Skin Microbiome

Heidi Kong, MD, MHS, interviewed by Maral Skelsey, MD, FAAD

MARAL SKELSEY, MD, FAAD: Welcome to this episode of *Dialogues in Dermatology*. I am Maral Kibarian Skelsey, your host. With me today is Dr. Heidi Kong, who is Senior Investigator and Chief of the Cutaneous Microbiome and Inflammation Section at the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the NIH. Dr. Kong is an expert on the microbiome. She published the first paper looking at the relationship between the skin microbiota and disease progression and performed the first study in which the skin of patients with atopic dermatitis was longitudinally sampled and sequenced. Thank you for being with us, Dr. Kong.

HEIDI KONG, MD, MHS: Thank you for having me.

MARAL SKELSEY, MD, FAAD: I'm wondering if you could just tell us, in the past ten years what have we learned about the skin microbiome?

HEIDI KONG, MD, MHS: What we've learned about the human skin microbiome originally was that we think of the human skin microbiome being comprised of bacteria, fungi, and viruses, and sometimes people include mites, as well. But from the very beginning, we determined that the skin microbiome is very site specific. That it depends on where on the body we're sampling, and that can help determine what the microbial composition is.—

--What do I mean by that? So, for example, my forehead may have much more Cutibacterium acne, relative abundances as compared to a sample on my left forearm. So we know that depending on where you're sampling, we will see different compositions of the skin microbiome, looking at bacteria, fungi, and viruses.—

--We've also learned that through puberty, not only do we see as dermatologists a major transition in the type of skin that people have as they go through puberty, but we also see that the microbiome transitions, and that is linked with changes in serum hormone levels. So we see that the physiology of the person makes a tremendous impact or influences the skin microbiome composition.—

--We and others have studied patients with atopic dermatitis and showed that in atopic dermatitis, for example, staphylococcus aureus, as well as in some patients staphylococcus epidermidis, can have a significant increase during disease flares as compared to other times of their disease. In studying other types of patients who have immunodeficiencies, we have seen that the microbiome can also be very different.—

--For example, there is a patient population called DOCK8 deficiency. These patients can have very severe eczema. They are at risk for developing malignancies, with early mortality. And so this is a patient population that I have been following at the NIH and as they go through the transplant process, because of their risk of early mortality. And when studying these patients before they go through transplant, we see that their skin actually, even if their skin looks completely normal, they have a high virome, meaning that DNA viruses on their skin are much more predominant than we see in healthy individuals.—

--So suggesting that the immune system is really important in shaping what microbes are present on skin. So in summary, from what we learned is the skin site makes a difference. Human physiology, such as puberty and hormones, can make a difference. We are also seeing that certain diseases, like atopic dermatitis, can make a difference, but also one's immune status is really important in shaping what we see on the human microbiome.

MARAL SKELSEY, MD, FAAD: What do we know about how microbes mediate the responses to the immune system and how the immune system senses their presence?

HEIDI KONG, MD, MHS: I think the easiest way to think about it is in thinking about mice. So there are studies in germ-free mice. And germ-free mice are mice that are studied in a lab. They are delivered, how do you get a germ-free mouse? They're delivered by C-section and they are raised and lived in a sterile environment. So they're given sterile food. They're in special cages that are sterile.—

--In germ-free mice, we see that their immune systems and other organ systems are actually very different than a regular lab mouse. So that suggests that exposures to microbes are important in development, and particularly their immune system. What's really interesting is in recent years, there have been studies of wild mice.—

--So these are mice that are either not the carefully, let me think of a word, in a lab mouse they're in a special cage and given special foods and they're protected in some sense. Whereas wild mice or wildling mice, where they have been exposed to the regular pathogens that a regular mouse might come into contact, their immune systems are actually more human-like. So even the specialized lab mouse doesn't have the same immune system as a wild type mouse.—

--So that again highlights our exposures and our microbes are likely really important for humans, too, in what's shaping our immune system.

MARAL SKELSEY, MD, FAAD: Is the gut microbiome more stable or less stable than the skin microbiome over time?

HEIDI KONG, MD, MHS: We've actually looked at some microbiome studies. And there is a transition. Their transitions tend to be earlier in life, whether it's potentially introduction of solid foods or whether infants are solely breastfed or not. So there are changes in the gut microbiome. Some of these are much older studies now, where different diets, longterm diets

can potentially show differences in the gut microbiome. So there is fluctuation in all of the microbiome.—

--That's what makes, whether it's skin microbiome, gut microbiome, even vaginal microbiome because there are shifts during the menstrual cycle for women, so there are fluctuations in the human microbiome areas in general. And so that's what makes it a particularly challenging area to study, because there are many confounders. And so even our skin microbiome studies are fairly tightly controlled. For example, if I have a healthy volunteer, we often have them go through a seven day skin prep.—

--You might wonder, what is a seven day skin prep? Well, generally one of our healthy volunteers cannot have had antibiotics in the prior year, in the prior 12 months. For a skin prep, we say no antimicrobial soaps, no antidandruff shampoos, avoiding pools, all sorts of things that potentially might be a confounder, we ask them to avoid that for seven days. And then 24 hours before they come in to see us, no bathing or applying anything on their skin.—

--Although humans are not as controlled as a lab mouse, but we try in our skin microbiome studies to have some consistency, so that we can better detect whether it's a true difference in microbiome versus somebody putting something on their skin that's actually giving us an incorrect signal.

MARAL SKELSEY, MD, FAAD: Despite concerns everybody has about promotion of resistant organisms and damage to commensal microbes, antibiotics are ubiquitous in the practice of dermatology. It's been estimated that we are responsible for 20 percent of the antibiotic prescriptions in this country and possibly over half of all antibiotics are deemed unnecessary. Can you talk about your research that you recent published on the effects of antibiotics on the skin microbiome?

HEIDI KONG, MD, MHS: We embarked on this study to look at whether or not antibiotics that are used in a standard clinical visit would change the human microbiome. So we had healthy volunteers who were randomized to receive either cephalexin or trimethoprim sulfamethoxazole, I'll just call it TMPSMX, or two different doses of doxycycline, 100 mg twice daily or 20 mg twice daily. For the TMPSMX and the cephalexin, we gave them 14 days of treatment and then for the doxycycline, two groups of 20 mg or 100 mg, we asked them to take it for approximately two months.—

--We followed these healthy volunteers in this pilot study for up to a year. So after they had stopped their antibiotic regimen, we continued to follow them. And so what we showed, compared to healthy volunteers who we follow over a similar period of time, that there were more persistent changes over time, but that it was still fairly individual. And we've previously shown that before, that in general the human skin microbiome is fairly individual.—

--So what we saw here is that not only did we see variation in people, but also different regimens had different effects. For example, with cephalexin, we saw more of a resilience or a return to a more similar microbiome as their baseline, as compared to some of the other regimens. What was really surprising to us was that within two weeks of starting these regimens, that we saw all of the healthy volunteers who took TMPSMX and all of them who received 100 mg twice daily of the doxycycline developed staphylococci on their skin that was resistant to those respective antibiotics.—

--And those antibiotic-resistant bacteria continued to be found on their skin to the end of the study. So what we're seeing here in this pilot study is that we as dermatologists when we give these prescriptions, even if it's a short period of time, we are eliciting in a fairly high proportion of these individuals the development of antibiotic-resistant staphylococci.—

--So why do we care? Well, antibiotic resistance is a worldwide issue and multidrug-resistant organisms are particularly problematic. And if somebody develops a resistance to say TMPSMX, which can be used for other types of infections, are some of our actions that we're doing now leading to potential problems in the future if they might need those antibiotics? Because bacteria can potentially share resistance genes with other bacteria.—

--It's important to still have the caveat that antibiotics are important, they're lifesaving. And sometimes there are not many alternatives, and so antibiotics need to be given. But it really highlights to us that dermatologists, the CDC has calculated that dermatologists prescribe more antibiotics per year per provider than any other provider group.—

--So dermatologists are really important, if we are going to consider antibiotic stewardship and trying to consider how are we prescribing antibiotics. And what can we do to reduce this problem of antimicrobial resistance.

MARAL SKELSEY, MD, FAAD: You bring up a really important point about the stewardship, antibiotic stewardship. And what are we doing as a profession, within our specialty to reduce the amount of antibiotics that are being prescribed?

HEIDI KONG, MD, MHS: That is a really, really important thing to think about, is what is it that dermatologists are doing or can do. I think what some others have published in the last few years, Dr. Barbieri and colleagues have highlighted that in a several year period that antibiotic prescriptions, particularly for skin surgeries, actually increased significantly over a very short period of time.—

--And so the question being, are those for the indications that are known, for example, are they in certain skin sites, anatomical sites for which there are guidelines that say these are areas that are at higher risk for developing concerning infections? Or is the patient of a particular high risk

group? I think it's really important to be aware of those guidelines of what is recommended for those patients that should receive antibiotics because they fall into a high risk category or do they not.—

--And so being aware of those guidelines I think are important. I think it's really important that we actually have more studies, because it's not really clear what other parameters are needed. For example, in other chronic inflammatory skin conditions, we often prescribe antibiotics. And what are the alternatives? Are we considering non-antibiotic alternatives? And if not, why? Do we need more therapeutic options?—

--Or do we need more head-to-head trials to compare efficacy? Or do we need trials to see what is the shortest period of time that somebody needs antibiotics? Do we need to give a full 10 day, 14 day course? Can we give something shorter? Will it still have the same efficacy? So there needs to be a lot more of these studies to really help guide a practicing dermatologist. Because there are some guidelines, but there are not a lot of guidelines.—

--There are some consensus statements, which are based on expert opinion, but there aren't enough of these really well-defined, randomized, controlled studies that give us enough evidence to say how should we better prescribe antibiotics so that we can be good antibiotic stewards.

MARAL SKELSEY, MD, FAAD: I was struck by how low a dose still resulted in antibiotic-resistant organisms. How long on the skin do these remain? How long in the skin and the gut?

HEIDI KONG, MD, MHS: That's a really good question about how long the antibiotics stay in the skin and the gut. So I think I didn't clarify that what you just brought up was that I talked about the 100 mg of doxycycline twice daily. But you're right, when we gave 20 mg twice daily, about

half of those healthy volunteers also developed antibiotic-resistant staphylococci that persisted on skin for the yearlong study.—

--So that is really a strong indicator that there is a dose response. That if you're getting 100 mg twice daily, all of those subjects developed resistance. Whereas if you're getting 20 mg, half of those developed resistance. So in our study, the drug is likely out of the system within several half lives, when we've checked for blood levels of the antibiotics. So the antibiotics are out of the system but those resistant bacteria persist.—

--So do they persist longer than a year? We don't know. Most people don't do a study that long. We struggled to even keep those people in the study for a year. So I think nobody has really systematically studied a larger group of people for a longer period of time. But around the time that our paper came out at the end of 2021, there were also several papers that just happened to have examined antimicrobial-resistant organisms in the gut.—

--And so there is this increase in the amount of studies that are showing that it takes just one hit and then you've induced what one group of authors has called antibiotic scarring. That the scarring persists for a long period of time. And again, I'm not saying that we shouldn't prescribe antibiotics. Antibiotics really are important. But it's a matter of the situation in front of you as you look at this patient, and that's in the clinic room, does this patient need antibiotics?—

--What are the other alternatives? Is there a more narrower-spectrum antibiotic I should consider? So these are all CDC recommendations: shorter durations, narrower spectrum, other alternatives. I think what would be really interesting is more systematic studies of comparing those regimens which incorporate, for example, in acne if one is going to give an antibiotic, other medications that often are prescribed at the same time, would that reduce the risk of antibiotic resistance development?—

--Because these types of studies are expensive and prolonged, it's not that common that people do those types of studies in the way we kind of did it, where we cultured the bacteria from multiple time points throughout the yearlong study and then we actually sequenced the bacteria to look for the resistance genes. Those are more intense studies and it's not as easy to do that for all of these studies that people do when they're comparing different regimens.

MARAL SKELSEY, MD, FAAD: I'm a Mohs surgeon, so I think a lot about the effect of immune system on cutaneous oncology. What do we know about the microbiome and the development of skin cancers?

HEIDI KONG, MD, MHS: There are several groups that are studying that, that I'm aware of, that are looking at different microbes. So I think the jury is still out exactly how it might influence cancer development in people. There have been some mouse studies, but I think there is still more to be understood about the role of the microbiome in skin cancers.—

--I think one of the challenges with microbiome studies is that they can show association but not necessarily causation. That somebody with a skin cancer may have, particularly if it's eroded, there might be a skin microbiome but is that because there is a barrier breakdown? Or is it really because there's a cancer? So is that more a side effect of it being a different type of skin, rather than causing the disease? So those are harder to study. Once the skin lesion is developed and if the microbiome is different, it's hard to attribute causality.

MARAL SKELSEY, MD, FAAD: I think similarly with wound healing and developing studies.

HEIDI KONG, MD, MHS: Yes, so for wound healing there are several groups that are examining the role of the microbiome. Again, certain bacteria can be associated with wounds versus intact skin. And there are groups that are exploring are there certain bacteria that might

be associated with poorer outcomes. So there are definitely groups which are looking at that idea of what is the role of the microbiome.—

--And is it a signal that somebody might be less likely to heal as quickly? Or what is the contribution of those microbes to wound healing?

MARAL SKELSEY, MD, FAAD: Finally, what would you like dermatologists to know about the microbiome?

HEIDI KONG, MD, MHS: I see the microbiome as the most interesting thing that I've seen about it from my viewpoint is that it may be a signal when things are potentially abnormal or there is a problem. What is harder for us to determine is what is normal or healthy. Because in our healthy volunteers that we've seen, the microbiome is so variable from one person to another, so the range of what is considered normal can be quite wide.—

--However, if you all of a sudden see lots of DNA viruses on their skin time after time, that actually is a possible signal that their immune system is not normal. I think there is potential of using that as a signal for what might be going on in the host. But again, it's a finicky system in that depending on where you sample, what are the other confounders that might be coming into play, it can be a challenging field to actually study, because there are these potential exposures that can affect what we actually see or get as a readout of the skin microbiome.

MARAL SKELSEY, MD, FAAD: Sometime in the future, maybe we'll have a microbiometer and we can determine levels of illness, thanks to all of your work. Well, thanks for being with us today and sharing your expertise, and for all the phenomenal work you're doing at the NIH. And thank you to our listeners for joining us for this episode of *Dialogues in Dermatology*.

HEIDI KONG, MD, MHS: Thank you so much.

Commentary

Abigale Clark, BA and Andrew Desrosiers, MD with Todd Schlesinger, MD, FAAD (ed.)

Although research on this topic continues to expand, the microbiome of the skin largely remains a mystery. In this episode of Dialogues in Dermatology, Dr. Heidi Kong, a Senior Investigator and Chief of the Cutaneous Microbiome and Inflammation Section at the NIH, discusses what we know about the skin microbiome thus far, including the latest research on the topic with Dr. Maral Skelsey.

One of the first things to be discovered about the skin microbiome is that it is very site specific. For example, a different combination of bacteria, fungi, and viruses will be found on the skin of the same person sampled at two different anatomic sites at any given time[1]. In addition, the skin microbiome varies with the changes in serum hormone levels that occur during puberty. With this, a person's physiology has a tremendous impact on the composition of the skin microbiome[2]. Further research has shown that individuals with atopic dermatitis have a significant increase of certain bacteria, such as staphylococcus aureus and/or staphylococcus epidermidis, during disease flares[3].

Importantly, the microbiome can be very different in those with immunodeficiencies. For example, there is a patient population with DOCK8 immunodeficiency who can have very severe eczema, malignancies, and early mortality. These patients have been followed at the NIH as they go through the transplant process, and have been found to have a higher-than-normal predominance of DNA viruses on the skin. According to Dr. Kong, immune status is especially important in shaping what is found in the human microbiome.

Recent research has explored the effects of antibiotics on the skin microbiome. In a pilot study, Dr. Kong's team found that in all healthy volunteers who took trimethoprim-sulfamethoxasole and all who received 100mg twice daily of doxycycline developed staphylococci on their skin that was resistant to those respective antibiotics. In addition, those specific antibiotic-resistant bacteria continued to be found on their skin at the end of the study[4]. The important finding here for dermatologists is that, when we give these prescriptions even for a brief period, we are eliciting the development of antibiotic-resistant staphylococci.

Although antibiotics are important and at times unavoidable, the CDC has calculated dermatologists prescribe more antibiotics per year per clinician than any other clinician group. It is important for dermatologists to be aware of guidelines for high-risk patient groups and anatomical sites that are at higher risk for developing concerning infections. Although there is a need for more studies to help guide a practicing dermatologist, the CDC recommends using shorter durations and narrower spectrum antibiotics when possible.

The most interesting finding thus far is that the skin microbiome may be a signal for when there is a problem, as exemplified in patients with immunodeficiencies. According to Dr. Kong, the skin microbiome has the potential to be used as a helpful signal of what might be going on in the host at some point in the future.

References

- Grice EA, Kong HH, Conlan S, et al. Topographical and temporal diversity of the human skin microbiome. *Science*. 2009;324(5931):1190-1192. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2805064/

- Oh J, Byrd AL, Park M; NISC Comparative Sequencing Program, Kong HH, Segre JA. Temporal Stability of the Human Skin Microbiome. *Cell*. 2016;165(4):854-866. URL: https://pubmed.ncbi.nlm.nih.gov/27153496/

- Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22(5):850-859. URL: https://pubmed.ncbi.nlm.nih.gov/22310478/

- Jo JH, Harkins CP, Schwardt NH, et al. Alterations of human skin microbiome and expansion of antimicrobial resistance after systemic antibiotics. *Sci Transl Med*. 2021;13(625):eabd8077. URL: https://pubmed.ncbi.nlm.nih.gov/34936382/