NATIONAL DERMATOLOGY RESIDENT LECTURE SERIES SUMMARY

Lecture: Melanocytes and Melanogenesis by Dr. Aaron Wong
Date: April 28, 2020 via Zoom
Compiled by: Misha Zarbafian, PGY3, University of British Columbia

Melanocytes

- Embryonic development
  - Melanocytes originate from the ectodermal-derived neural crest
  - Melanocyte precursors are called melanoblasts
- Location in body
  - Melanocytes end up in the skin, hair follicle, ear, eye, and CNS
    - Think skin pigmentation, deafness, ocular findings
    - Highest density: face & genitalia

Melanization

- Involves transcription of necessary proteins, melanosome biogenesis, transfer of melanosome to keratinocytes
- Biological regulators
  - Mitf (Micropthalmia-associated transcription factor – "Master regulator"), Wnt, Endothelins (ET), Steel factor, Protein kinase C, Tyrosinase & Tyrosinase-related proteins
  - **Basic summary –** Mitf activation by:
    - Wnt
    - Steel factor binding to C-kit (MAPK pathway)
    - α-MSH-ACTH binding to MC1R
  - Melanin synthesis
    - Derivative of DOPA (eumelanin & phaeomelanin)
    - Function: protect DNA from UV; converts light to heat
    - Located in modified lysosomes called melanosomes
    - Biosynthesis issues → oculocutaneous albinism (OCA)
  - Melanosomes
    - Lightly pigmented skin: melanization stages II/III, smaller size, <20 per cell, distributed in groups of 2-10, degraded quickly
    - Darkly pigmented skin: melanization stage IV, larger size, >200 per cell, distributed as single melanosomes, degraded slowly

Melanosome has to be Transferred from Melanocyte to Keratinocyte

- Griscelli syndrome
  - Type 1 (neuro): MyoVa (myosin Va)
  - Type 2 (immune): Rab27
  - Type 3 (skin): Melanophilin (Mlph) & myosin Va (rarely)
  - Silvery hair common finding in all types
  - Uneven clumps of melanin in hair medulla (Chediak-Higashi "punctate pattern")
- Chediak-Higashi Syndrome
  - Gene/Protein: LYST or CHS1 encoding lysosomal trafficking regulator
    - Leads to GIANT organelles
  - Skin: OCA, silvery hair, slate-gray skin

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  - Heme/Immune: Easy bruising, infections, hemophagocytic syndrome
  - Neurologic deterioration
  - Labs: giant intracytoplasmic granules
  - Treatment: Stem cell transplant
- Hermansky-Pudlak Syndrome
  - Gene (HPS 1, 3, 4, 5, 6, 7) & AP3B1; trafficking issue
  - Clinical:
    - "4 Ps": Puerto Rico, Platelet dense bodies (missing), Pigment dilution (OCA), Pulmonary fibrosis

Melanocytopenic versus Melanopenic

- Melanocytopenic: decreased numbers of melanocytes
- Melanopenic: less or defective melanosomes
- By default, melanocytopenic conditions would be melanopenic as well
  - Piebaldism
    - Autosomal dominant (gene: C-kit proto-oncogene)
    - Protein: tyrosine-kinase receptor (phosphorylates Mitf)
    - Clinical: white forelock, reticulate depigmented, melanocytopenic areas
    - Management: reassurance, rule out deafness, cover-up, melanocyte transplant/transfer
  - Waardenburg Syndrome
    - Ocular (Heterochromia irides, dystopia canthorum)
    - Auditory (Sensorineural deafness)
    - Cutaneous (Depigmentation, white forelock/poliosis)
  - OCA
    - Generally, as the OCA # increases, affected individuals have more melanin
    - Disorder of melanization – defective genes affect melanin synthesis
    - OCA 1 is temp-sensitive (tyrosinase inactivates at T>37℃)
  - Vitiligo:
  - Subtypes: ponctué, inflammatory, figurate papulosquamous, blue, trichrome, quadrichrome, pentachrome, hypochromic
  - Management: active non-intervention, camouflage/make-up, topical steroids/calcineurin inhibitors, phototherapy, excimer laser, autologous transplant techniques, micopigmentation/tattooing, depigmentation, afa-melanotide, JAK kinase inhibitors, support group

Questions During Presentation

- List 5 diseases that can present with a white forelock (poliosis)
  - Inherited: Piebaldism, tuberous sclerosis, Waardenburg syndrome
  - Acquired: Vitiligo, alopecia areata, halo nevi, Vogt-Harada-Koyanagi
- List 3 syndromes that can present with silvery hair (do not confuse with poliosis)
  - Chediak-Higashi, Griscelli syndrome, Elejalde, OCA1, Hermansky Pudlak