Ask A Biologist Vol 096 (Guest: Rosa Krajmalnik-Brown)

Microbes Living Inside Us

On this program we talk a lot about cells. In particular plant, animal, and microbial cells. But did you know there is a world of microbes that make their home inside and on our bodies. Before you start to worry, you need to know most of these microbes are important for us to live. In fact, without them we would not be here. This tiny world is the focus of **Rosa Krajmalnik-Brown's** research. It spans the microbes that live with us and those that are helping us clean up our environment. There is even a discussion about how poop is helping treat some people and that is something you don't usually get talk about.

Transcript

Dr. Biology: This is Ask A Biologist, a program about the living world, and I'm Dr. Biology.

Dr. Biology: If you do much reading or watched much television lately, you know that bacteria have a really bad reputation. Just about everything you hear about these tiny organisms has them causing all sorts of problems. But it turns out that many bacteria are good. In fact, we owe our lives to a large collection of these good microorganisms. And when I say large, I'm not kidding.

Dr. Biology: The average human adult is made of around 37 trillion cells. I think that is the last count. but those cells are only about half of our total cell count in our body. So what makes up the rest? The other half are microscopic colonies of cells that make their home inside and on your body. These are the bacteria, viruses, fungi, and archaea. I know you're getting grossed out right now, but it gets even better. The bulk of these cells make their home in our gut, which is literally the bowels of our body.

Dr. Biology: So what does the cell microbiome do for us? That's one of the questions my guest is of exploring. I've caught up with Rosa or is she prefers Rosy Krajmalnik-Brown, a researcher in the Sweete Center for Environmental Biotechnology at the Biodesign Institute, and also a professor in the School of Sustainable Engineering and the Built Environment and Arizona State University.

Dr. Biology: Today we get a chance to talk about her work in human intestinal environmental microbiology. T hat's a mouthful, but there's a lot to learn today and in particular about how these microorganisms relate to obesity and autism. We might even get the inside story on a treatment using poop. Yes, you did hear that correctly, and if that's not enough, we're going to pop outside the body and learn about another collection of microorganisms that are being used to help clean the environment.

Dr. Biology: Welcome to the show, Rosy.

Rosy: Thank you for having me at this show.

Dr. Biology: When we talk about biomes, it's often those we can see like we happen to live in the desert, so there's a desert biome. Other people might live in and say the rainforest biome. These communities of plants and animals have been studied by biologists for hundreds if not thousands of years. But there are biomes we cannot see without special microscopes that are as important and in many ways the next frontier of discovery. These would be the microbiomes since the news only seems to report about bad microbes. Let's talk a little bit about the good microbes. You've been studying these tiny helpers and looking for ways we can use them. What's the focus of your research?

Rosy: The overall scheme of my research is to use these microorganisms to provide a service to society. And so there are many different services that we can provide by using these microorganisms. One of them is cleaning the environment another one is providing bio energy, and another one that I know has gotten a lot of attention lately is enhancing our health. These little organisms live inside our bodies and can help us be healthier.

Dr. Biology: Right, it's not only be helpful to us, they're critical.

Rosy: They are absolutely critical.

Dr. Biology: So let's talk a little bit about the gut biome. What are we talking about when we say the Gut biome?

Rosy: The gut biome are all the organisms that live in our intestines and these organisms live in a symbiosis with us. We need them, we need them to survive and they of course need us, which is why it's a symbiosis. They help us digest our food. They provided vitamins. They provide cofactors. They train our immune system and they also produce chemicals that many people have been hypothesizing that interact with our brain. And so they do a lot. The first thing that we know for years that they do is that they help us digest our food, but their interaction with us is beyond digesting our food.

Dr. Biology: Now we're talking about really, really tiny organisms, single cells, mostly single cells. How do you tell one microbe from another?

Rosy: Well, one of the reasons why this research that I've been doing has, I would say exploded in the last few years, is the fact that now we have a way to tell these microorganisms by their genomes, by genetics. I often ask people, why do you think that 20 years ago we didn't have as much research in the gut microbiome? And the real reason is that now we can explore these communities using high throughput sequencing. Sequencing techniques have become more available and cheaper, and this has helped us analyze microbial communities, which is another big topic that I study. I study how these little organisms interact with each other and then how they interact with their environment, how the environment interacts with them, but most importantly is how they interact with each other. And this is really difficult to parse out if you don't have these advanced techniques such as genomics, Dr. Biology: Right. So when we talk about genes, we're talking about DNA. We're talking about codes, the blueprints for life, how things are supposed to be done inside cells, what the cells are supposed to be doing. So when you have these sequencers, they basically read that code.

Rosy: They do. So one of the things that we do with microbes, there is a gene that we use that it's a marker gene that allows us to identify microbes. It is the 60S RNA gene drive ribosomal gene. This is a gene that it's critical. It doesn't change that much, but it has certain variability. And because of that, if we sequence this gene, we're able to say, well, this microbe is in this family, in these species. And that allows us to make catalogs of the microbes that live with each other.

Rosy: So going back to genes and to sequencing, we also know that our body, on a cell-to-cell ratio, we're about half human and half microbe. But if we look at the genes and the menu of possibilities of reactions that happen in our body of metabolic activities, there's about two order of magnitudes more of these genes of microbes in our body than our own genes, which means that what a microbe and all these microbes together can do in our bodies, it's almost more than what we can do by ourselves.

Dr. Biology: Okay? Every year we have an anniversary. It's on April 25th, and it's to celebrate the first time we published the human genome. And that's a giant code that makes up, you know, a human and how a human works, and you said that when we compare that with the microbes that are in our body, the entire genome library of those microbes, it's how many times larger than the human genome?

Rosy: 100 times I said two orders of magnitude. We have about 100 times more genes in our body that belong to microbes than the genes that belong to us.

Dr. Biology: Oh, and that's why some scientists have called it our body's second genome.

Rosy: Ahuh

Dr. Biology: With all that, now we're being able to tell what the different microbes are. We used their DNA, we do the sequencing. How do you know a good microbe from a bad microbe?

Rosy: Well, that's a really good question. And just by DNA we don't. So people tried to say, hey, these microbe are salmonella. It's probably a pathogen. I have news for you. There are salmonella's that are not pathogens. So just by the DNA, we cannot tell if it's a pathogen. In order for us to be able to actually assign pathogenicity to a microbe, we need to see them doing something bad. And so just by the last name, we cannot know. There's a lot of E-coli that are in our, in testing. There's a lot of E-coli that naturally living there and they do no harm. But there are some that are pathogens.

Dr. Biology: So when we say pathogens were saying something that can cause a disease.

Rosy: Something that can make you sick. Yeah.

Dr. Biology: Right. But a lot of those microbes are getting a bad rep from just a few.

Rosy: Exactly. We have in our body, so many good microbes that help us every day and keeping these good microbes happy is one of the aims of my research. And learning how to keep these microbes and be a good interaction between them and with us so we can have a healthy outcome is one of the themes

Dr. Biology: I always like to do some reading on my scientists, and one of the interesting things is that it's not necessarily the good and the bad that we have inside of us. It's actually the number and types that we have in us. Right. So your work has, it relates to obesity and autism. It's not necessarily a good and bad, right?

Rosy: Right. But you said something that is really true and interesting. Scientists that work on the gut microbiome use a metric called diversity. Diversity tells us how many different types of microbes that we have in our population, in our community and research in the gut microbiome has, as a generalization, we think that a healthy gut, is a gut that it's very diverse and there's been many diseases for which we've seen this correlation that it's mainly a correlation, a less diverse gut. It's a less healthy gut. And the way I usually explain this to people is when you have diversity, you usually have a few different bacteria that can do the same job. So if you have 10 workers that can do the same job and one of them gets sick, the job will still get done.

Rosy: But if you have one worker that does the job and gets sick, the job doesn't get done. And the same happens with our microbes in our intestines. If we have a high number of different microbes in a high diversity, it's a healthy community and it's a community that at the end of the day we'll do their job. If those numbers drop, then you don't have a diverse gut. Then you don't have the force and you don't have the extra worker that will do the job if one gets sick.

Dr. Biology: What is causing some people to have a less diverse gut?

Rosy: That is a very good question. Of course, there's a lot of speculation about it. One of the possible causes is the excess use of antibiotics because of course antibiotics kill bacteria. That's what they're made for and you know when they're needed, they're needed to kill bacteria are making us sick. But nowadays we overuse antibiotics.

Rosy: We overuse antibacterials. People like to wipe their hands with antibacterials without any reason, and we also are exposed to chemicals that we were not exposed before. There's also the hygiene hypothesis, which is the hypothesis that we're also not exposed to good microbes enough because we've sanitized our environments. We don't play as much outside. We don't play with the dirt. We don't interact with farm animals and we're just in buildings that are super clean and super sanitized. And so that also reduces the amount of microbes, good microbes, good bacteria that we are exposed with.

Rosy: Another really important thing is diet and more diverse diet will also lead to a more diverse microbiome. If we had many different things, if we had many different foods and vegetables and fiber, fiber is one of the most important things to feed your microbes. Then you're feeding your micro, send you, we'll end with higher diversity.

Rosy: But if you're eating something like what we call a Western diet, which is McDonald's high fat food and a lot of sugar, you're really only feeding a certain little amount of diversity in a little amount of microbes that will take over the space and the population and that's what you will have in your gut. So it's very important to eat healthy, eat lots of fruits. Eat lots of vegetables, lots of fiber because that will also help our microbiome.

Dr. Biology: In your research, there are two areas that you've been spending more time, in particular with the gut, autism and obesity. What are we finding?

Rosy: I'll talk about autism first. We started working on autism, I'm going to say about eight or nine years ago. And one of the reasons I was convinced that this was a question worth pursuing was, and my collaborator, Jim Adams, who I wouldn't be doing autism research without him. He is the reason why I started even exploring the question and I had a few conversations.

Rosy: And in these conversations, one of the themes that came up is that kids with autism have a lot of GI, gastrointestinal problems. They have constipation, they have diarrhea, their tummy hurts. And if you can modulate some of this GI problems, their behavior, and of course they're more comfortable if you're more comfortable, if you're Tommy's not hurting, if you don't have to be running constantly to the bathroom, then you can focus a little bit more.

Rosy: That was the initial reason. There was a study in 2000 that showed that a treatment of Vancomycin, which happens to be an antibiotic, actually led to improvement of behavior in kids with autism temporarily while they were taking the Vancomycin. So the problem with that studies that once the children were off the Vancomycin, they regressed to where they were before. So it was just while they were taking the Vancomycin. But that also kind of gives us a clue that there might be an interaction between the bacteria and the gut and behavior.

Rosy: So Jim and I started asking the simple question, first off, is the gut microbiome of kids with autism and kids that are typically developing different? Can we see any differences? That was the very first question we asked. And I had already been doing a lot of research with microbial communities and with sequencing. And I had already published a paper on the microbiome and bariatric surgery. So I said to him, look what we did. Look at this really nice paper. We can do the same for autism. And that's what we did. So we use these high throughput sequencing techniques and we assess initially 20 children with autism and 20 children that were typically developing. And their microbiome was different, of course, otherwise this wouldn't have continued. And the first thing we observed was that diversity was lower in the kids with autism.

Rosy: I would almost say as expected because this is a kind of a signature of an unhealthy gut. And then we found a few bacteria that are involved in fermenting food that we're missing. There's one that we've been following the name of these bacteria, Prevotella. Prevotella helps us digest our food and is being correlated with higher low fiber consumption and so if we look at our kids with autism in that study, they were basically depleted of Prevotella and are typically developing kids had some Prevotella at lower numbers than if we compare with developing countries, because this is also a signature of, we would call it westernization. And so after we found that kids with autism have lower diversity, we did a second study where we replicated these findings, we replicated the lower diversity and we replicated the missing Prevotella and a couple of more fermenting microbes.

Rosy: We said one of the things that we could maybe do to help is can we add more microbes? Can we change the microbiome by adding more microbes? And this has been an uphill battle where we have really exciting results but was not easy. So we decided to go with a very, I will say, aggressive approach, which was to do what is called fecal transplant for these kids with autism.

Dr. Biology: Ah yes, because you had to figure out some way to get the bacteria inside them.

Rosy: We actually thought about a probiotic, but the fecal transplant we thought was the best approach to really get high numbers, high diversity, to hopefully help these children with this increase in diversity. And I usually don't call it a fecal transplant. And the reason we don't call it a fecal transplant, and it's important for me to stay this, it's because it was a whole treatment. It wasn't just the fecal transplant.

Rosy: So the treatment included two weeks of Vancomycin. Then the children fasted for a day and we completely emptied the gut. And then we did the transfer of beneficial microbes. These microbes were not just poop, which is what people think about when you do a fecal transplant. These microbes were highly processed by some collaborators. They do come from poop, they take the poop and they purify it. And what we got to use in our study was about 90 something percent bacteria, which is what we wanted. It's very purified, only very healthy donors are allowed to donate for this process. And the material we got was very well screened for potential pathogens and viruses. So something I always tell families, I will tell you about their results. And the really exciting do not try this at home because it needs to be really supervised by a physician and it needs to be with the right material, not just poop.

Rosy: Even though people call that a fecal transplant is a little bit more than a fecal transplant. And so how about the results? So what we found is that we were able to increase diversity, which great, that's one of the things that we wanted and we were able to increase dramatically the numbers of Prevotella, which is also good outcome. But most excitingly, the GI symptoms, the gastroenterological symptoms in these children improve dramatically. And we also had improvement in behavior. So it was 18 children. It was an open label trial with leads to some placebo effect. We are aware of that, but they're very promising results.

Dr. Biology: So stay tuned.

Rosy: Stay tuned and very promising and resorts and we are about to publish in the next week or two, a follow up study where we came back to these children two years later to see how they were doing.

Rosy: And again, I'm going to say these are really promising, but I would keep them as promising. We actually need to do more research on this. We need to look larger clinical trials with a control placebo arm. That is what we need to move the field forward right now.

Dr. Biology: Exciting.

Rosy: Yeah. Very exciting.

Dr. Biology: All right, so now we've learned about autism and how the gut biome can make a big difference. What about obesity?

Rosy: It's interesting because in my lab right now, we don't call it obesity. What we're doing, even though it relates to obesity. We've done some work with bariatric surgery and how the microbiome changes after bariatric surgery, especially the after gastric bypass, it changes dramatically. They changes are so big that we were able to see a big change just with three people which usually, you don't see that in their gut microbiome.

Rosy: A lot of people have looked into obesity and there's a lot of hypotheses of how the microbes that live in our intestines can make us fatter maybe, or can make maybe make us leaner depending on how they're working. So one of the hypotheses is that they help us extract more energy out of our food. And so depending on the microbes you have, you might get more calories out of what you're eating. That's one of the hypotheses. They also produce chemicals that communicate with the brain and they interact with our immune and hormonal system. But there's a big question that right now my lab is investigating with an NIH funded grant, which is, since there's a lot of hypotheses. We actually want to quantify the contribution of the microbiome to energy extraction to how much energy we get out of the food that we eat. So we're working on that with our collaboration with the Translational Research Institute in Orlando.

Rosy: My collaborator, Steve Smith is an expert in human bioenergetics and the team here at ASU, which I lead are the experts in microbes, energetics, so we're putting these two together to hopefully answer that question.

Dr. Biology: You also do some work outside the body?

Rosy: Yes, and I've been doing that for longer than I've been doing microorganisms inside the body. My PhD is in environmental engineering. I have always, always worked with microbes and since my PhD I've been also working with tiny microbes that can clean up the environment. They can clean up contaminated soil, contaminated groundwater.

Dr. Biology: This is a great story. Now we're going to work on cleaning up the environment using these tiny organisms. What's one of your favorite projects?

Rosy: All my projects are my favorite projects. It's hard to pick, but we have been working for, I'm going to say if I count my PhD, probably close to 20 years with some tiny bacteria that can respire, toxic chemicals, chlorinated solvents, the most common solvents are perchloroethylene (PCE)and trichloroethylene. We actually have a lot of super fund sites contaminated with these two compounds in Arizona. And these microorganisms that can respire on these compounds, but they do is the same way we use oxygen. They use these compounds and they take out the chlorines and they make them not toxic anymore. So we go from a trichloroethylene for example, and we end up with ethylene, which is not toxic. So these are amazing tiny creatures that live off cleaning the environment. And the exciting part of the story is that it's actually being done in the field. So it's not just the other microbes that we grow in the laboratory and that we're excited about the results that we get in a little small tube. Now there are commercial companies that sell these microbes and there are consulting companies that buy these microbes and they inject them in the ground water and they clean up.

Dr. Biology: How long does it take?

Rosy: Depends on how much contamination, but one of my amazing PhD students, which now is a professor at ASU, Dr. Anca Delgado, work with creating cultures of some of these microbes in the lab. During her PhD and we were able to not only make these little cultures but we scaled up the production. We have large tanks where we were continuously making these cultures and we had a consulting company that said, Hey, I read your papers and I think we would be great if we could use that big reactor that you have to use these cultures in a contaminated site in New Jersey. And we said, you know what we've been producing some much that, why don't we send you some of our microbes so you test if they actually work on the field, because it's not the same to work in the lab. than to actually work in the real challenging environment.

Rosy: And what we hear from him was I think within six months they were able to lower the contamination to an undetectable level, which was amazing. But of course this was a small contaminated site with small concentration. If you go to larger sites, it takes years. One of the sites that is contaminated here in Arizona. I met a consultant working on this side and he said something like, well this is a problem that would take maybe about a hundred years to solve if we just let it happen and I'm not sure what would be the motivation to change this 100 years to 50 years if we do your technology. I actually think that that's huge because for me, going from a hundred years to 50 years means I am alive or not see it. Right?

Dr. Biology: Right.

Rosy: It means the future of our children, it doesn't sound like much, but even if you can do it twice as fast, then we're talking groundwater, we're talking your future. I mean water is a resource that um, that we're running out of. So we need to make sure that whatever we have gets cleaned up.

Dr. Biology: Right. So it's safe.

Rosy: So it's safe, exactly.

Dr. Biology: When you're doing your work outside of the body and we're working with microbes to clean up, there are three terms that you often use, bioaugmentation, biostimulation and bioremediation. And we got a little bit of the bio remediation because that's basically fixing what was contaminated and it's no longer contaminated

Rosy: Using bio.

Dr. Biology: Yes. Right. But what about bioaugmentation and biostimulation?

Rosy: Okay, so one of the ways we manage microbial communities to change them for an outcome is we have two terms in environmental engineering, which are bioaugmentation and biostimulation. And these apply to the environment or they apply also to what we can do in the gut microbiome. So bioaugmentation is adding new microbes, you can think about it as probiotics or maybe fecal transplants.

Rosy: And biostimulation is providing the food that microbes need to grow. So if we think about the human gut, we can think about prebiotics. So probiotics or fecal transplant is bioaugmentation and prebiotics is biostimulation. So it can be used to clean up the environment to manage these communities, to clean up the environment, or it can be using the gut to manage these communities to get a healthier outcome.

Dr. Biology: So stimulation, are we talking about feeding?

Rosy: Feeding, we provide food to the microbes. So in the environment, for example, we usually provide lactate which is a substrate for fermentation. And when we do it in the humans, we do prebiotics, which are usually non fermentable fibers that will make it to the intestines and the microbes will have food. So we're providing food and ideally you want to do that in a way that you're providing it for the microbes that you want to stimulate for the right microbes.

Dr. Biology: Right. For the good ones are the ones that maybe you don't have as many of that you need.

Rosy: Yeah, but sometimes it's not that selective sometimes who provides something that most microbes will eat. So yeah.

Dr. Biology: Now on this show, I have three questions I ask all my scientists, you can't get out of here without answering them. Let me just start off.

Rosy: Laughter

Dr. Biology: We'll start off with an easy one.

Rosy: Okay.

Dr. Biology: When did you first know you wanted to be a scientist?

Rosy: I think it was in middle school, like in seventh grade. My chemistry professor who started the year by telling us about the scientists and their inventions. That's how he started telling us about the history of chemistry. Or maybe he was telling us about the history of chemistry, but my mind was going into, wow, this is amazing people did these things to change, you know, the way we perceive the world and science. So one day I want to invent something. One day I want to be one of these amazing people that can discover something new. So it was about seventh grade that I started getting interested.

Dr. Biology: Okay, so now I'm going to get a little harder. I'm going to take it all away. You've been doing this for 20 some years. You have a passion for science, right? But I'm taking it all away and you're at a university, so I'm going to take away your teaching because I know we all love to teach. What would you be or what would you do?

Rosy: I love singing and dancing, and I guess that's some point. When I was little, I also liked acting a lot. So not that I can conceive of myself as an actress or an answer or a singer. But those were the three things that I used to do besides, you know, science.

Dr. Biology: Oh, I've had a few of my scientists say that they would like to be an actor or a singer. Yeah, absolutely

Rosy: So I used to do drama classes when I was in elementary school and my brother used to joke that I didn't need the drama classes, that I was a drama queen, without the drama class. [laughter]

Dr. Biology: Uh, there was a few of those too. Yeah.

Rosy: Yeah. But I always loved singing and dancing. That also has been my passion, but I never thought that you could make a living out of that. I mean, you can, of course you can be really famous, but I was not the best at it and I was just good. So that's ...

Dr. Biology: One last question. What advice would you have for a young Rosy? Someone that did the same thing where they, they were excited about the scientists and what they have done. What advice would you have for them?

Rosy: To follow their passion and to make sure that they do something that matters because then it's also easier. So for me, I've always done research that it's use-inspired and so we get to the very details of science, but it's always something that, it's translational. It's always something that can be used by people that can help people. And that, you know, for a young Rosie, that helps a lot to follow your passion and to work hard because it doesn't matter how passionate you are, if you don't put in the work, it doesn't happen. It is a, uh, 99% perspiration and 1%

inspiration, [laughter] which is what I tell my kids also, but, you know, I'm not sure they get it. You need to work hard for what you believe in and uh. And do something you're passionate about because then it's also easier to work hard. When something really rocks your boat and you're passionate about. It's easier to putting the hours to put in the time when you come to work and it's fun to come to work.

Dr. Biology: Well, I couldn't agree more Rosy. I want to thank you for sitting down with me on Ask A Biologist.

Rosy: Thank you for inviting me. It has been fun. It has been a pleasure

Dr. Biology: You've been listening to ask about. I'll just in my guest has been Rosy Krajmalnik-Brown, a professor in the School, of Sustainable Engineering and the Built Environment at Arizona State University. Rosy is also a researcher at the Sweete Center for Environmental Biotechnology at the Biodesign Institute.

Dr. Biology: If you'd like to learn a little bit more about her, you can pop over to our Ask A Biologist website and read the story about her called Mending Microbes. The easiest way to do that is to simply search on 'mending microbes' with ''ask a biologist' in your search window and you will find the story.

Dr. Biology: The Ask A Biologist podcast is produced on the campus of Arizona State University and is recorded in the Grassroots Studio housed in the School of Life Sciences, which is an academic unit of The College of Liberal Arts and Sciences. And remember, even though our program is not broadcast live, you can still send us your question, or questions about biology using our companion website. The address is askabiologist.asu.edu or you can just Google the words, Ask A Biologist. I'm Dr. Biology.