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REVIEW

ARE MICE PIGMENTARY GENES THROWING LIGHT ON HUMANS ?

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In this article the rapid advances made in the molecular genetics of inherited disorders of hypo and hyperpigmentation during the past three years are reviewed. The main focus is on studies in mice as compared to homologues in humans. The main hypomelanotic diseases included are, piebaldism (white spotting) due to mutations of c-KIT, PDGF and MGF genes; vitiligo (microphathalmia mice) mutations of c-Kit and c-fms genes; Waardenburg syndrome (splotch locus) mutations of mice PAX-3 or huaman Hup-2 genes; albinism (mutations of tyrosinase genes), Menkes disease (Mottled mouse), premature greying (mutations in light/ brown locus/ gp75/TRP-1); Griscelli disease (mutations in TRP-1 and steel); Prader-willi and Angelman syndromes, tyrosinase-positive oculocutaneous albinism and hypomelanosis of Ito (mutations of pink- eyed dilution gene / mapping to human chromosomes 15q 11.2 - q12); and human platelet storage pool deficiency diseases due to defects in pallidin, an erythrocyte membrane protein (pallid mouse / mapping to 4.2 pallidin gene). The genetic characterization of hypermelanosis includes, neurofibromatosis 1 (Cafe-au-lait spots) and McCune-Albright Syndrome. Rapid evolving knowledge about pigmentary genes will increase further the knowledge about these hypo and hyperpigmentary disorders.

Skin pigmentation in mammals is related to melanins in the melanosome occurring in specialized dendritic cells called melanocyte which originate from neural crest. Regulation of this skin pigmentation is by epidermal-melanin unit composed of a melanocyte and approximately 36 kerationocytes.

Normal skin colour is an admixture of red (oxyhemoglobibn), blue (deoxygenated hemoglobin), yellow (carotene) and light brown, deep brown, to black (melanin). It is generally agreed that there are two categories of melanin pigmentation of human skin: the constitutive or intrinsic and the facultative or inducible skin colour. Constitutive melanin pigmentation implies the genetically determined cutaneous melanin pigmentation in the absence of direct or indirect influences (e. g., solar radiation, hormones, chemicals or other environmental factors). Whereas facultative melanin pigmentation designates increase in melanin pigmentation above the constitutive level and arises from the complex interplay of solar radiation and certain pituitary hormones upon the genetically endowed melanogenic potential of the individual. The variation of skin colour among the human race depends upon the differences in the functional activity of melanocytes. Black and Asiatic Indians have melanocytes capable of synthesizing a large number of pigment laden melanosomes and have higher level of tyrosinase activity. Fair-skinned individuals (e. g., Celtics and white-skinned Caucasoids) possess melanocytes which are functionally less active with lower

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tyrosinase activity and synthesize a smaller number of melanosomes than brown or black-skinned individuals.[1] The epidermal and follicular melanin units consist of two types of melanins, the eumelanins and the pheomelanins. Eumelanins are brown-black, insoluble high molecular weight polymers produced by melanocytes from oxidative polymeriation of 5,6-dihydroxyindoles and are drived from tyrosine through hydroxylation by tyrosine via the formation of DOPA (3,4 dihydroxyphenylalanine). Pheomelanins are yellow-red, alkali soulble, sulphur rich pigments, formed by interaction of cysteine and glutathione with DOPA through oxidative polymerization of cysteinyl DOPAs[2] (Fig. 1).

The melanocytes possess the enzyme tyrosinase which plays an imporytant role in the syntheses of melanins. The melanins are synthesized in specific organs, the melanosomes, which are transferred to keratinocytes of the epidermal-melanin unit via the dendritic process of melanocytes. Recent advances in molecular genetics have shown that a single melanocyte can manufacture both pheomelanin (red-yellow) and eumelanin (brown-black) [3] and the skin colour depends upon the proportion of these melanin mixtures in the epidermal skin.[2] Most disorders of pigmentation of skin and hairs are due to alterations of melanosome transfer from melanocytes to keratinocytes. Some others are related to defect in migration or survival of cells derived from neural crest referred as neurocristopathy (piebaldism, Waardenburg's syndrome). The genetic influence of skin colour in human is not well understood. It is probably as complex as those of mice which have more than 150 genes at about 50 distinct loci, that influence skin and hair colour.[4] Recent advances in cloning of sequences of gene mutations in mice have led to better understanding of human homologue of many anomalies of hair and skin colour. The murine genes that have been particularly studied are related to the following control mechanisms: those affecting the migration, proliferation and survival of melanoblasts and the melanocytes; those controlling the quantity of melanin produced; those that decide the kind of melanins synthesized; and those that reflect the ultrastructure and morphology of the melanocytes and the melanosomes.[5] In the first group, genes controlling embryogenesis of melanocyte system, notably the genes controlling the activity of tyrosinase-kinase receptors and melanocyte development have significantly increased the knowledge about genodermatoses like piebaldism and Waardenburg syndrome. The proto-oncogene c-kit / Steel, enconding the tyrosinase-kinase receptors of melanocyte growth factor (MFG) has been found to play a role in the migration and proliferation of follicular pool melanocytes of the mice. Mutations of these genes in mice lead to piebldism (white spotting). The homologue of this gene in humans has been cloned. Clinical heterogenicity of phenotypes of human piebldism is due to mutations of c-kit gene and a receptor of platelet derived growth factor (α-PDGF) which has been observed in one patient of piebaldism.[6,7] Piebalsism is epitomized by the white forelock in humans and white spotting in mice, characterized by reduction in number to complete absence of pigment cells.

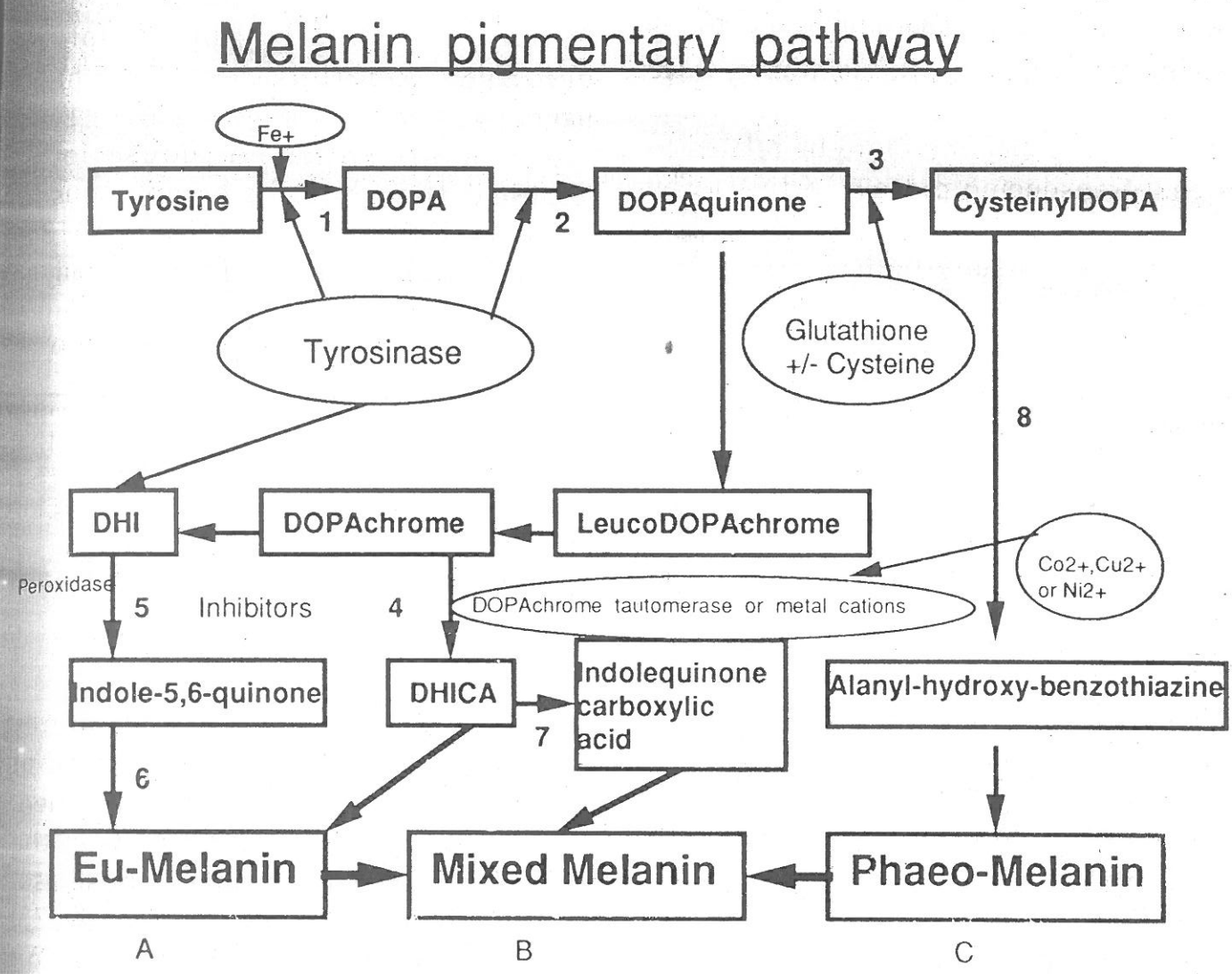

Fig.1. A,B,C, Schematic of mammalian pigmentary pathway modified from reference[2].In the initial reaction, tyrosine hydroxylase (1) is specifically catalyzed only by tyrosinase, which can also catalyse DOPA oxidation(2). Activation of tyrosinase is probably by ferrous ions. If glutathione and/ or cysteine is available, DOPA quinone will stoichiomertically be diverted to the production ot cysteiny DOPAs (3). Intracellularly, these sulfhydryls are regulated by g-glutamyl transpeptidase and glutathione reducatase, among others. In their absence, DOPA quinone will quickly cyclize to produce leudo DOPA chrome tautomerase (TRP-2) and.or divalent metal cations (Co2+,Cu2+ or Ni2+), DOPA chrome will be diverted to DHICA (4), whereas, in the absence of those factors, DOPA chrome will decarboxylate to produce KHI. DHI is then oxidized to indole-5,6-quinone (5), a reaction catalyzed by tyrosinase or peroxidase, thence incoroporated within eu-melanins. DHICA is presumed to be similarly oxidized to a carboxylated indole-quinone(7); preliminary findings suggest that this cataltic activity might be performed by TRP-1. There are many inhibitory factors (6) of the reactions leading to melanin production, and it is generally accepted that there are many other undiscovered melanogenic factors that can influence other parts of this reaction sequence, notably those on the phaeomelanic side of the pathway (8) . Although genetically inbred mice produce eu-melanin, in humans there is usually a variable mixture of the two types, which are referred as "mkixed melanins".

Abbreviations: DOPA, 3,4-dihydroxyphenlalanine, DHICA, 5.6-dihydroxyindole-2carboxylic acid, DHI, 5,6-dihydroxyindole

The prevalent hypothesis for the cause of vitiligo is a combination melanocytic autotoxicity and secondary immune response. The vitiligo mutations in the C57/BL ler-vit/vit mouse were shown to be allelic with microphthalmia mi locus and may therefore be related to signal-transducing protein, activated by both the c-kit and c-fms. Mi-mutant mice are phenotypically piebald like white spotting (w) and steel mutants, and osteopetrotic like c-fms mutants.[9] In addition ectopic expression of c-fms can subsititute for a defective w allele but not defective mi.[8].

Mutations of the splotch locus of mice encoding the gene PAX-3 result in a phenotype somewhat similar to Waardenburg syndrome type I. PAX-3 homologue in humans (Hup 2) has been detected in patients of Waardenburg syndrome (WS) type I. Heterogenicity of WS may be as a result of mutations of PAX-3 gene. WS manifests as variable combinations of deafness, pigmentary disturbances such as heterochromia irides (different coloured eyes), white forelock, white skin patches, dystopia canthorum (outward displacement of the inner canthi of the eyes) (WS1) and limb abnormalities (WS2).[10]

Genes controlling the quality of melanin synthesized by melanocytes have been cloned corresponding to multiple mutations of the tyrosinase gene that results in tyrosinase negative (no melanin synthesis), yellow mutant (small to moderate amounts of melanmin synthesis) and temperature sensitive oculocutaneous asbinism (tyrosinase that is inactivated at high temperature). Homologues of murine counterpart have been cloned in humans.[11,12]

Menkes disease is an x-linked genetic disorder of copper-transport abnormality characterized by lack of pigmentation, defective keratinization of hair, neurological degeneration and arterial and bone abnormalities. A mouse locus 'Mottled', thought to be homologous to Menkes locus has been assigned to Xq13.3 in humans. This gene (member of a cation-transporting P-type ATPase subfamily) detects an 8.5 kilobase messenger RNA in most tissues exmined.[13]

Although the gene related to the types of melanin within the microenvironment of the hair follicle to regulate coat colour pigmentation is well characterized in the mouse agouti extension loci, the human analogue of these remains unknown.[14,15]

Numerous pigmentation genes controling the morphology and type of melanocytes have been recently identified. These include three related genes of the tyrosinase-gane family namely tyrosinase, tyrosinase-related protein-1 (TRP1/gp75) product of the brown locus on chromosome 4 (human chromosome 9) and dopachrome tautomerase (TRP-2) is encoded on chromosome 14 by the slaty gene[16,17] (Fig. 1). A mutation of brown locus named 'light' results in hair pigmented at the tip but light or not pigmented at the bottom. The phenotype of light mice shows light bases as soon as the hair forms. This hypomelanosis may be as a result of premature death of melanocytes (premature or programmed), perhaps melanocytotoxicity as a result of intermediate metabolities of melanogenesis.[17,18] This mouse model may be a model for human premature

greying. Pmel 17 gene family putative silver (si) locus (chromosome 10) and chicken melanosomal matrix protein MMP-115 corresponds to human Pmel 17 gene on chromosome 12.[16] Tyrosinase gene family maintains the proximal part of melanin synthesis and Pmel 17 gene family the distal part of melanin biosynthesis. [16] Mutations in TRP-1 and TRP-2 change the quality of colour of the pigment produced. It is possible that TRP-1 may interchange with a product of a different murine gene si which encodes a protein of melanocyte matrix.[19] This recent demonstration of the dilute coat colour locus encoding the novel myosin heavy chain that produces a recessive type of hypomelanosis in mice may shed some light in the pathogenesis of hypomelanosis associated with Griscelli disease. [19]

Pink-eyed dilution gene has been identified as the murine homologue of a gene mapping to human chromosomal region 15q 11.2--q12. The mutation of the mouse pink-eyed dilution locus [20] is associated with two types of hypomelanosis, the Prader-Willi and Angelman syndromes. The genetic product of pink-eyed dilution locus is unknown, but may be related to a structural anomaly of the melanosomes. It has been already suggested that this gene may also be associated with tyrosinase-positive (type II) albinism and hypomelanosis of Ito.[20] The pallidin represents a protein mutation in the pallid mice which is a model for the human platelet storage pool deficiency diseases (Hermansky-Pudlak syndrome and Chediak-Higashi disease). The pallid is a mutation at the erythrocyte membrane protein 4.2 gene and produces defects in at least three subcellular organelles: platelet dense granules, melanosomes and kidney lysosomes.[21]

The genetic characterization of hypermelanosis is much less cloned compared to hypomelanosis already described. These represents the diseases with cafe-au-lait (CAL) spots, dermal hypermelanosis (Mongolian spots, naevus of Ota). A mutation in the gene encoding the α subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome has been identified.[22] Also the gene for the neurofibromatosis 1 has been characterized but the molecular and cellular mechanisms determining CAL remain unknown.[23] In dermal hypermelanosis there is actopic localization of melanocytes in the dermis probably as a consequence of embryogenic abnormality (migration, and differentitation of melanoblasts), the mechanism of which remains unknown. The presence of melanocytes in muscles, glandes etc. in transgenic mice suggests that the tyrosinase-kinase receports encoded by the ret oncogene may play an important role in exbryogenesis and perhaps in the pathogenesis of certain diseases with ectopic melanocytes like naevus of Ota. [24]

It can be expected that soon other genes of pigmentation will be cloned and sequenced. Moreover the molecular mechanisms of these genes have to be defined that has already been cloned. The knowledge about cutaneous pigmentation and the associated affections are evoluting very rapidly that will further lead to better understanding of these diseases.

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