Acne and Rosacea Symposium AAD virtual meeting April 23, 2021 20 min

Update on Acne Pathogenesis: 2021

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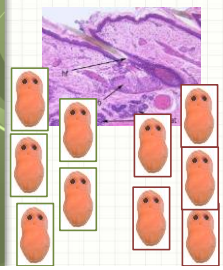
Disclosures

- Consultant to Galderma and Novartis

Updates

- *C. acnes*
- Genetics of severe acne
- Diet and obesity and acne

C. acnes: many soldiers, targets and weapons in the defense or offense of its follicular domain



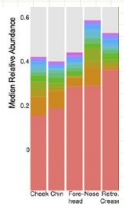
Targets:
Keratinocytes
Sebocytes
Monocytes
Bacteria

Weapons:
Short range:
TLR2-mediated cytokine secretion
Inflammasome activation
Induction of antimicrobial
TH17 clones

Weapons:
Long range:
Perforins
Short chain fatty acids
Extracellular vesicles

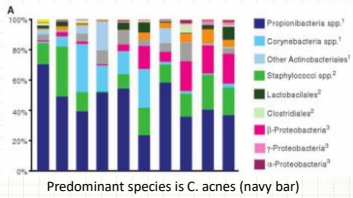
C. acnes Colonization of Skin: Good or Bad?

Preadolescent Microbiome



Predominant species is Strep (orange bar)

Adult Microbiome



Predominant species is C. acnes (navy bar)

Coughlin CC et al. Pediatr Dermatol. 2017;34:661–664 Grice EA et al. Science. 2009;324:1190-1192.

Antagonism between S. epidermidis and *C. acnes*

- Staph lipotechnoic acid (LTA) activates TLR2 in keratinocytes to produce a microRNA that destabilized TLR-2 and prevented *C. acnes*-induced inflammation
- Other studies have shown that certain strains of *C. acnes* are able to inhibit growth of *S. epi* and *vice versa*

Xia X *et al.* J Invest Dermatol (2016) 136, 621e630; Christensen *et al.* BMC Genomics (2016) 17:152; Wang Y *et al. Appl Microbiol Biotechnol.* 2014 January ; 98(1): 411–424

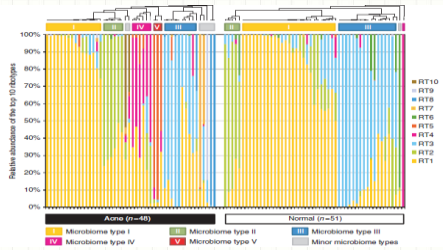
Antagonism between S. aureus and *C. acnes*

- The fermentation products of *C. acnes* significantly suppress the growth of a strain of community-acquired MRSA
- Bacterial interference, or bacteriotherapy, in which commensal bacteria are used to prevent colonization of the host by pathogens, has been shown to be a promising modality for prevention and treatment of infections

Shu, M et al. PLoS ONE 8(2): e55380. doi:10.1371/journal.pone.0055380

ALL *C. ACNES* ARE NOT CREATED EQUAL: IS THIS A THERAPEUTIC OPPORTUNITY?

Acne subjects have greater proportions of *C. acnes* ribotypes 4 &5



Fitz-Gibbon *et al. J Invest Dermatol* 2013; **133**: 2152-60.

C. acnes phylotypes differ in antibiotic resistance

- C. acnes phylotypes
  - Differ in their disease associations
  - Have markedly varying rates of antibiotic resistance.
- The acne- associated ribotypes 4 and 5 of phylotype IA-2 contain a mutation in the 16S gene that increases resistance to tetracycline.
- Most acne patients with these strains had not previously been treated with antibiotics

Yu *et al.* Typing of *Propionibacterium acnes* Br J Dermatol 2015;172: 1204-1209

C. acnes phylotypes and immune response

- **Acne-associated phylotypes** induced 2-3 fold higher levels of IFN-γ and IL-17 in peripheral blood mononuclear cells compared to healthy phylotypes.
- *C. acnes* **phylotypes associated with healthy skin** induced 2- to 4-fold higher levels of IL-10
- These data suggest that *C. acnes* phylotypes may have an increased propensity to induce acne due to induction of both Th1 and Th17 responses

Yu Y *et al.* Journal of Investigative Dermatology 2016; 136: 2221-2228p

Therapeutic implications: *C. acnes* phylotypes

- It may be possible to utilize healthy strains in a topical probiotic for treatment of acne.
- Additional research may lead to *C. 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* Br J Dermatol 2015;172: 1204-1209

C. acnes strains associated with health induce Th17 clones with antimicrobial activity

- *C. acnes* strains associated with **acne** induce higher IL-17 levels in monocytes compared to *C. acnes* strains associated with health.
- Only *C. acnes* strains associated with **health** induce Th17 clones that secret molecules sufficient to kill *C. acnes*.
- Overall, these data suggest that *C. acnes* strains may differentially modulate the CD4+ T cell responses, leading to the generation of Th17 cells that may contribute to either **homeostasis** or **acne pathogenesis**.

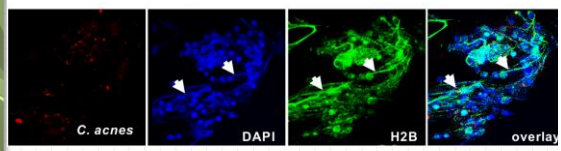
Agak G *et al.* J Invest Dermatol. 2018 February ; 138(2): 316–324

C. acnes induces antimicrobial TH17 clones that trap and kill bacteria

- Killing of *C. acnes* and bacterial pathogens by antimicrobial Th17 clones was dependent on the secretion of granulysin, granzyme B, perforin, and histone H2B.
- Antimicrobial Th17 cells can release fibrous structures composed of DNA decorated with histone H2B that entangle *C. acnes* that we call T cell extracellular traps (TETs).

Agak G et al. *J Clin Invest.* 2021;131(2):e141594

Antimicrobial Th17 cell clones secrete extracellular traps that ensnare bacteria



White arrows indicate T cell extracellular traps and ensnared *C. acnes*.

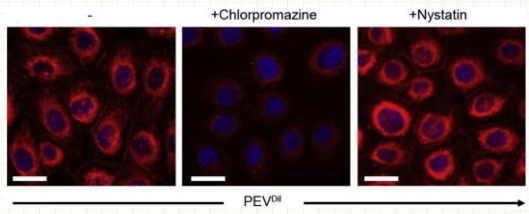
Agak G et al. *J Clin Invest.* 2021;131(2):e141594

C. acnes secretes vesicles that induce keratinocyte inflammation

- *C. acnes*-induced extracellular vesicles significantly induced inflammatory cytokines IL-8 and GM-CSF in keratinocytes and a skin reconstitution model
- These vesicles induced dysregulated epidermal differentiation in by increasing proliferating keratinocyteS

Choi EJ *et al*. JID (2018) 138: 1371-1379

C. acnes secretes extracellular vesicles (red staining) that are endocytosed by keratinocytes

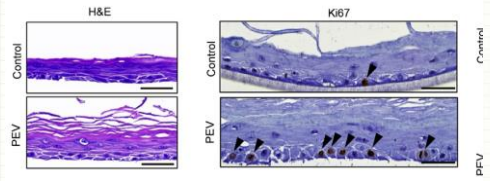


Choi EJ *et al*. JID (2018) 138: 1371-1379

Clatherin-dependent Endocytosis

Caveolae-dependent endocytosis

C. acnes secretes vesicles that dysregulate epidermal differentiation and increase keratinocyte proliferation



Choi EJ *et al.* JID (2018) 138: 1371-1379

C. acnes secrete fatty acids that induce inflammation in sebocytes

- Short-chain fatty acids (SCFAs) produced by *C. acnes* drive inflammatory gene expression in sebocytes.
- SCFA inhibit histone deacetylase (HDAC) activity in human sebocytes that resulted in an enhanced cytokine response to Toll-like receptor-2 activation
- These data demonstrate how changes in the metabolic state of the skin microbiome can promote inflammatory acne.

Sanford J *et al.* J Immunol. 2019 March 15; 202(6): 1767–1776 .

ACNE GENETICS

IGF-1 polymorphisms and acne severity

- Mean plasma IGF-1 level in 80 acne cases was significantly higher than in 80 controls (P = .04).
- Plasma IGF-1 positively correlated with acne severity (P = .01).
- Individuals homozygous for the 192-base pair (bp) polymorphism had
  - 4.29 times odds risk of having acne
  - a significantly higher mean level of IGF-1 compared with those not homozygous for the allele
  - A 3.08 times odds risk of having higher severity grade of acne compared with those not homozygous for the allele

Rahaman S *et al.* J Am Acad Dermatol 2016;75:768-73.

Genome-wide meta-analysis implicates mediators of hair follicle development and morphogenesis in risk for severe acne

- Genes including WNT10A, LGR6, TP63 and LAMC2 that have established roles in controlling the development, morphology and activity of hair follicles are associated with severe acne.
- The authors hypothesize that genetic susceptibility to acne results, in part, from variation in the structure and maintenance of the pilosebaceous unit that creates a follicular environment prone to bacterial colonization and resulting inflammation.

Petridis C *et al.* NATURE COMMUNICATIONS | (2018) 9:5075 | DOI: 10.1038/s41467-018-07459-5

GATA6 is decreased in infundibulum of acne lesions

- GATA6, which is expressed in the upper pilosebaceous unit of normal human skin, is down-regulated in acne.
- GATA6 controls keratinocyte proliferation and differentiation to prevent hyperkeratinization of the infundibulum, which is a key pathological event in acne
- When overexpressed in immortalized human sebocytes, GATA6 limits lipid production and cell proliferation.

Oules B *et al.* NATURE COMMUNICATIONS 2020 https://doi.org/10.1038/s41467-020-18784-z

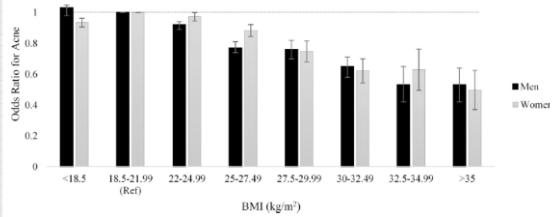
OBESITY, DIET AND ACNE

Acne and obesity

- A nationwide, population-based, cross-sectional study was conducted in 2002-2015 using medical data on 600,404 youths during compulsory military service in Israel. BMI was measured at age 17 years.
- Acne was diagnosed by dermatologists. Unadjusted and adjusted odds ratios (aORs) of acne in relation to BMI (stratified into 8 groups) were calculated
- Overweight, obese, and severely obese participants had 20%, 35%, and 50% decreased odds of having acne compared with normal-weight participants.

Snast, I *et al*. J Am Acad Dermatol 2019;81:723-9

Multivariable logistic regression analysis of the association of BMI with acne



Snast, I *et al*. J Am Acad Dermatol 2019;81:723-9

Why this inverse association of acne and BMI?

- Due to the cross-sectional study design, authors could not infer a causal relationship between BMI and acne.
- It is possible that the protective effect of excessive BMI against acne is attributed to the increase in aromatase activity and peripheral conversion of androgens to estrogens induced by excessive adipose tissue
- Estrogens are known to decrease sebum production and to oppose androgens' effects on the sebaceous glans, thus possessing a protective role against acne
-
- Obesity and intra-abdominal fat were shown to negatively correlate with total testosterone concentration and to positively correlate with estradiol level
- Circulating adiponectin however is lower in obesity

Snast, I *et al*. J Am Acad Dermatol 2019;81:723-9

Glycemic factors, insulin resistance and adiponectin levels in acne: Turkey

- Adiponectin inhibits proinflammatory cytokines and induces IL-10, suppresses toll-like receptors and increases insulin sensitivity.
- It is inversely associated with dietary glycemic index and load
- 50 patients with acne; 36 controls were studied (mean age 18-19 +/- 3 yrs)
- Milk and dairy product consumption, serum glucose, insulin, IGF-1, IGFBP-3, and measures of insulin resistance did not differ significantly between the acne and control groups
- Glycemic index and glycemic load values were significantly higher in the acne group than healthy controls (P = .022 and P = .001, respectively)
- Mean serum adiponectin concentration was significantly lower in the patients with acne vulgaris than in the healthy control subjects

Cerman AA *et al*. JAAD 2016;75: 155-62

Dairy and acne: a Norwegian cohort study in 2489 high school students

- Association of total dairy intake and acne
  - Boys & girls None
  - Boys None
  - Girls OR 1.8
- Association of high intake of full fat dairy and acne
  - Boys & girls OR 1.56
- Association of skim dairy and acne
  - None
- Association of acne and moderate intake of any type of dairy
  - None

Ulvestad M *et. al*, JEADV 2016: DOI: 10.1111/jdv.13835

A case-controlled study of dairy and acne in teenagers: Penn State

- 225 acne patients and controls ages 14-19 years
  - 120 with moderate acne and 105 controls
  - Dermatologist graded acne (global acne assessment scale)
  - BMI calculated
- A random phone survey consisting of a 3- day dietary recall was completed at 3 different points in time
- Data were analyzed using a nutrition research software package and the diet was evaluated for dairy, glycemic index, and fat
- Intake of low fat/skim milk but not full fat milk was associated with acne (p=0.01)

LaRosa C *et al.* JAAD 2016; 75:318-322.

Take aways

- Strain differences of *C. acnes* have varying effects on the follicular environment in promoting health or disease
- Genetic polymorphisms in genes relating to IGF-1 and hair follicle development may associate with acne
- Inconsistencies still exist in data on diet and acne

Q&A session

- Friday April 23 3:30-4:30PM CDT