Apocrine, Eccrine, and Sebaceous Glands

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Objectives:

- Enhance knowledge of apocrine, eccrine, and sebaceous glands.
  - Understand development, molecular and cellular features of glands.
  - Use this knowledge to understand diseases of appendageal glands.
Apocrine Glands:

- Described by Schefferdecker in 1917, noted cells secreting by “pinching off” apical portion of cell

Fetal Skin 21 weeks

Axillary skin from a 20-year-old male size of apocrine and eccrine glands
Apocrine gland microanatomy:

- Myoepithelial cell
- Decapitation secretion
- Duct
Apocrine Gland Function-The Scent of Attraction?

- Humans have a vomernasal organ to detect pheromones-less prominent than most mammals. Does it significantly impact human behavior?

- Females prefer apocrine odors of MHC-divergent males (genetically diverse)
- Females prefer the odor of physically symmetric (handsome) males.
- Females prefer images of males when cycling
Apocrine Secretions:

- Lipids:
  - $C_6 - C_{11}$ straight-chained, branched and unsaturated acids
  - males produce E-3-methyl-2-hexenoic acid (trans) (3M2H)
  - in females $C_6 - C_{11}$ straight-chained acids predominate over 3M2H
  - Lipids are carried to skin surface bound to apocrine secretion odor-binding proteins (ASOB1 and ASOB2 (apolipoprotein D))
ABCC11 gene regulates body odor

The ABCC11 G180R mutation
  - alters surface levels of key odorant precursors
  - is associated with changes in skin microbiome
Genetics of body odor:
(J Invest Dermatol 130:529–540 2010)

- Axillary odor is determined by variants in the ABCC11 gene, an ATP-driven efflux pump protein expressed in apocrine glands
  - Lipid transporter expression mirrors Apo D (ASOB2)

- Individuals homozygous for SNP 538G>A with a G180R mutation have less axillary odor
  - SNP predominates in Asians who have a near complete loss of body odor
γ-glutamyl transferase plays a role in body odor:

- Glutathione-conjugated sulfanylalkanols are substrates for ABCC11 and γ-glutamyl transferase 1: a potential new pathway for the formation of odorant precursors in the apocrine sweat gland

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- Glutathione conjugated 3M3SH (3-methyl-3-sulfanylhexan-1-ol) is precursor of odorant molecules

- γGGT1 catalyzes Glu-3M3SH to Cys-Gly-3M3SH which is key substrate for producing odorant molecule
Ear Wax - dry vs. wet?:

- Ceruminous gland is an apocrine gland
  - 1000-2000 per ear
- Wet ear wax-Caucasians and African ancestry
- Dry ear wax-Asian and Native Americans
- Japanese Family with Paroxysmal Kinesigenic Choreoathetosis also had wet ear wax
- Mapping of PKC gene led to localization of wet ear wax gene to chromosome 16.
- Mutation in ATP binding cassette C11 gene (ABCC11).
Composition of Caucasian and East Asian Earwax:

Diseases of Apocrine Glands: Fox-Fordyce Disease:

Therapy includes steroids, retinoids, antibiotics, dermabrasion and surgery.
Diseases of Apocrine Glands: Bromhidrosis

- Bromhidrosis: excessive, over-powering body odor.

- Treatment-decrease apocrine secretions:
  - Hygenic measures
  - Lasers
  - Botox A
Diseases of Apocrine Glands: Hidradenitis Suppurativa

Severe disease / Hurley III:

• Immunomodulatory therapies:
  – Infliximab >> adalimumab
  – Anakinra, ustekinumab
    (investigational)

• Surgical modalities:
  – CO2 laser
  – Unroofing
  – Excision and grafting

Micheletti, Sem Cutan Med Surg, 2014
Genetics of apocrine gland development:

- **Ulnar-mammary syndrome (OMIM#181450)**
  - Rare autosomal dominant disorder
  - Hypoplasia/aplasia of upper limbs on ulnar side, mammary glands, and nipples
  - Hypoplasia/aplasia of apocrine glands, lack body odor
  - Genomic deletion of TBX3 results in haploinsufficiency of this T-box transcription factor

Mutations in human TBX3 alter limb, apocrine and genital development in ulnar-mammary syndrome

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Eccrine Glands:

- 2-4 million, weight 100g, approx. one kidney.
  - Maximal rate: 2-20 nl/min/gland (6-60 ml/min)
- Thermoregulation:
  - Efferent nerves from preoptic sweat center of hypothalamus descend through spinal tract
  - Non-myelinated, sympathetic postganglionic nerves
  - Most abundant on foot-620/cm²
  - Least abundant on back-64/cm²
Eccrine Glands:

- **Development:**
  - At 15 weeks sweat gland primordia develop on palmar and plantar surfaces as epithelial buds
  - Cords of cells grow downward from the buds to form eccrine ducts by 19 weeks
Eccrine Glands:

Cellular composition:

- Dark cell:
  - CFTR, Cl- transporter

- Clear cell:
  - Na+, K+ ATPase (ouabain sensitive)
  - H+ ATPase (H+), carbonic anhydrase 2 (HCO3-),
  - CFTR

- Myoepithelial cells: Contract with cholinergic stimulus
Progenitor cell populations in eccrine gland:
Lu et al, Cell 150:136-150 2012

• Murine genetic experiments identified 3 types of progenitor cells in eccrine glands

• Eliminated specific cell types using Diptheria toxin and determined which cells proliferated to reconstitute the gland
Progenitor cell populations in eccrine gland:
Lu et al, Cell 150:136-150 2012

Cre recombinase expressed in keratin 14 expressing cells
Give tamoxifen to induce production of diphtheria toxin receptor
Progenitor cell populations in eccrine gland:

Lu et al, Cell 150:136-150 2012

- Removing SD cells induces SD basal cells to proliferate
- Removing SG lumenal cells induces lumenal cells to proliferate
- Removing Myo cells induces Myo cells to proliferate
Fox1A is expressed in dark cells and null cells have lower levels of Best2 and Na/K/Cl cotransporter.
Role of Fox1A/Best2 in sweat production:

Best2 is a Ca+2 activated anion transporter

Best2 is a Ca+2 activated anion transporter
What is Sweat?:

- Na+ is 10-20 mM
  - duct resorbs sodium via aldosterone.
- K+ 4-20 mM
- Cl- 20-25 mM lower than Na+
- HCO3- is 15-20 mM, makes up anion deficit
- Lactate 10 mM, derived from glycolysis of glandular cells
- pH 7.2-7.3 in primary fluid, 5-7 at surface, duct acidifies sweat
- Urea, NH3, proteins, kallikreins, EGF
- Increased Na+ in CF due to decreased ductal resorption
Disorders of Eccrine Glands:

- Miliaria-obstructed secretion
  - Crystallina-stratum corneum

- Rubra or pustulosa-mid-epidermis

- Profunda-DEJ
Disorders of Eccrine Glands:

- **Hyperhydrosis:**
  - Botox A, sensitivity may decrease with time
  - Microwave radiation-heats dermal-SQ junction

Cholinesterase reactive nerves around secretory coil.

D-duct
S-secretory coil
Disorders of Eccrine Glands:

- Hypohydrosis:
  - X-linked hypohidrotic ectodermal dysplasia
  - Sjogren’s, neuropathies
  - ? Promote eccrine gland formation through gene therapy
Sebaceous glands:

- Sebaceous gland forms by early 5th month.
- Sebum-production proceeds rapidly
  - Peripheral cells remain immature (germinative) and contain glycogen and little lipid
  - As cells migrate to the center lipogenesis increases.
  - Highest density on face 400-800 per cm²
First function of Sebaceous glands:

- Prominent activity before birth produces vernix caseosa protects fetal skin from amniotic fluid
- Neonatal sebaceous glands will remain active until maternal androgens wane.

- Higher proportions of wax ester and triacylglycerols with longer fatty acid chains in newborn girls.

Sebum Production

- **Sebum**
  - **Squalene, wax esters**
    - are lipids that are unique to the sebaceous gland
  - **Oleic and palmitoleic acid**
    - May be antibacterial?
  - **Sebum has no known function in humans**
    - Not responsible for moisturization
    - e.g. young children have virtually no sebum and their skin is fine
    - Hair waterproofing?

Thibourtot D. J Invest Dermatol. 2004:123(1);1-12
Blimp 1-regulator of sebaceous gland progenitor cells:

- Blimp 1 transcriptional repressor defines a progenitor cell population in SG that can differentiate into proliferative sebocytes.
Hedgehog signaling plays a role in sebaceous gland physiology

- Hh inhibition decreases sebocyte production
- Hh stimulation increases size of sebaceous glands
Cannabidiol may be sebostatic?

Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes

- Cannabidiol inhibits sebogenesis
- Activates TRPV4 which downregulates lipogenesis and proliferation
Acne

Follicular hyperkeratinization

P. acnes

Inflammation

Sebum production

Event Oriented Thinking

Thinks in straight lines

A → C → D

B

In event oriented thinking everything can be explained by causal chains of events. From this perspective the root causes are the events starting the chains of cause and effect, such as A and B.

Systems Thinking

Thinks in loop structure

A → B → C → D → E

In systems thinking a system’s behavior emerges from the structure of its feedback loops. Root causes are not individual nodes. They are the forces emerging from particular feedback loops.

www.thwink.org
**P. acnes**

- Weakly positive gram-positive anaerobic diphtheroid
- Secretes lipases break down sebaceous lipids > free fatty acids
- Stimulates defensins, cathelicidin, granulysin
- Produces enzymes leading to rupture of comedone walls
- Activates Toll-like receptors (TLR2, TLR4) > IL-8 > recruit neutrophils/macrophages
- Promotes Th17 and Th17/Th1 response

Leyden et al. JID 65:382, 1975
Acne subjects have greater proportions of *P. acnes* ribotypes 4 & 5

NLR: Nod-like receptors act as intracellular sensors of microbial components NLRP3 implicated in acne
**P. Acnes** activates the inflammasome in monocytes via NLRP3

- Human monocytes stimulated with *P. acnes* secrete IL-1β via NLRP3 and caspase-1 activation.
- In acne lesions, caspase-1 and NLRP3 were expression in association with tissue macrophages.
- These data suggest a role for inflammasome activation in the pathogenesis of acne.

Therapeutic implications of *P. acnes* phylotypes

- It may be possible to utilize healthy strains in a topical probiotic for treatment of acne.

- Additional research may lead to *P. acnes* type-specific therapies including
  - vaccines
  - novel drugs targeting type-specific virulence factors, or
  - use of healthy-skin associated phylotypes in topical probiotic treatments.

*Yu et al.* Typing of *Propionibacterium acnes*: Accepted BJD Jan 8-2015
Probiotic approaches to treating Acne:

A Precision Microbiome Approach Using Sucrose for Selective Augmentation of Staphylococcus epidermidis Fermentation against Propionibacterium acnes

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*Int. J. Mol. Sci. 2016, 17, 1870

- Sucrose promotes fermentation in S. epi but not P. acnes
- This promotes production of SCFAs by S. epi that inhibit P. acnes growth
- These SCFAs may represent a novel therapeutic for acne
Ablation of sebaceous glands by laser:


• Free electron laser that emits in the 1620-1720nm
• These wavelengths are preferentially absorbed by \textbf{-CH2-} bonds in lipids
• Heats and destroys sebocytes and surrounding germinative cells
• May be possible to determine function of sebaceous gland by deleting it from follicle.
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• Authors in publication cited

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