Rebooting the *C. acnes* Narrative

>>As a skin scientist, I find it fascinating that there is so much attention these days on the skin microbiome. One of the biggest misconceptions when it comes to the microbiome in general is that all microbes within a given species are the same. But this couldn't be farther from the truth. As we learn more and more about the interaction of the microbiome with our human cells, we are starting to realize that the benefits observed when using probiotic bacteria species are not universal but very strain specific. Even within the same species of microbe there can be significant differences that can be either beneficial, benign, or detrimental to the human host. When we hear about strains of bacteria that become antibiotic resistant, we are comparing microbes within the same species, but one is antibiotic resistant and the other is not. That is a significant difference.

This is the case with the species *Cutibacterium acnes*. This species is ubiquitous and lives on everyone's skin, yet, what we have recently learned is that there are some pretty distinct differences in the characteristics of the many hundreds of strains of *C. acnes*. Because of the significant differences between strains of *C. acnes* genetically and morphologically, scientists have recently revised the naming convention for a few of the major groupings of strains within this species[1]—the first group has been designated as *C. acnes* subspecies acnes, the second as *C. acnes* subspecies defendens, and the third as *C. acnes* subspecies elongatum. These groupings correlate to phylogenetic groupings that have high associations as to whether or not the strain is pathogenic or protective in nature.

For a very long time *C. acnes* has been implicated as a (often even the) cause for acne. Yes, certain strains are found to be prevalent with those who have acne, but it is much harder to prove that they actually are the cause of acne (the old causation vs. correlation debate). This is apparent when comparing samples of the skin microbiome of acne sufferers with those of healthy individuals. Those with perfectly clear skin can have many of the same *C. acnes* types living in their skin as those that have acne, and yet they may hardly ever see a blemish.[2] This is because it is not just the presence of any particular strain(s) of *C. acnes*, but also just as important (if not more important) are 1.) what other microbes are involved and 2.) the way in which your skin and immune system respond to the presence of all these microbes and their metabolites. For all the talk about *C. acnes* causing acne, little is said about the fact that multiple studies have shown that acneic skin has relatively less *C. acnes* and more presence of other bacteria species, including an increase of *Staphylococcus epidermidis*, especially in the hair follicles where they can produce biofilms that can contribute to the blockage of the pore.[2-4] Yet, many publications say that *S. epidermidis* keeps *C. acnes* under control to prevent acne when the opposite may very well be true at times.

This point—that simply the presence of certain *C. acnes* strains is not enough to cause disease—has been corroborated by multiple research studies. One such study looked to show how immune cells from different people may react differently to the exact same pathogenic *C. acnes* strain.[5] What was observed was that while the immune cells of both healthy patients and acne sufferers both had an increase in inflammatory signals, the acne patients' cells were not able to produce enough anti-inflammatory cell signals to counteract this increased inflammation. In other words, the immune cells of those with acne simply were more predisposed to being inflamed. This suggests why two people can have the same strain of *C. acnes* on their skin but only one may have acne. Healthy individuals can obviously deal with pathogenic strains, otherwise everyone who had them on their skin would have disease. It is also the individual's immune system that contributes to whether the strains may cause skin issues. If we think about it, there are numerous autoimmune diseases like arthritis and psoriasis where the person's own immune system is not functioning correctly, thus leading to disease. Given the study just cited, could the same not be true for acne? It is not just the strain of *C. acnes* that can be the difference between healthy skin and disease, but also a properly functioning immune system; thus, why acne is not communicable.

Now, some good news is that there is also some research that protective strains of *C. acnes* can influence and train your immune system to seek out and kill pathogenic *C. acnes* without sacrificing your protectives strains, possibly

helping to prevent systemic inflammatory issues such as acne.[6]

But what are some of the key differences between the groupings of *C. acnes* strains that makes them more or less prone to be associated with disease? Well, some *C. acnes* can actually have different genes than other strains or have differences in the way the genes are expressed. One example of such significant genetic differences between *C. acnes* strains is a series of CAMP genes.[7] In a study where the different subspecies of *C. acnes* were compared, the pathogenic *C. acnes* strain was shown to produce more of the gene products for CAMP2, CAMP3 and CAMP5 and produced little to no gene product for CAMP1, where the opposite is true for a protective *C. acnes* strain where it produced more CAMP1 but not much of the others. These are the same genes in the same species (albeit different strains) of bacteria, yet they are functioning very differently which changes how they can potentially affect a human host as some of these gene products can be inflammatory. And indeed, pathogenic *C. acnes* strains do secrete inflammatory substances. Many scientific studies have used pathogenic strains such as strain 6919 to intentionally cause inflammation in the studies. However, we now know that certain strains of *C. acnes* don't cause inflammation but actually do the opposite. I observed this in my own research when my team stumbled across a strain of *C. acnes* subsp. defendens from a skin swab of a volunteer. When testing our protective strain on human cells, we were blown away at the fact that not only did the *C. acnes* strain not cause any inflammation, but it stopped inflammation even when we attempted to cause it (Data on file). This aligns with the research cited above, suggesting certain *C. acnes* strains may not simply be commensal, but may even be somewhat symbiotic in nature.

Adding to the differences between pathogenic and protective strains, the protective strains tend to have a CRISPR element—a type of bacterial immune system that keep the integrity of the bacteria's genome intact.[8] The pathogenic strains most often do not have these, which allows for integration of genetic material from phages and other pathogenic strains, which can lead to the emergence of pathogenic traits.

One last thing I wish to bring to everyone's attention is that the *C. acnes* species, specifically the protective strains, is critical to the health of our skin. The substances protective strains secrete not only keep the skin safe from pathogens, but also safe from environmental stressors like free radicals. Here's a list of goodies that *C. acnes* affords our skin (not exhaustive):

Propionic acid: A targeted antimicrobial, shown to actively suppress the growth of pathogens such as *S. aureus*, including MRSA and to have exhibited broad-spectrum antimicrobial activity against *Escherichia coli* and *Candida albicans* as well; It Inhibits biofilm formation;[4] It's a tyrosinase inhibitor;[9] Its salt form is a potent antioxidant.[10]

RoxP: A potent antioxidant that is specific to *C. acnes* and suggested to be as potent at Vit C or Vit E.[11]

Cutimycin: An antibiotic that is produced specifically by *C. acnes* that targets Staphylococcus species, including both *S. aureus* and *S. epidermidis.*[12]

Reduction in porphyrins: While pathogenic *C. acnes* strains are famous for their porphyrins, the amounts of these secreted by the protective strains tend to be little-to-none.[13,14]

As we are learning, the interplay between our human cells and the skin microbiome's most prevalent species, *C. acnes*, is nuanced and somewhat complicated. How we get along with this species depends on both us (our genetics, the environment we provide) and them (the particular mixture of strains, how they react to the environment we provide). *C. acnes* as a species is ubiquitous on the skin of the entire human population, and the benefits that "protective" strains of *C. acnes* bring to the skin are on par with some of the best skin care products. So, it is my hope that we can stop painting the whole of the species with one broad stroke and that from now on we can continue our discussion of this important species, and its implications on skin health, with these distinctions in mind. ■

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