Appendageal Glands and Associated Diseases

American Academy of Dermatology
77th Annual Meeting
March 2, 2019

I have no relevant conflicts of interest to disclose.

John T. Seykora MD PhD
Department of Dermatology
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 C6 - C11 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

Functional characterisation of a SNP in the ABCC11 allele—Effects on axillary skin metabolism, odour generation and associated behaviours

Mark Harker1,2, Ann-Marie Carvell3, Vernon P.J. Marti1, Svetlana Riazanskaia1, Hailey Kelso5, David Taylor3, Sally Grimshaw3, David S. Arnold4, Ruediger Zillmer3, Jane Shaw4, Jayne M. Kirk4, Zee M. Alcasid5, Sheila Gonzales-Tanon6, Gertrude P. Chan7, Egge A.E. Rosing8, Adrian M. Smith9

1 Unilever Research & Development, Quarry Road East, Port Sunlight, United Kingdom
2 Unilever Philippines Inc., 1351 United Nations Avenue, Pasig, 1607 Manila, Philippines
3 Unilever Research Laboratory, 1351 United Nations Avenue, Pasig, 1607 Manila, Philippines
4 Unilever Research Laboratory, 1351 United Nations Avenue, Pasig, 1607 Manila, Philippines
5 Unilever Discover, Colworth Science Park, Sharnbrook, United Kingdom

Twenty-four hour mean malodour scores of the different genotype groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>MMS 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>2.60</td>
</tr>
<tr>
<td>GA</td>
<td>3.40</td>
</tr>
<tr>
<td>GG</td>
<td>3.50</td>
</tr>
</tbody>
</table>

C.

P = 0.020

P < 0.001

3M3SH+Cys-Gly (μg/mL)

Subject Genotype

AA
GA
GG

a.

Mean relative abundance (%)
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-glutamyltransferase 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

Tim Baumann¹,², Sophia Bergmann¹, Thomas Schmidt-Rose¹, Heiner Max¹, Annette Martin², Bernd Enthaler¹, Lara Terstegen¹, Dorothea Schweiger¹, Hubert Kalbacher⁴, Horst Wenck¹, Gabriele Jedlitschky² and Zorica Jovanovic¹

- 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
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
Role of Fox1A in sweat production:

Fox1A is expressed in dark cells and null cells have lower levels of Best2 and Na/K/Cl cotransporter
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 resorbtion
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 5\textsuperscript{th} 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 cm\textsuperscript{2}

Split skin labia minora, x50
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?

Thiboutot 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

Event Oriented Thinking
Thinks in straight lines

Systems Thinking
Thinks in loop structure

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. 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

The inflammasome

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:

- 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 -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.
Acknowledgements and Follow up

- Dr. Diane Thiboutout
- Authors in publication cited
- Questions: john.seykora@uphs.upenn.edu