findings provide an example of a little-known phenomenon: regulation of a differentiated eukaryotic phenotype through pos. control by substrates in the pathway.

- Stepien K, Porebska M, Wilczok T
Interaction of chloroquine with melanosomes and model melanin-protein complexes. 1988
Abstract : The interaction of chloroquine with intact melanosomes isolated from cattle eyes, melanosomes treated with protein solubilizing agents, melanin granules, and DOPA melanin-human serum albumin complexes, was studied to det. the effect of proteins on ligand binding in melanosomes. The proteins present in melanosomes or model melanin-protein complexes did not shield the chloroquine binding sites in the melanin mols. Thus, the interaction of chloroquine with melanosomes depends on the melanin content in the melanosomes.

- Szabo G, Hirobe T, Flynn EA, Garcia RI
The biology of the melanocyte. Prog Clin Biol Res 256:463-474, 1988.

- Shirama K, Harada T, Kohda M, Hokano M
Fine structure of melanocytes and macrophages in the Harderian gland of the mouse. Acta Anat (Basel) 131:192-199, 1988.
Abstract : The presence of dendritic cells containing melanin granules has been demonstrated employing silver impregnation and electron microscopy in the interstitial tissue of the Harderian gland of the mouse. Two types of melanocytes, either with or without the various developmental stages of melanin granules, were found in the gland. Cells with developing granules were more dendritic and contained a large number of cytoplasmic organelles. The other cells were ellipsoidal or slender in shape and contained few cytoplasmic organelles and a large number of fully melanized granules, but no developing granules. In general, the granules of the Harderian gland melanocytes resembled granules from other organs (particularly the skin of the eyelids). The general size range of the granules was 0.2-0.9 micron. Each granule was enclosed by a membrane. The Harderian gland macrophages

contained fully pigmented melanin granules of various sizes. The granules were enclosed by a membrane either singly or in groups. Some of the melanin granules within the phagosomes showed signs of degradation, revealing the underlying matrix.

- Telegina TA, Pavlovskaya TE
Catalysts of the melanin-melanoidin type in the abiogenesis of peptides. Izv. Akad. Nauk SSSR, Ser. Biol. 112-117, 1988.
Abstract : A review with 25 refs., on the possible role of melanin- and melanoidin-type catalysts in abiotic peptide formation. These compds. have been obsd. to form in AcH/NH4+ salt systems and to display photoprotective and catalytic activities. Melanin-melanoidin polymers formed abiotically are suggested to have played an important role in the prebiotic synthesis of peptides.

- Varotti C, Metri M, Masina M, Neri I, Passarini B
Fluorescence of cells with melanogenetic activity. G Ital Dermatol Venereol 122:539-541, 1987.

3. MSH, OTHER HORMONES, DIFFERENTIATION

- Baker BI
Relative importance of MCH and MSH in melanophore control. Prog Clin Biol Res 256:505-515, 1988.

- Batten TFC, Baker BI
Melanin-concentrating hormone (MCH) immunoreactive hypophyseal neurosecretory system in the teleost Poecilia latipinna: light and electron microscopic study. Gen. Comp. Endocrinol. 70:193-205, 1988.
Abstract : Neurons contg. immunoreactivity for melanin-concg. hormone (MCH) were located in the brain in the teleost P. latipinna by light microscopic (peroxidase antiperoxidase) and electron microscopic (immunoAu) methods. Neuronal cell bodies contg. MCH-immunoreactive granules .ltoreq.150 nm in diam. were found in the tuberal hypothalamus, mostly within the nucleus lateralis tuberis, pars lateralis. Bundles of immunoreactive fibers were traced through the preoptic area as far forward as the olfactory bulb, and through the posterior hypothalamus up into the pretectal thalamus and midbrain. The main projection was, however, to the neurohypophysis, where MCH fibers were obsd. to form contacts with pituicytes, basement membranes around blood vessels, and the endocrine cells of the pars intermedia. Occasionally MCH-immunoreactive terminals were also seen near the corticotrophs of the rostral pars distalis. These results support the hypothesis that MCH may act as a systemic hormone, a central neurotransmitter, and a modulator of pituitary function.

- de Lauro C
Melanin concentrating hormone (MCH) control of

chromatophores. Prog Clin Biol Res 256:547-557, 1988.

- Giuffre L, Schreyer M, Mach JP, Carrel S
Cyclic AMP induces differentiation in vitro of human melanoma cells. Cancer 61:1132-1141, 1988.
Abstract : Treating human melanoma lines with dibutyryl adenosine 3':5'-cyclic monophosphate (dbc AMP) resulted in morphologic changes associated with the altered expression of cell surface antigens. After treatment, cells developed long cellular projections characteristic of mature melanocytes and showed the presence of an increased number of Stage II premelanosomes. In addition, induction of melanin synthesis, detected as brown perinuclear pigmentation, was observed. The AMP further drastically reduced the growth rate of the five melanoma cell lines that were tested. The influence of dbc AMP was completely reversible 3 days after the agent was removed from the culture medium. The antigenic phenotype of the melanoma lines was compared before and after dbc AMP treatment. This was done with four monoclonal antibodies directed against major histocompatibility complex (MHC) Class I and II antigens and 11 monoclonal antibodies defining eight different melanoma-associated antigenic systems. Treatment with dbc AMP reduced the expression of human leukocyte antigen (HLA)-ABC antigens and beta-2-microglobulin in five of five melanoma lines. In the two HLA-DR-positive cell lines dbc AMP reduced the expression of this antigen in one line and enhanced it in the other. No induction of HLA-DR or HLA-DC antigens was observed in the Class II negative cell lines. Furthermore, dbc-AMP modulated the expression of the majority of the melanoma antigenic systems tested. The expression of a 90-kilodalton (KD) antigen, which has been found to be upregulated by interferon-gamma, was markedly decreased in all the five cell lines. A similar decrease in the expression of the high molecular weight proteoglycan-associated antigen (220-240 KD) was observed. The reduced expression of Class I and II MHC antigens as well as the altered expression of the melanoma-associated antigens studied were shown to be reversible after dbc AMP was removed. Our results collectively show that the monoclonal antibody-defined melanoma-associated molecules are linked to differentiation. They could provide useful tools for monitoring the maturation of melanomas in vivo induced by chemical agents or natural components favoring differentiation.

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Melanin concentrating hormone (MCH) mechanisms of action. Prog Clin Biol Res 256:531-545, 1988.

- Hitselberger MH, Schleicher RL, Beattie CW
Effects of estradiol on estrogen receptor, progesterone receptor, and tyrosinase in hamster melanoma transplanted into athymic mice. Cancer Res 48:3720-3727, 1988.
Abstract : Nuclear estrogen binding was characterized in HM-1, a malignant hamster melanoma cell line transplanted into male and female athymic mice following acute,

subchronic, and chronic injection of estradiol. Nuclear binding was saturable, of high affinity (10(10) M-1) and readily soluble in low salt buffer. Saturation analyses revealed that [3H]estradiol in excess of 5.0 nM apparently bound to a second class of lower affinity (10(9) M-1), higher capacity cytosol sites. Enzyme-linked immunoassay with a specific monoclonal antibody (H222 Sp gamma) directed against the human estrogen receptor protein was in excellent agreement (r = 0.93) with values obtained using hydroxyapatite to separate bound from free ligand. Nuclear estrogen receptor content in HM-1 cells was increased maximally 1 h after acute s.c. injection of a low dose (0.1 microgram) of estradiol. The increase in nuclear receptor content was accompanied by an apparent rapid reduction in cytosol binding. Subchronic (3 days) and chronic exposure (35 days) to estradiol also produced a significant, dose-related increase in tumor nuclear estrogen receptor content. Cytosol binding for progestin was low (less than or equal to 2 fmol) to absent in HM-1 xenografts not exposed to estradiol. Subchronic and chronic exposure to estradiol induced a dose-related, specific, high affinity (10(9) M-1) cytosol binding protein for progestin(s) in HM-1 xenografts carried in male and female athymic mice. In contrast, progestin binding to nuclear receptor was not increased in estrogen-primed animals, nor did acute injection of progesterone (100 micrograms s.c.) increase the amount of saturable, high affinity (10(9) M-1) nuclear progestin receptor in control or estradiol-primed athymic mice. In contrast to the induction of progestin binding, tyrosinase activity was not altered by a similar exposure to estradiol when assayed at a saturating concentration of tyrosine. These observations suggest that the estrogen receptor in HM-1 cells may be functional but that pigmentary changes observed in mammals following chronic exposure to estradiol may not be mediated by a direct effect on the rate limiting enzyme of melanin synthesis.

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Structure-activity studies on melanin-concentrating hormone.
Prog Clin Biol Res 256:517-530 , 1988.

- Kishida M, Baker BI, Bird DJ
Localization and identification of melanocyte-stimulating hormones in the fish brain. Gen.Comp.Endocrinol. 71:229-242, 1988.
Abstract : The existence of MSH in fish brains was investigated by a range of techniques : RIA, HPLC, bioassay, and immunocytochem. Immunoreactive alpha.MSH (ir.alpha.MSH) was detected by RIA in all regions of carp and trout brains, with the highest concn. in the asal hypothalamus. In trout, ir.alpha.MSH cell bodies were located by immunocytochem. only periventricularly, in the medial basal hypothalamus near the third ventricle, whereas in the carp ir.alpha.MSH staining was seen both in periventricular cells and also in some of the magnocellular neurons in the lateral hypothalamus. When white-adapted fish were transferred to a black tank for 6

days, the melanin-concg. hormone (MCH) content of the basal hypothalamus of both carp and trout increased 2- and 4.6-fold, resp., but the .alpha.MSH content did not change in either species. Anal. by HPLC of pituitary gland, hypothalamic, and optic tectal exts. revealed that the pituitary contains desacetyl, monoacetyl, and diacetyl .alpha.MSH, although the ratio of these forms differed in the 2 species. The hypothalamus and optic tectum, however, contained predominantly the desacetyl form of .alpha.MSH. Bioassays for MSH in the HPLC fractions revealed the existence of presumptive .beta.MSH in both the pituitary and hypothalamus. An argument is advanced that the periventricular ir.alpha.MSH neurons are homologous with the proopiomelanocortin cells of the arcuate nucleus in mammals, and that the immunocytochem. alpha.MSH-like activity in the MCH neurons may not be authentic alpha.MSH.

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Melanin concentrating hormone analogues : contraction of the cyclic structure. 1. Agonist activity. J Med Chem 31:949-954, 1988.
Abstract : Melanin concentrating hormone (MCH) is a heptadecapeptide, Asp-Thr-Met-Arg-Cys-Met-Val-Gly-Arg-Val-Tyr-Arg-Pro-Cys-Trp-Glu-Val, which is synthesized in the hypothalamus and secreted by the neurohypophysis of teleost fishes. This hormone exhibits both MCH-like as well as alpha-MSH (alpha-melanocyte stimulating hormone) like activity. We have examined the role of the disulfide bond for the two contrasting melanotropic activities of MCH. Nine analogues of the parent peptide were synthesized and characterized for biological activity. The disulfide ring was contracted from the 5-14 to the 7-14, 8-14, and 10-14 residues with concomitant substitution of alanine for Cys at position 5 in each ofthe heptadecapeptides. Similar substitutions were made in a series of MCH analogues. In addition, the following cyclic peptides also were synthesized: [Cys7]MCH, [Cys8]MCH, and [Cys10]MCH. The fish-skin bioassay is sensitive to MCH at a concentration of 10(-12) M. All ring-contracted analogues were inactive at 10(-6) M or lower concentrations; less than 1/1,000,000 compared to MCH (1.0) except [Ala5,Cys8]MCH (0.0008; 1/1250), [Cys10]MCH (0.000 09; 1/10,000), and [Cys8]MCH (0.000 001; 1/1,000,000). In the frog-skin bioassay, [Ala5,Cys10]MCH, although lacking MCH-like activity in the fish-skin bioassay, was equipotent to MCH in its alpha-MSH-like component of activity. Most other analogues were either inactive or much less active than MCH in stimulating melanosome dispersion. These results demonstrate that the disulfide bond between positions 5 and 14 is essential for the MCH-like activity since contraction of the ring generally leads to inactive peptides. Contraction of the disulfide bridge does not, however, have as great an effect on the MSH-like activity of MCH.

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Purification and characterization of melanization and reddish

coloration hormone (MRCH) in lepidopteran insects. Prog Clin Biol Res 256:437-451, 1988.

- Powell KA, Baker BI
Structural studies of nerve terminals containing melanin-concentrating hormone in the eel, Anguilla anguilla. Cell Tissue Res 251:433-439, 1988.
Abstract : Eels were adapted to black- or white-coloured backgrounds and the pituitary glands were prepared for light and electron microscopy. Immunocytochemical staining was used to study the distribution of the neurohypophysial melanin-concentrating hormone in the neurointermediate lobe. The hormone was located in small, elliptical, electron-opaque neurosecretory granules, measuring approximately 120 x 90 nm. The neurones terminated on blood vessels in the centre of the neurohypophysis and on the basement membrane separating neural and intermediate lobe tissues. The results of both light and electron immunocytochemistry and of radioimmunoassay are consistent with a higher rate of hormone release from eels adapted to white backgrounds than from those adapted to black backgrounds. In addition to this, when fish that had been adapted to white tanks were transferred to black tanks, there was an accumulation of irMCH in the gland and an increased numerical density of secretory granules at nerve terminals. These results reinforce the proposal that MCH is released during adaptation to a white background, to cause melanin concentration and to inhibit MSH release, and that its release is halted in black-adapted fish.

- Schoofs L, Jegou S, Andersen AC, Tonon MC, Eberle AN, Huybrechts R, De Loof A, Vaudry H
Coexistence of melanin-concentrating hormone and alpha-melanocyte-stimulating hormone immunoreactivities in the central nervous system of the locust, Locusta migratoria. Brain Res. 450:202-208, 1988.
Abstract : The distribution of melanin-concg. hormone (MCH) in the central nervous system of the locust L. migratoria was studied by the indirect immunofluorescence technique, by using antibodies against salmon MCH. Most MCH-immunoreactive perikarya were found in the optic lobes at both sides of the brain, dorsally with respect to the lamina ganglionaris. The same neurons also contained alpha-MSH-like material. In addn., a moderate no. of MCH-like neurons, which were devoid of alpha-MSH-immunoreactive substances, were obsd. in the pars intercerebralis. Bright immunofluorescent fibers were visualized in various regions of the central nervous system of the locust: the optic lobes, the ocelli, the proto- and deuterocerebrum, the subesophageal connectives, and the corpora cardiaca. In the ventral nerve cord and the subesophageal ganglion, where alpha-MSH-like cell bodies were encountered, MCH-immunoreactive perikarya were absent and immunoreactive fibers were scarce. The coexistence of MCH and alpha-MSH-immunoreactive material within the same specific neurons might indicate an evolutionary relationship of both peptides.

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Melanins and their importance in pathogenic fungi. Curr Top Med Mycol 2:338-387, 1988.

4. PHOTOBIOLOGY AND PHOTOCHEMISTRY

- Bielec J, Pilas B, Sarna T, Knox C, Truscott TG
Photosensitisation of melanins covalently bound to dyes. 1988
Abstract : The effects of binding to melanin of 2 synthetic dyes, 5-(4,6-dichloro-1,3,5-triazin-2-yl)aminoerythrosin (AE) and 5-(4,6-dichloro-1,3,5-triazin-2-yl)aminofluorescein (AF) in terms of dye fluorescence, dye triplet quantum yield, the rate of photosensitized O consumption, and the rate of photosensitized prodn. of melanin free radicals are reported using steady-state fluorescence, laser flash photolysis, and ESR techniques. The dyes react as though they are bound near the surface of the polymeric melanin and the results involving singlet O formation and consumption may suggest a melanin site-specific interaction.

- Chedekel MR, Zeise L
Sunlight, melanogenesis and radicals in the skin. Lipids 23:587-591, 1988.
Abstract : A review, with 56 refs., on melanin formation by melanocytes, melanins and photoprotection, and melanin metabolites and their photochem. behavior. The photobiol. of melanogenic intermediates is discussed.

- Forlot PE
Pigmentogenic effects of psoralens. NATO ASI Ser., Ser. H 15:241-244, 1988.
Abstract : The enhancement of skin pigmentation by psoralen plus sunlight is examd. and the resulting photoprotection of skin is discussed.

- Kollias N, Bager A
Melanin and photoprotection. NATO ASI Ser., Ser. H 15:235-239, 1988.
Abstract : The role of melanin in skin photoprotection is examd. by comparing the minimal erythema dose (MED) to UVB in Mediterranean skin type and psoriatic patients to that in Caucasian subjects. Melanin levels were apprx.3-fold higher in Mediterranean skin types and skin cancer incidence lower by a factor of 29 than in Caucasians. Only a weak correlation between MED and pigment level was obsd. by monochromatic or broadband UVB radiation.

- Kollias N, Bager AH
Quantitative assessment of UV-induced pigmentation and erythema. Photodermatol 5:53-60, 1988.
Abstract : In this paper we present methods that we have developed to measure pigmentation in human skin. This involves the measurement of diffuse reflection spectra from

human skin in vivo and referencing them to either totally depigmented skin, or the skin of the same individual if we are measuring variations in pigmentation. Changes in the pigmentary system brought about by UV radiation can be measured for each individual. Absolute measurements lead to estimates of the melanin concentration in the skin, while differential measurements lead to estimates of the quantity of additional or reduced pigment content of some skin lesions. The same instrumentation has been successfullyused to assess UV-induced erythema as well as other vascular changes. The determination of the minimum detectable erythema dose can be performed even in the darkest-skinned subjects without loss of sensitivity as in the case of laser Doppler instruments. It has been shown that what is perceived by the eye as erythema is a very complexphenomenon, encompassing a large number of vascular reactions that can be studied in detail through diffuse reflection spectroscopy. Some of the possible responses are presented, as well as the contributing chromophores that have been identified so far.

- Menon IA, Ranadive NS, Shirwadkar S, Persad S, Haberman HF
Role of melanins and drugs in cutaneous photosensitivity.
NATO ASI Ser., Ser. H 15:249-252, 1988.
Abstract : The effects of irradn. of skin sites injected with photosensitizers or melanin were studied with respect to vascular permeability and neutrophil accumulation. Irradn. increased both parameters in the presence of rose bengal and pheomelanin. The mechanisms of actinic damage mediated by the photobiol. properties of pheomelanin are briefly discussed.

- Persad S, Menon IA, Basu PK, Carre F
Phototoxicity of chlorpromazine on retinal pigment epithelial cells. Curr Eye Res 7:1-9, 1988.
Abstract : As it is known that chlorpromazine (CPZ) can bind to melanins as well as cause ocular phototoxicity, we investigated the cytotoxic effects of UV-visible irradiation of melanotic and amelanotic retinal pigment epithelial (RPE) cells in the presence of CPZ. At low concentrations (5 micrograms/ml) of CPZ a photosensitization reaction took place which lysed the cells as measured by the release of 51Cr from cells labelled with chromium. At concentrations of CPZ less than 5 micrograms/ml, no significant cell lysis occurred when the cells were incubated at 37 degrees C in the dark. As the concentration of CPZ was increased to 25 micrograms/ml or more, high percentages of cells were lysed. When the melanotic RPE cells were exposed to different concentrations of CPZ and grown in culture, the cell growth (multiplication) diminished drastically with low concentrations (less than 2 micrograms/ml CPZ). Vitamin E decreased the cell lysis both in the dark and upon irradiation. Oxygen radical scavengers such as glutathione, B-carotene, mannitol, D-penicillamine as well as superoxide dismutase and catalase did not decrease cell lysis. The phototoxic effects of CPZ was found not to be due to stable photoproducts formed during irradiation of CPZ.

- Tomita Y, Torinuki W, Tagami H
Stimulation of human melanocytes by vitamin D3 possibly mediates skin pigmentation after sun exposure. J. Invest. Dermatol. 90:882-884, 1988.
Abstract : An increased amount of immunoreactive tyrosinase was found in human melanocytes after 6-day culturing with vitamin D3 (cholecalciferol). Most of these melanocytes became more dendritic and swollen in a fashion similar to that noted in the skin after UV irradn. However, 7-dehydrocholesterol (pro-vitamin D3) or alpha.,25-dihydroxyvitamin D3 (activated vitamin D3) had little effect on the same system. Because vitamin D3 is known to be photochem. converted from pro-vitamin D3 in the skin by UV irradn., the mechanism of human skin pigmentation after UV irradn., thus far unknown, maybe at least partly explained by this stimulating effect of vitamin D3 on melanocytes.

- Young RW
Solar radiation and age-related macular degeneration. Surv Ophthalmol 32:252-269, 1988.
Abstract : Age-related macular degeneration (AMD) involves a progressive impairment of the outer layers in the center of the retina. Experimental studies have demonstrated that bright light preferentially damages precisely the region that degenerates in AMD. The evidence that solar radiation is responsible for some of the deteriorative changes that lead to AMD is examined in this review. In the primate eye, the high-energy portion of the solar spectrum is most hazardous to retinal molecules, with damaging effects increasing as photon energy rises. This action spectrum is explicable by the quantum laws which describe the interaction of radiation with matter. High-energy visible and ultraviolet photons can produce molecular damage by a photochemical mechanism. The lesion is exacerbated by oxygen, which initiates free-radical chain reactions (photodynamic effects). Melanin exerts a protective effect against damage from sunlight. In the human retina, documented lesions from solar radiation range from the acute effects of sun-gazing to injuries resulting from prolonged periods of exposure in brightly illuminated environments. The damage occurs in the same region that degenerates in AMD. A cataractous lens and ocular melanin both protect the retina against AMD, as predicted by the radiation hypothesis. Identification of an environmental factor that evidently plays a role in the etiology of AMD provides the basis for a program of preventive medicine.

5. NEUROMELANINS

- Issidorides MR, Pappas GD
Fine structure of neuronal spherical arginine-rich bodies of substantia nigra and locus coeruleus in the human brain. Hum Neurobiol 6:239-246, 1988.

Abstract : Neuronal spherical bodies, rich in arginine, of catecholamine neurons in man display staining reactions of mitotic chromosomes and myelin basic protein. They show a unique fine structure and density in the EM after phosphotungstic acid hematoxylin block-staining. With an electron-lucent core, a dense rim and a limiting double membrane they stand out and are differentiated from all other neuronal inclusions, especially melanin. Protein bodies were found inside mitochondria, where they apparently originate as small globules in the matrix. They later enlarge into spheres by obliterating the cristae, but retaining the outer membranes of the parent mitochondrion. The arginine-rich basic protein of the spherical bodies, it is argued, may be involved in the modulation of excitability of the catecholamine neurons in man.

- Jurecka W, Mainitz M, Gebhart W, Metze D, Bruck HG, Kofler K
Pigmented neurofibroma. Hautarzt 39:166-169, 1988.
Abstract : In a 24-year old male melanin synthesis was demonstrated in a neurofibroma by light and electron microscopy.. Although it is unclear whether the tumor cells are pigment-synthesizing Schwann cells or whether they originate from a coexisting melanocytic tumor, this tumor again demonstrates the close relationship between peripheral nerve sheath tumors and melanocytic malformations, as for example cellular blue nevi.

- Kopin IJ, Markey SP
MPTP toxicity : implications for research in Parkinson's disease. Annu Rev Neurosci 11:81-96, 1988.
Abstract : In summary, the parkinsonism induced by MPTP in man closely resembles time-telescoped Parkinson's disease. Parkinsonian symptoms can be duplicated in all aspects under controlled conditions in subhuman primates; the biochemical changes are replicated in mice, dogs, and to varying degrees in other species. Mechanisms of bioactivation by MAO-B of MPTP to MPP+, concentration of MPP+ in neurons with a catecholamine uptake system, and vulnerability to cellular toxic effects of MPP+ are the basis for the specificity of MPTP targeting of nigrostriatal dopaminergic neurons. It is hoped that an understanding of the mechanism of species specificity and cellular toxicity will in time explain the pathogenesis of idiopathic Parkinson's disease and suggest new opportunities for effective therapy.

6. GENETICS

- Carefoot WC
Evidence that the mottled (mo) and pied (pi) plumage genes of the domestic fowl are identical. Br Poult Sci 28:753-754; 1987.
Abstract : 1. An investigation was conducted among the

progeny from crosses between Exchequer Leghorn and Ancona bantams into the relationship between two plumage phenotypes, pied and mottled, both of which are arrangements of non-pigmentation expressed on a background of eumelanin. 2. Both the pied and mottled phenotypes had previously shown to be caused by recessive genes, denoted pi and mo respectively. 3. The progeny consisted entirely of intermediaries between the two parental phenotypes, indicating that pi and mo are one and the same gene for which I retain the symbol mo.

- Kwon BS, Halaban R, Kim GS, Usack L, Pomerantz S, Haq AK
A melanocyte-specific complementary DNA clone whose expression is inducible by melanotropin and isobutylmethyl xanthine. Mol Biol Med 4:339-355: 1987.
Abstract : Two groups of cDNA clones were isolated by screening a lambda gt11 cDNA library of normal human melanocytes with antityrosinase antibodies : one group of 13 was related to the human tyrosinase gene. The properties of the other group of three cDNA clones was investigated by the use of a representative clone, Pmel 17-1. The cDNA hybridized to an mRNA species of approximately 2600 bases from human and murine melanocytes. The transcript of Pmel 17-1 (17-1 mRNA) was expressed preferentially in melanocytes and its abundance paralleled the melanin content. The expression of Pmel 17-1 mRNA increased after stimulation of human and murine melanoma cells with agents that increase the levels of melanization. Immunocompetition assays with monoclonal antibodies to gp75, a known pigmentation-associated antigen of melanocytes, suggested that Pmel 17-1 encodes a 75,000 Mr glycoprotein that is highly abundant in melanotic cells and shares some immunological homology with tyrosinase. The gene for Pmel 17-1 did not map at or near the c-albino locus in mice. The cDNA of Pmel 17-1 detected a single hybridizing restriction fragment in both human and murine DNA, indicating that the gene has been conserved between these two species and exists as a single gene in each.

- Woolf CM, Swafford JR
Evidence for eumelanin and pheomelanin producing genotypes in the Arabian horse. J. Hered. 79:100-106, 1988.
Abstract : The ultrastructural imaging of melanocytes coupled with analyses to detect S-contg. melanosomes by energy-dispersive x-ray spectroscopy were used to test the hypothesis that the yellowish-red and black pigments found in Arabian horses result from pheomelanogenesis and eumelanogenesis, resp. These procedures detected pheomelanosomes in follicles at the base of hairs in chestnut horses and eumelanosomes in follicles at the base of hairs in black horses. By analyzing tissue obtained by skin biopsy, these procedures also demonstrated that skin melanocytes in a chestnut horse produce eumelanosomes, and follicular melanocytes in the same horse produce pheomelanosomes. It was also shown that the type of follicular melanosome present in light bay horses is correlated with the color of the hair. The results of this study give exptl. evidence for the

Odriozola-Adalsteinsson hypothesis that the e allele is responsible for the chestnut phenotype; they also give fine structure and chem. confirmation of the action of the A and E loci in the Arabian horse as currently proposed for the mouse and other mammals.

7. TYROSINASE AND OTHER ENZYMES

- Jimenez M, Kameyama K, Maloy WL, Tomita Y, Hearing VJ
Mammalian tyrosinase : biosynthesis, processing, and modulation by melanocyte-stimulating hormone. Proc Natl Acad Sci U S A 85:3830-3834, 1988.
Abstract : We have examined the rate of synthesis and degradation of tyrosinase (monophenol, 3,4-dihydroxyphenylalanine : oxygen oxidoreductase, EC 1.14.18.1), the critical enzyme involved in mammalian pigmentation, using pulse-chase metabolic labelling of murine melanoma cells and immunoprecipitation of protein extracts with antibodies directed specifically against the enzyme. We have found that tyrosinase is synthesized and glycosylated within melanocytes rapidly, since significant quantities of pulse-labeled enzyme could be detected within 30 min. The maximum amount of enzyme was processed within 4 hr, and the t1/2 of tyrosinase in vivo was 10 hr (compared to 120 hr with purified enzyme), suggesting that tyrosinase activity in melanocytes is at least in part regulated by rapid synthesis and active degradation. We also have examined the melanogenic stimulation caused by melanocyte-stimulating hormone, using metabolic labeling, radiometric assays, and immunofluorescence techniques; responding cells increased their melanogenic potential more than 7-fold within 4 days without increasing their levels of tyrosinase synthesis. The results demonstrate that a pool of inactive tyrosinase exists in melanocytes and that rapid increases in enzyme activity elicited by melanocyte-stimulating hormone reflect an alteration in the activity of a preexisting pool of intracellular tyrosinase.

- Kurbanov K, Spiridonova NA
Role of glutathione reductase (GR) and dopachrome oxidoreductase (DCOR) in melanogenic activity of skin. Izv. Akad. Nauk Turkm. SSR, Ser. Biol. Nauk 58-61, 1987.
Abstratct : The title enzymes were detd. in skin and organs of guinea pigs. GR is most active in adrenal glands and lowest in kidneys. The specific activity of the enzyme correlates with melanogenesis in skin and organs with the exception of kidneys. Initiation of melanogenesis by solar radiation or loading by tyrosine or methionine causes more sharp changes in GR activity of animals with prevalence of pheomelanins in skin. Solar radiation induces activity of DCOR in all animals, and esp., in black guinea pigs. The loading of animals by tyrosine or methionine results in increase of enzyme activity in black and yellow guinea pigs,

but reduces the activity of DCOR in white animals. Thus GR and DCOR may actively take part in regulation of melanogenic activity of skin, GR through glutathione metab., and DCOR via eumelanin synthesis.

- Martinez-Cayuela M, Faus M, Gil A
Effects of some reductants on the activity of cherimoya polyphenol oxidase. Phytochemistry 27:1589-1592, 1988.
Abstract : Ascorbate, cysteine, mercaptoethanol, and H2O2 affect the polyphenol oxidase (PPO) activity of cherimoya epicarp in different ways. At relatively low concns., 0.1 mM to 0.2 mM, ascorbate, cysteine, and mercaptoethanol decrease melanin formation from catechol without modifying the rates of the reaction whereas at higher concns., they decrease both the rates of the reaction and the final product levels. One to 10 .mu.M cysteine or mercaptoethanol has no affect on the rate of hydroxylation of tyramine, but 20 .mu.M cysteine or mercaptoethanol inhibit almost completely monophenol hydroxylation; these compds. increase the lag phase. At 0.1-0.3 mM, ascorbate reduces the lag period in the hydroxylation of tyramine and increases the rate of oxidn. but higher levels of reductant produce a rapid drop in the rate of oxidn. One to 20 mM H2O2 lowers the final melanin levels from catechol, but increases the concns. of these products from DOPA and dopamine. High levels of H2O2 (40-320 mM) decrease the final amt. of melanins formed from each substrate due to a bleaching effect. Preincubation of partially purified PPO in the presence of H2O2 in the absence of a substrate results in the total inactivation of the enzyme with the monophenol oxidase activity being lost at a faster rate than the o-diphenol oxidase activity.

- Platen H, Kutzner HJ
Effect of copper on growth and tyrosinase activity of streptomycetes. 1987
Abstract : Tyrosinase contains Cu, which is essential for enzyme synthesis and for melanin formation. For most strains of Streptomyces complex media generally contain sufficient Cu for the formation of this pigment. An exception is S. griseus; however, when supplemented with .apprx.5 .times. 10-3M Cu, complex media allow melanin formation by this species also. On a synthetic medium streptomycetes can grow with <10-7M Cu; however, no tyrosinase activity can be detected. Apparently, Cu is not necessary for growth, although some strains showed a significant increase of biomass after supplementation with Cu. On the other hand tyrosinase-activity occurred in synthetic medium with most strains only with 10-5 or 10-4M Cu; concns. >5 .times. 10-4M inhibited growth. Growth in Cu-contg. media resulted in a significant enrichment of this metal in the cell biomass.

8. MELANOMA

- Aubert C, Voulot C, Bouge F, Galindo JR
Melanogenesis and malignancy in experimental B16 melanoma variants. Prog Clin Biol Res 256:155-167, 1988.

- De Pauw-Gillet MC, Wang F, Simonon A, Borlon A, Van den Brule F, Dequinze B, Bassleer R
Effects of copper sulfate given alone or with alpha-MSH and L-tyrosine on B16 melanoma cells cultured in serum-free media. 1987
Abstract : CuSO4 (0.1 mM) inhibited proliferation in B16 melanoma cells cultured in 2 or 3 dimensions and in various serum-free media. This effect was accompanied by stimulation of melanogenesis and some degree of cell death. Simultaneous addn. of .alpha.-melanotropin (.alpha.-MSH) (0.2 .mu.g/mL) and/or L-tyrosine (2 mM) can somewhat modify these antiproliferative effects of CuSO4 in melanoma cells in culture.

- Holmquist ND, Torres J
Malignant melanoma of the cervix. Report of a case. Acta Cytol 32:252-256, 1988.
Abstract : A malignant melanoma of the cervix, a rare neoplasm, was found to have an unusual cytologic pattern, similar to that of a leiomyosarcoma. A biopsy sample was diagnosed as cervical malignant melanoma of the spindle cell type. Some neoplastic cells in the tissue contained melanin pigment, whereas none of the abnormal cells in the cervical scrapes, except for an abnormal giant cell, had visible cytoplasmic pigment. The abnormal cells in the cervical scrape specimen were spindle-shaped, as were their nuclei, which is why the cytologic pattern was interpreted as that of a leiomyosarcoma. Evidence from this and previously reported cases shows that malignant melanoma must be considered as a possible source of exfoliated abnormal nonpigmented spindle-shaped cells in a cervicovaginal cell sample.

- Larsen TE, Mogensen SB, Holme I
The evaluation of possible melanoma risk groups of patients in a series of pigmented naevi. Clinical and histological intercorrelations. Acta Derm Venereol (Stockh) 68:134-139, 1988.
Abstract : The trends of the clinical/histological intercorrelations in two series of pigmented naevi have been compared. One series of naevi represents patients who are habitual sunbathers and/or who have travelled to Southern sunny climates. The other series includes naevi from easily sunburned patients. The sunburner-group is correlated to histological features such as mitoses, atypia and fibrosis of the tumour as well as to an irregular/atypical tumour type. Such trends are not found in the other target group. The sunburners have a poor ability tosuntan, while the sunbather group includes good suntanners. This indicates the

importance of the melanin UV-filter effect of the skin as a protection against the promotion of potential MM-precursors, such as irregular/atypical naevi.

- McLaughlin WH, Thramann WMJ
Preliminary observations of malignant melanoma therapy using radiolabeled alpha-methyltyrosine. J Surg Oncol 37:192-197, 1988.
Abstract : A strategy for cancer therapy using astatine-211-labeled alpha-methyltyrosine (211At-AMT) was studied in cultured B16 melanoma cells and compared to the radiotoxicity of iodine-125-labeled iododeoxyuridine (125IUdR), a thymidine analogue. Both 125I and 211At deliver lethal doses of irradiation to melanoma cells when administered as 125IUdR and 211At-AMT. The alpha decay of astatine-211 is more effective however, needing only a fraction of the cellular radioactivity of 125IUdR to effect comparable clonogenic survival. Compared with 125IUdR, 125I-AMT is not cytotoxic because the range of the low energy electrons released does not interact with DNA. Uptake of radiolabeled AMT by melanotic cells is enhanced by theophylline. This preliminary evidence suggests that 211At-labeled melanin precursors may be exquisitely cytotoxic to B16 melanoma cells.

- Mishima Y, Ichihashi M, Hayashibe K, Ueda M, Hatta S, Funasaka Y, Imokawa G
Control of melanogenesis and melanoma oncogenesis. Prog. Clin. Biol. Res. 256:127-141, 1988.

- Nakamura T, Seki S, Matsubara O, Ito S, Kasuga T
Specific incorporation of 4-S-cysteinylphenol into human melanoma cells. J Invest Dermatol 90:725-728, 1988.
Abstract : The incorporation of 4-S-cysteinylphenol (4-S-CP), a tyrosine analog, into malignant melanoma cells was evaluated. 4-S-CP was specifically incorporated into the melanotic melanoma cells (HMV-II), which have activity for melanin synthesis, but was scarcely incorporated into HeLA S3 or HMV-I cells, which have no activity for melanin synthesis. Electron microscopic autoradiography revealed that the intracellular localization of 4-S-CP was closely correlated with melanogenesis and that 4-S-CP served as an initial substrate for tyrosinase and was utilized in melanin synthesis. On the basis of these findings we hypothesize that tyrosinase is required for intracellular incorporation of 4-S-CP. This specific incorporation of 4-S-CP into melanoma cells should be useful in the development of an effective procedure for chemotherapy of malignant melanomas and in analysis of melanin synthesis.

- Naoi M, Takahashi T, Ito S, Fujita K, Nagatsu T
Accumulation of N-methyl-4-phenylpyridinium ion (MPP+) in human melanoma cell line, HMV-I and -II. Neurosci Lett 87:57-62, 1988.
Abstract : N-Methyl-4-phenylpyridinium ion (MPP+) was found to be accumulated in human melanoma cell lines, HMV-I and

-II, which originate from human melanoma and differentiate into subclones, HMV-I and -II. HMV-II cells can produce a large amount of melanin, while the other cells produce less. After 3 day culture of these cells in the presence of 1-100 microM MPP+, MPP+ was accumulated in both types of cells and a much larger amount of MPP+ was accumulated in melanin-rich HMV-II cells than in HMV-I cells, even though the uptake velocity of MPP+ into both types of cells was almost the same. In addition, both types of cells could survive, even with MPP+ accumulation. Protein amounts, a non-specific enzyme, beta-galactosidase activity, and intracellular DOPA concentrations in both types of cells, were not affected by the presence of MPP+. These results suggest that MPP+ is accumulated in non-dopaminergic cells and the accumulation is enhanced by the presence of melanin.

- Price JE, Tarin D, Fidler IJ
Influence of organ microenvironment on pigmentation of a metastatic murine melanoma. Cancer Res 48:2258-2264, 1988.
Abstract : The purpose of these studies was to investigate the relationship of the host microenvironment to the metastatic and pigmented phenotypes of the SW-1 variant of the murine K-1735 melanoma. The SW-1 subline was isolated from an amelanotic lung metastasis in a C3H/HeN mouse given an s.c. injection of the K-1735 melanoma. Cells of this line were highly metastatic and produced tumor deposits in many organs. In all sites except the brain, these lesions were predominantly amelanotic. K-1735 SW-1 cells were isolated from metastases in various organs and subsequently reinoculated into normal syngeneic recipients. Whereas the metastatic phenotype remained stable and thus was heritable, pigmentation was unstable and appeared to be modulated by the site of tumor growth. Further differences in the phenotype of K-1735 SW-1 cells growing in vivo and in culture were revealed by assays for tyrosinase activity. K-1735 SW-1 cells growing in culture did not produce melanin nor did they respond to agents that can stimulate melanin production in another mouse melanoma, the B16 line. K-1735 SW-1 cells do not, however, lack tyrosinase, since these cells are capable of producing melanin when growing in certain organs in vivo. We conclude that the host organ environment may influence a phenotype of malignant melanoma cells, i.e., pigmentation. These findings also suggest caution when extrapolating the results of in vitro biochemical assays to properties of tumor cells growing in vivo.

- Reiman HM, Goellner JR, Woods JE, Mixter RC
Desmoplastic melanoma of the head and neck. Cancer 60:2269-2274, 1987.
Abstract : The pathologic and clinical findings in cases of desmoplastic melanoma of the head and neck seen at the Mayo Clinic in Rochester, Minnesota, during the past 20 years were analyzed. The nine cases acceptable for study included six usual and three neurotropic variants as defined by light microscopic criteria. Immunopathologic studies of all cases using S-100 protein and desmin, and electron microscopy in

four cases, were unsuccessful in distinguishing between the two subtypes. Clinical behavior was aggressive regardless of histologic subtype. Extensive surgical treatment when the diagnosis is made is advocated. The combination of the rarity and the subtle histologic features of desmoplastic melanoma continues to make the correct diagnosis of this entity a challenge for the clinician and pathologist.

- Yamada K, Larsson BS, Roberto A, Dencker L, Ullberg S
Selective incorporation of thiouracil into murine metastatic melanomas. J Invest Dermatol 90:873-876, 1988.
Abstract : The uptake and retention of 14C-thiouracil and 125I-thiouracil in small lung metastases of B16 murine melanoma was studied in beige mice injected intravenously with melanoma cells. By impulse counting of excised tumor and organ pieces, a high concentration of radioactivity was found in the lung metastases, as compared to normal tissues. The highest tumor/organ concentration ratios appeared 24 h after injection of the radiolabeled thiouracil. A separate autoradiographic study on the disposition of 14C-thiouracil in mice with melanoma metastases confirmed the impulse counting results and also showed the absence of any other site of retention of radioactivity except for hair follicles and to some extent the thyroid. The selective uptake of 14C- and 125I-thiouracil in melanomas depends on their acceptance as false melanin precursors, making them specific markers for growing melanin. The results indicate that radiolabeled thiouracil may be useful for clinical diagnosis and, possibly, therapy of malignant melanotic melanomas.

9. EYE

- Aula P, Kaila T, Huupponen R, Salminen L
Timolol binding to bovine ocular melanin in vitro. J. Ocul. Pharmacol. 4:29-36, 1988.
Abstract : The binding characteristics of 3H-timolol to bovine iris melanin were detd. The effects of pH, EtOH, 2.5 .mu.M isoxuprine and 1 .mu.M d- and l-propranolol on 100 nM 3H-timolol binding were also detd. In satn. expts. 3H-timolol (from 1.25 nM to 5 .mu.M) was equilibrated with 0.5 mg/mL melanin. The binding was saturable with the binding max. of about 1 .mu.M timolol/g melanin. The binding of 100 nM 3H-timolol to melanin increased up to 5 h and amounted 24% of the added radioactivity. The best fit of the assocn. consts. was obtained by using a 2-fit model. The assocn. rate consts. were 4.92 .times. 105 M-1 min-1 and 5.95 .times. 106 M-1 min-1. The dissocn. was rapid in vitro and uniphasic with a dissocn. rate const. of 5.08 .times. 10-3 min-1. The pH, EtOH and both enantiomers of propranolol did not appreciably alter the timolol binding, while isoxuprine diminished it.

- Banks CN
Melanin : blackguard or red herring? Another look at chloroquine retinopathy. Aust N Z J Ophthalmol 15:365-370, 1987.

- Burns MS, Tyler NK, Bellhorn RW
Melanosome abnormalities of ocular pigmented epithelial cells in beagle dogs with hereditary tapetal degeneration. Curr Eye Res 7:115-123, 1988.
Abstract : Eyes of laboratory beagle dogs with an inherited tapetal degeneration were abnormally lightly pigmented. The development of pigmentation was followed morphologically from 7 days postnatal to 9 years of age. At all postnatal ages the iris pigmented epithelia contained no normal melanosomes, only organelles resembling secondary lysosomes or residual bodies. The ciliary body pigmented epithelium contained a variety of melanosome organelles at the earliest stages examined, but in fewer numbers than in normal animals. These included premelanosomes, partially melanized and some fully melanized pigment granules. However, the melanin deposition was usually patchy and irregular. With time, many of these granules appeared to condense into residual bodies. The retinal pigmented epithelium in peripheral and inferior posterior regions of affected animals never contained normal appearing melanin granules at any stage of postnatal development. The iris and choroidal stroma had melanosomes of normal size and shape, but many fewer than in normal animals. These results imply that there is local cellular control over melanosome production and regression, since the melanosome abnormalities do not follow the anterior to osterior development of pigment in ocular epithelia. It is proposed that a defect in synthesis of the matrix component of melanosomes could result in absent or abnormal deposition of melanin and initiate a process of autophagy of these organelles.

- Feeney-Burns L, Burns RP, Gao CL
Ocular pathology in melanomatous Sinclair miniature swine. Am J Pathol 131:62-72, 1988.
Abstract : Eyes of cutaneous melanoma-bearing miniature Sinclair swine were examined by light and electron microscopy during growth and maturation of animals. The histology of ocular depigmentation, which occurs during melanoma arrest and skin depigmentation, was studied in eyes of animals that had successful and unsuccessful tumor regression. In 12 animals one eye was removed at an early stage and the second eye at a later stage of disease or maturation. The histologic and clinical course of the ocular changes was correlated with changes in the cutaneous tumors. Animals showing rapid cutaneous tumor regression developed acute uveitis that was characterized by an influx of mononuclear cells into the stroma of the ciliary body; later this spread to the iris and choroid. In late stages the cornea sometimes developed a band of calcium precipitates beneath the basalepithelial cells (band keratopathy). Uveal melanocytes developed watery cytoplasm typical of cells with ruptured plasma membranes.

Released melanin granules were taken up initially into the lysosomal compartment of mononuclear cells having the various morphologic features of lymphocytes and monocytes; later, melanin also appeared in fibrocyte lysosomes. The relationship of these processes to various cell-mediated immunity phenomena is being studied.

- Inomata H
Necrotic changes of choroidal melanocytes in sympathetic ophthalmia. Arch Ophthalmol 106:239-242, 1988.
Abstract : There are various theories as to the origin of epithelioid cells in the choroid with sympathetic ophthalmia. Some investigators propose a transformation of choroidal melanocytes as the origin, and others suggest a histiomonocytic derivation. One reason this controversy exists may be the relative lack of investigations into necrotic changes of choroidal melanocytes. The structural alterations in the choroidal melanocytes of an injured eye with sympathetic ophthalmia were studied, and the sequence of events involved in degeneration and necrotic changes were elucidated. The damaged melanocytes developed vacuolation, and the melanin granules were gathered into autophagosomes or had disappeared. The nuclei of the severely damaged melanocytes became pyknotic. Degenerated cell nuclei were phagocytized by macrophages. It is concluded that choroidal melanocytes may not transform into epithelioid cells and that they disappear from the choroid following degeneration.

- Kenneally CZ, Farber MG, Smith ME, Devineni R
In vitro melanoma cell growth after preenucleation radiation therapy. Arch Ophthalmol 106:223-224, 1988.
Abstract : The in vitro efficacy of 20 Gy (2000 rad) of external beam irradiation delivered to patients with choroidal melanomas prior to enucleation was investigated in 11 patients whose tumors were grown in cell culture. Phase-contrast microscopy was used to compare growth patterns between irradiated and nonirradiated tumors. Cell types were determined by histologic stains, and electron microscopy identified intracytoplasmic melanin. Irradiated melanomas did not grow and did not attach to culture flasks, thus demonstrating that preenucleation irradiation alters the in vitro growth of melanoma cells.

- Sanyal S, Zeilmaker GH
Retinal damage by constant light in chimeric mice : implications for the protective role of melanin. Exp. Eye Res. 46:731-743, 1988.
Abstract : Adult chimeric mice, contg. varying proportions of albino and pigmented cells in their ocular tissues, were exposed to const. light for 5 wk and the distribution of the surviving rod perikarya in the retina and of the pigmented cells in various eye tissues were compared. In chimeras which were mostly albino, the retinal lesion was similar to that in pure strain albino mice; in chimeras with relatively more pigmented cells in their ocular tissues, the retina was unaffected as in fully pigmented mice. In chimeras with amts.

of pigmented cells in their ocular tissues varying between these 2 ends, lesions of intermediate degrees could be obsd. Surviving rod cells in such chimeric retinas were always found in regions adjoining the periphery. The location of the rod perikarya in such regions did not show an exact correlation with that of the overlying pigmented cells but regions of the outer nuclear layer with surviving rod perikarya were generally located in the half or quarter of the retina in which the overlying pigment epithelium also contained more pigmented cells than in the other regions. The proportions of the surviving photoreceptor cells varied between such chimeras. The lesion appeared to be less extensive in individuals with more pigmented cells in the epithelium but no exact correlation was recorded. Thus, while pigmentation in the iris reduces the amt. of light reaching the retina, melanin in the pigment epithelium, in addn. to preventing light reflection, may also play an antitoxic role, possibly as an antioxidative agent.

- Stroeva OG, Bibikova AD
A hormone-sensitive stage in the development of the retinal pigment epithelium in Hunter rats with hereditary retinal dystrophy. Ontogenez 19:30-36, 1988.
Abstract : The sensitivity of the retinal pigment epithelium (RPE) to the melanotropic effects of alpha-MSH and dbcAMP was assayed in an organ culture of the eye scleral part in the Hunter rats with inherited retinal dystrophy. The melanin synthesis was estimated by liquid scintillation on the RPE isolated enzymatically after 48-h cultivation. One eye from every animal was cultivated in a medium without natural components and with the hormone or dbcAMP (experiment), while the other in a hormone-free medium (control). The melanin synthesis was estimated by 14C-thiouracil incorporation. The result was expressed as a cpm/microgram DNA (experiment) to cpm/microgram DNA (control) ratio. In addition, the index of labelled nuclei was determined using 3H-thymidine autoradiography in the central RPE zone of the eyes from young rats of the same litter. The experiments with alpha-MSH confirmed the earlier data according to which the RPE of the 3 day old Hunter rats were insensitive to melanotropic hormones. This was not due to defects in the cytoplasmic melanin-synthesizing system, since under the influence of dbcAMP the melanin synthesis in the RPE increases more than four-fold as compared with the control; dbcAMP stimulates also the total protein synthesis, as estimated by 3H-leucine incorporation. The RPE of the 4 day-old rats proved to be sensitive to alpha-MSH: the melanin synthesis increases more than twice suggesting the healthy state of the RPE membrane melanotropic receptors. Alpha-MSH also stimulates the total protein synthesis.

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ERRATA

In the last issue of the PCRB (nr 4) :

- Front page : read "L. Wolfram (Stamford)" instead of "A. Breathnach (London)"

- Page 9 : Authors' name missing (Commentary) :

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Abstracts from all pigment researchers interested in attending our meeting will be welcomed. For further information and abstract forms, please contact :

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PIGMENT CELL RESEARCH

PIGMENT CELL RESEARCH, SUPPLEMENT 1, 1988
Kirk D. Wuepper, M.D., Editor
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