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Exploring Fungi in Cancer-Type Tumors & Cancer Therapeutics

Mario:
An international collaboration of researchers and institutions have identified fungal communities in cancer tumors. How will this emerging data impact the development for therapeutics for cancer?

Welcome to *Project Oncology* on ReachMD. Im Mario Nacinovich. And joining me today to share research on fungal ecologies in cancer therapeutics is Dr. Gregory Poore, a bioengineering researcher at UC San Diego and the cofounder and chief analytics officer at Micronoma.

Dr. Poore, thank you so much for joining me today.

Dr. Sepich-Poore:
Thank you, Mario, for having me.

Mario:
So, to start us off, Dr. Poore, what led you and the other researchers to take a look at cancer-associated fungi?

Dr. Sepich-Poore:
I'd be happy to. Back when I was in college, I very tragically lost my grandmother to pancreatic cancer. She was diagnosed in stage IV metastatic disease and had just over a month in order to live before passing. At that time I was really wondering why there weren't better solutions for earlier cancer detection and also why my grandmother had been resistant to therapy.

As a second-year med student, I came across what might be a major factor that we were missing in the diagnosis and treatment of pancreatic cancer. Namely, that was bacteria. There was a surprising study published in Science in 2017 that documented that more than 75 percent of pancreatic tumors had bacteria living within them, and you could actually cultivate these bacteria and demonstrate that they were able to directly metabolize gemcitabine, which at the time was the gold standard chemotherapy given to pancreatic cancer patients, meaning that bacteria were mediating treatment resistance to these patients' therapies. And this was at the time when I was deciding what my PhD project was going to be, and I hypothesized at that time that it was very likely bacteria were going to be found in other cancer types as well, which led us to mine the largest database in existence at that time of cancer sequencing data known as the Cancer Genome Atlas.

And in that analysis we used a database comprising about 60,000 microbial genomes as a reference including bacteria, viruses and archaea, and we profiled the Cancer Genome Atlas's compendium of about 600 terabytes' worth of whole genome sequencing data and transcriptome data, and in that analysis we found a few major things. And I'll tell say how this is relevant to the fungi story. Specifically, that no major cancer type was sterile. And on top of that we were able to distinguish which samples belonged to which cancer types solely by using their microbial information. In other words, the cancer type's microbiome was unique to that specific cancer type.

And we were interested in looking at this in particular because while we were in the review process of our paper, there was another paper published in Nature by George Miller at NYU that also documented the existence of fungi in pancreatic cancer. And, in fact, he could treat mouse models of pancreatic cancer just giving amphotericin B, which is a selective antifungal agent, and could also cause these pancreatic tumor models to grow by adding in certain kinds of fungi. So this really excited us and gave us the foundation and interest in order to look for fungi.

Mario:
Now let's take a look at your study. What could you tell us about it?

Dr. Sepich-Poore:
We analyzed over 17,000 tissue and blood samples across 35 human cancer types and 4 international independent cohorts. I think the major takeaway from this massive data analysis and effort was that fungal DNA was lowly abundant but was found in every human cancer type that we examined. Something that was also really interesting is that because we had previously analyzed many of the same samples for bacteria, when we added in the fungal data, we were looking to see if there were going to be positive or negative correlations or interactions between them, and we were really surprised to find that traditionally, as we expected outside of the human body, wherever we find bacteria, there are fungi, and we found the same thing in tumors. But what was really remarkable is that there were strong positive correlations between them, meaning the more number of bacteria that we found, the more number of fungi that we also found, the more diverse the communities of bacteria that we found, the more diverse the communities of fungi that we also found. And this led us to hypothesize that there maybe interactions between fungi and bacteria and the kinds of immune responses that we would observe.

And so we analyzed these data looking for fungi, bacteria and immune cell relationships across 20 cancer types and identified different subgroups that could actually stratify survival across these 20 cancer types. We also found that intratumoral fungi were capable of even predicting immunotherapy response, and we also found trace amounts of this fungal DNA present in plasma samples as cell-free microbial DNA. And even though it was trace amounts, it was actually sufficient to diagnose healthy versus cancer patients even in stage I disease.

Mario:
And turning to the results, can you share some of your key findings with us? What did you learn about the fungi being present in human tumors?

Dr. Sepich-Poore:
Yeah. It's an excellent question. And to add on what I just said, I want to comment on how these fungi-bacterial synergies present in the tumor suggested a kind of permissive tumor microenvironment. It's allowing these fungi and bacteria to interact with each other in a way that produces synergy. And we're not quite sure what the mechanism is, but this synergy I think is really important for both understanding how the cancer microbiome will function, particularly that over time, and also how it also may be druggable.

Another key finding that is very translational is this idea that small amounts of this fungal DNA as well as bacterial DNA was detected in blood samples from the same patients. And this may sound like a very new idea, to some of your audience, but it actually goes back to a very old paper originally published in 1977 in The New England Journal of Medicine. And I was actually taught this idea as a medical student, that if I ever came across a patient with streptococcus bovis as a bacteria in the blood of a patient or perhaps streptococcus bovis endocarditis, which is an infection in the heart valves, then I always needed to look for the presence of colorectal cancer. And at the time when I was learning this as a medical student, it was really fascinating to me because I didn't quite see the relationship between a bacteria in the blood and a subsequent cancer diagnosis. But what our study has shown is that these microbes are cancer-type-specific, as in they're actively able to grow and thrive within these tumors, and if they're being found in the bloodstream, it's actually an indicator that this cancer exists in the patient. And so, if we're able to detect these cell-free DNA fragments from these fungi and bacteria, it actually allows us to diagnose cancer earlier and so I think there's a lot of excitement around how we can either augment existing diagnostic approaches using this microbial information or how we can develop new types of diagnostics just based on them alone.

Mario:
For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Mario Nacinovich, and I'm speaking with Dr. Gregory Poore about fungi in human tumors.
Now that we reviewed some of the study's key findings, Dr. Poore, what does this mean for future research at the microbiome level?

Dr. Sepich-Poore:
Sure. I think an easy way of thinking about it is that no microbe is left behind. What this picture creates is that there is this multidomain community in which these microbes are interacting with each other, so bacteria are interacting with fungi which may be interacting with viruses, all thriving within this immunosuppressed tumor microenvironment. And I think there's a lot of excitement, about in because we know that the microbiome is inherently modifiable. What I mean by that is that on the basis of antimicrobials and on the basis of supplementation, we have the ability to directly change the microbiomes that are present within our human bodies quite easily.

And so, the question then becomes "Well, how can we modify our microbiomes in order to enhance antitumor activity? There may actually be some good microbes that are helping the immune system recognize the tumor. It's also possible, as the literature has already shown, that there are certain microbes that are worse for the cancer progression.
And so I think delineating in the next few years which microbes within the tumor are good for the patient, which microbes are bad for the

patient and which microbes are just kind of passive passengers is going to be a major activity that will hopefully have huge benefits for patients in the long-term.

Mario:
What sort of impact do you think your study's findings will have on drug development for oncology?

Dr. Sepich-Poore:
I think there's a few different ways that we consider this. So, starting with fungi, fungi are extremely low abundant in tumors. And to give a rough approximation there's about 1 percent of the total cell count of a tumor appears to be bacterial. Fungi are about 100-fold less abundant than bacteria, so there's a very, very small amount of the cells in a tumor that are actually fungal in nature, and there's also a relatively small amount that's bacterial. But I think the key thing here is that the low abundance does not necessarily mean it's unimportant. It's not so much about the low abundance as long as these bacteria and fungi are immunologically potent. And so I think from the development of drug targets, it's first going to be really important to figure out which fungi are the bad actors and which fungi are the good actors, and it's the same thing with the bacteria; which bacteria are the bad actors, and which bacteria are the good guys. And once we separate those out, we can start trying to selectively target the bad actors, both the fungi and the bacteria that are present within these tumors, while still trying to retain the good actors, the ones that are helpful for developing antitumor immunity.

But taking a step back from that, assuming that we're able to do that, that distinguishment, that separation between good actors and bad actors, there's a huge amount of promise for drug development in oncology, most notably because these bugs, if I may call them colloquially, are completely independent genetically, meaning that it is much easier to target them with minimal side effects than it is to target a cancer which looks mostly like a normal human cell but with small aberrations associated with it. And so, once we can identify, again, which fungi and bacteria are bad actors, I think it opens up a wealth of opportunity in oncology drug development because they are much easier to target selectively than cancer cells are from their normal host counterparts.

Mario:
And finally, Dr. Poore, I'd like to give you the last word. Do you have any final takeaways that you'd like to share with our audience today?

Dr. Sepich-Poore:
I would like to suggest that, the utility of all this information, can be extremely translational both for diagnostics, prognostics and therapeutics, but it can also help improve the theoretical models of cancer that we've been building for the last 10 to 20 years. And specifically I want to highlight cancer clonal evolution. Cancer clonal evolution is really important when we think of treatment resistance. Like, in the case of my grandmother, she became resistant to her therapy within two to three weeks, and it was unclear to both the physicians and others why she was resistant to therapy and why didn't it end up helping her, and this idea can very often be modeled by using clonal evolution as a process. The challenge though is that none of the existing clonal evolution models have accounted for bacteria or fungi. And we know based on research that's been done in the last five years that these microbes can impact the cancer cell genome. Virtually, every aspect of cancer cell state can be directly modified by these intratumoral microbes, and yet they're not currently included in these models of cancer clonal evolution.

And the reason why I think, again, this is so important is because if we're going to understand why certain patients eventually become resistant to certain therapies, we really need to include this microbial information. And I think by doing so in the future, we'll have a much better understanding of not only predicting who's going to respond and not respond but also being able to change someone from a nonresponder to a responder. And so that's something that I'm, I'm really, really excited about, but I think it's going to take a lot of good and smart people working on this problem to figure it out.

Mario:
Well, with those final thoughts in mind, I'd like to thank my guest, Dr. Gregory Poore, for joining me today to share his insights on cancer-type-specific fungal ecologies and bacteria. Dr. Poore, it was great speaking with you today.

Dr. Sepich-Poore:
It was nice to speak with you too, Mario. Thank you so much.

Mario:
I'm Mario Nacinovich. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology, where you can Be Part of the Knowledge. Thanks for listening!