Science Translational Medicine Podcast

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Host – Orla Smith

Hello, I'm Orla Smith. Welcome to the *Science Translational Medicine* Podcast for October 26th, 2011. In this show, I will be speaking with Dr. Jeffrey Gordon of Washington University in St. Louis about his new study that looks at the effects of probiotic yogurt on the gut microbiomes of humans and mice.

We all enjoy a tasty yogurt and benefit from its nutritional value. Some yogurts contain probiotic bacteria that provide additional health benefits, but how they do this isn't clear. One possibility is that probiotic bacteria directly affect the vast population of symbiotic microbes that inhabit our gut, the so-called gut microbiome. But testing this possibility is a daunting task. Undeterred, Jeffrey Gordon and his team fed a popular probiotic yogurt to identical twins and to gnotobiotic mice …these are germ-free mice seeded with a model human gut microbiome. They then analyzed the human and mouse gut microbiomes by deep sequencing, transcriptomics, and metabolomics to see if they were altered by consumption of the yogurt.

Here now is Dr. Gordon on the line to tell us what he found.

Interviewer – Orla Smith
Welcome, Dr. Gordon, and thanks for joining us.

Interviewee – Jeffrey Gordon
Thank you for having me.

Interviewer – Orla Smith
So what are probiotic foods?

Interviewee – Jeffrey Gordon
Well, probiotic organisms are microbes that people intentionally consume that have purported health benefits. These microbes can be consumed in the form of capsules, they can be introduced to foods – yogurts represent one example. And one of the questions that this field is asking is, "What are the effects of these organisms on individuals? Do these effects vary as a function of age? Do they vary as a function of cultural traditions –

different populations consume different foods – is that going to be a factor that influences their activities? And how – given the considerable variations in the composition of microbial communities that exists among people – can we discern the effects of these organisms as a function of these different variables? Can we create, basically, a discovery pipeline where we can analyze their effects under highly conditions – more controlled than we can achieve with human studies? And, having interrogated those models, can we translate the information to humans – guiding clinical trials, knowing what to analyze in human subjects that consume these different preparations, and gaining a greater degree of insight about their effects?" Basically, to step back at this very exciting time in the discovery of these microbial components of our cells and develop a means to do microbiome-directed diagnostics and therapeutics.

Interviewer – Orla Smith
Now, why did you choose to study the effects of the probiotic yogurt on the gut microbiomes of identical twins?

Interviewee – Jeffrey Gordon
Well, we're captivated by the opportunities that twins might provide at early stages in understanding the effects of things like probiotics or foods on the structure and dynamic operations of microbiomes. And, if you are a monozygotic, or genetically identical twin, you've obviously been born with a shared set of human genes; you've also had very common early environmental exposures. And we felt that in the field, that studying twins offers an opportunity for an individual in a twin pair, a so-called co-twin, to serve as his or her own control as a function, for instance, of consuming a yogurt. But the other twin could also serve as another control, so that we could factor in intrapersonal variation in the structures and dynamic operations of a microbiome, but also interpersonal variation.

Interviewer – Orla Smith
And how did you test whether the yogurt affected the gut microbiomes of the twins?

Interviewee – Jeffrey Gordon
Well again, using this conceptualized experimental design where each person could serve as their own control; and where the genetically identical co-twin could serve as another control; and where different sets of twins can serve as other types of reference controls, we had each twin – in these twin pairs that we studied – consume a yogurt but following a preliminary period of observation of their gut microbial communities. So, we wanted to see how much those communities varied prior to consumption of the yogurt; what the impact of the yogurt would be on their community, at several different levels; and then, once the yogurt was no longer being consumed, how did the community adjust?

Interviewer – Orla Smith
So, when you analyzed your deep sequencing data, what did you find?

Interviewee – Jeffrey Gordon
Well, when we gave the twins the yogurt, we found that there was no significant change in the representation of bacterial species in the gut microbiota, nor was there a significant change in the representation of microbial genes in that community. The yogurt didn't seem to disturb or disrupt the structure of the microbial community. We also saw – as we had seen earlier in studies of twins – that even identical twins have different collections of bacterial species represented in their gut microbiota; that the species repertoire was more conserved between sets of twins, co-twins, that is to say within a family there was a sharing of microbial species; and that there was a greater difference between different sets of twins in terms of which microbial species were represented. If you go beyond species, however, there was a greater sharing of genes. So there's a core group of genes that are represented in the gut microbiomes of all people, and this core was represented in this group of twin pairs.

Interviewer – Orla Smith
Now, you also ran a whole series of parallel experiments feeding probiotic yogurt to these gnotobiotic mice. Can you tell us more about this fascinating mouse model?

Interviewee – Jeffrey Gordon
Well, we knew going into this study that we would have to set up two tracks of investigation. We felt that it was very, very important to be able to create a model of the human microbiome where all the species in the gut were known and all the genes in their genomes were defined. And this was done by taking cultured representatives of the normal human gut community whose genomes had been sequenced and putting these organisms into the intestines of mice that had been reared under germ-free conditions. So these mice were sterile – they were born sterile, they remained sterile – in these special gnotobiotic isolators. Gnotobiotic, by the way, comes from the Greek word gnostos meaning "known" and bios, "life". So these animals are reared under conditions where we can either keep them under a germ-free state, or at various stages of their lives we can introduce microbes. In this particular case, we did a transplant of a organ – it was a human organ in a sense, except for it was a microbial organ – in the form of 15 prominent members of the normal human gut microbiota and established a model community that resembled in many aspects the human, much more complex human, gut microbiota. And then, having established this community of 15 organisms harboring about 58,000 genes, we were then able to deliberately introduce the five different strains of bacteria present in this commercial, fermented dairy product. And we had sequenced the genomes of these fermented milk product associated strains, so we not only knew the genes in the genomes of this model human community, but we also knew the genes in the microbial consortia that was being introduced. So we could follow in these animals over time what the properties of the model community were, while they consumed the diet that was rich in plant polysaccharides and low in fat, a healthy diet, and then see the impact of adding these strains of yogurt-associated microbes not only on the relative representation of the different members of the model community but also on the dynamic operations of that model community – which genes were expressed, which metabolites were produced as a function of the introduction of these strain consortia?

Interviewer – Orla Smith
And so, what did you find in these gnotobiotic mice?

Interviewee – Jeffrey Gordon
We found that the consortium of bacteria were able to insinuate themselves into the model community. Two members of the community were able to maintain themselves at levels that we were able to detect. One, in particular, was a very prominent member of the community, and we saw that the community adapted to the now presence of these fermented milk product-associated bacterial consortia, and, in turn, the members of the consortia adapted to the presence of the model community. And they did so in very interesting ways. There were significant changes in gene expression – genes involved in a number of metabolic processes, most notably processes related to the metabolism of carbohydrates, complex carbohydrates, that are normal components of our diet. The most prominent member of the administered yogurt consortia – *Bifidobacteria animalis* subspecies *lactis* (if you want to say that rapidly in public) – the most prominent member adapted its patterns of gene expression so that it was able to degrade components of our diet that contain xylans. And these components are represented in fruits and vegetables and other things that we normally consume. So, it adapted by up-regulating these genes and was able to consume these products that were represented in the diet. At the same time, different members of the model human microbiome adapted to the representation, or the presence, of these yogurt strains by changing their patterns of carbohydrate metabolism. And, in particular, there was a concerted change in the expression of genes that were involved in starch metabolism, starch and sucrose metabolism, very common components of our diets. It was very fascinating for us to see that different members of this model community adapted in different ways, with respect to starch and sucrose metabolism. One member, in particular, up-regulated a gene that was very important for future metabolizing these sugars; in other cases, the response was shared by multiple members of the community. You get the picture from this very defined model of how each organism is able to not only sense the representation of these fermented milk product-associated strains but to adjust their metabolism in ways that presumably benefit themselves, the community, and perhaps the host.

Interviewer – Orla Smith
So, in the twin study, the five bacterial species in the yogurt didn't actually take up residence in the gut, did they?

Interviewee – Jeffrey Gordon
No, that's a very good point. The twins consumed these yogurts for a total of 7 weeks, and then when the twins stopped consuming the yogurt, all traces of the strains in the yogurt were lost within 2 weeks. A few of the twins showed a more prolonged pattern of, or time course of, loss, but these are strains that have to be consumed on a daily basis in order for these organisms to maintain their presence in the gut ecosystem. So, they certainly aren't entrenched members of the normal human gut microbiota. I'll say at the

same time that the member of the strain consortium in this yogurt that was most prominent in the mice was also most prominent in the humans – this *Bifidobacteria animalis* subspecies *lactis*. And, because of its prominence, we were able to ascertain its lifestyle not only in the gnotobiotic mice but also in humans. What was captivating to us is that because of the complexity of the human gut microbiota, we wouldn't really have known where to look and it would have been hard to see without the guidance provided by the mouse models, which were much more simplified and defined. And, in fact, the lessons learned from these gnotobiotic mice directed us to look at features of carbohydrate metabolism and to find, by the way, that the very changes that we noted in mice also occurred in humans.

Interviewer – Orla Smith
And what do these findings tell us about the stability of the gut microbiome in healthy humans?

Interviewee – Jeffrey Gordon
The microbiome is a fascinating metabolic organ. It's able to maintain itself despite the fact that we're constantly perfusing our guts with various liquids and foods. Who's there in the microbial community – at least by the time an individual is an adult – seems to remain the same. It's just a proportional representation of organism changes with factors, such as diet. We know that diet is a critical shaper of the structure and functions expressed by gut communities. And we did see in this study of twins that there was a very distinct repertoire of organisms and genes in each individual, and they remained constant, although their proportional representation would change over time within the twin. Now, the change in proportional representation was not significant for any of the observed species when you consumed the yogurt strains. What changed, rather, was patterns of gene expression and presumably, metabolism.

Interviewer – Orla Smith
So, is the gut microbiome less stable in people with diseases, such as ulcerative colitis or irritable bowel syndrome?

Interviewee – Jeffrey Gordon
That may be one theme that's emerging from studies of the microbiome – that there's greater variability in an unhealthy gut microbiota. We really have to understand in greater details the factors that shape community structure and function. And I do think that the marriage of gnotobiotics – the study of these mice with defined populations of microbes – and this new aspect, called metagenomics – the culture independent characterization of the structure and dynamic operations of gut microbial community – is a marriage not only of convenience, but a marriage of necessity. And like all good marriages built on mutual respect and devotion. And I think that that's going to be very important as we move forward to establish a preclinical research pipeline where we can ask questions like the ones you just posed to us – is there greater instability or lability in the microbial communities of individuals who are ill with a variety of different disease

than those of healthy individuals? And I think we can address those questions first and foremost in the guts of these mice.

Interviewer – Orla Smith
So, can probiotic foods help in treating diseases such as colitis where the gut microbiome has been severely disrupted?

Interviewee – Jeffrey Gordon
That's a great question. And I'm going to answer it in several different ways. It's not only colitis – can the gut microbiome be intentionally manipulated in ways that can improve our capacity to harvest components of our diet? Can we improve the nutritional status of individuals by having an idea of the consumers' microbial community structure? And are there individuals who are at risk for diseases like obesity or malnutrition where their gut community structure is such that it affects the harvest or partitioning of nutrients and energy from the diet to the host? We think we can. Our approach has been to try to set up – using the same systems we've been talking about – a pipeline for identifying next generation probiotic species. And let me just give you a quick thumbnail sketch of how this works. We're now able, we've learned to culture the majority of bacterial species present in an individual. And, as a consequence, we can create personal culture collections from individuals who are at risk for diseases or who represent different cultural traditions or who already have manifest disease. And these personal cultural collections can be introduced into germ-free mice to create a humanized animal where the humanization is at the level of their gut microbes. And another facet of their humanization is that they're given human diets. So we can basically do global surveys at the intersection between what somebody eats and the response of their different microbes. Because we have these personal culture collections arrayed out in test tubes, we can return to these collections and take those organisms that are most responsive in these mouse models to different perturbations– whether it be diet or otherwise – and try to understand why they respond as they do and to manufacture different types of consortia of microbes that may have beneficial effects in certain dietary contexts, at particular ages, etc. So, I think that there is a great deal of opportunity to discover new sets of organisms that respond to perturbations, like diet perturbations, to test their efficacy at different doses in these humanized mouse models, and then to, in an informed way, design, execute, and interpret clinical studies in humans with the ultimate aim of trying to develop safe and effective ways for manipulating our microbial cells in ways that enhance our health and prevent different diseases.

Interviewer – Orla Smith
Dr. Gordon, thank you so much for joining us today and congratulations on a fascinating paper.

Interviewee – Jeffrey Gordon
Thank you so much.

Host – Orla Smith
That was Jeffrey Gordon of Washington University in St. Louis. Check out his paper in the October 26th issue of *Science Translational Medicine* by going to our website at stm.sciencemag.org.

I'm Orla Smith, thanks for listening!

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