



## **Curcumin Pathways & Synergy with Sulforaphane**

With Dr. John Gildea and Dr. Martin Katz

David Roberts (00:00):

Hey everybody, it's David Roberts and you are listening to the Mara Labs Podcast. And today, we will be talking about Curcumin and I have Dr. John Gildea and Dr. Martin Katz with me and...

Dr. John Gildea (00:10):

Hello.

Dr. Martin Katz (00:11):

Hello.

David Roberts (00:11):

Hey guys, thanks for coming. We will be talking about specifically the pathways that curcumin interacts with and John, you said recently, before podcast that you read a couple good papers on pathways and what curcumin does. Why don't you share with the listeners, the pathways that you read about and why you found this paper so interesting?

Dr. John Gildea (00:38):

Yeah. A number of reviews in the last couple of years have tried to tally up the different cell signaling pathways that curcumin can interfere with. And I think the biggest walkway message that I see is that it almost shows up in my brain as snake oil and that there are a lot of pathways that are associated with health versus lack of health. And so, many times it's pushing on the pathways that are pro-health, that you wonder how it can be so selective in that. One of the really obvious ways is inflammatory cascades and so the prime target for curcumin is the NF-kappaB pathway. So we haven't talked that much about the signaling that's upstream of NF-kappaB because NF-kappaB is the portion of that signaling that turns on from inflammatory genes and so you want to block that pathway.

Dr. John Gildea (01:42):

But upstream of NF-kappaB is a whole series of pathways, including the lipopolysaccharide pathways, the TNF-alpha pathways, and this signaling molecule in the center is a complex that's the NF-kappaB complex. And when you're turning off this system in general, you're driving that system to degradation. So you can parallel that with the Nrf2 pathway where it seems to be the opposite. So it's normal circumstances to be off, and then, sulforaphane stabilizes it and turns on Nrf2 so it's the opposite for NF-kappaB. It's off until it's stabilized and then turns on NF-kappa B and turns on all the [inaudible 00:02:35] inflammatory cascades. So that's the main pathway that makes it involved in so many different unhealthy states of being, so when you summarize all of those, there's a whole bunch of them.

Dr. John Gildea (02:48):

So TNF-alpha, TGF-beta is a [inaudible 00:02:53] cascade, or STAT3 three is also another pathway they're commonly affected in neoplasia, but they're also involved in basic states of whether a cell is under stress or not. So, I would say, summarizing another big pathway that's in this area is PI3-kinase. So PI3-kinase is anti-apoptotic. So those are big cascades, PI3-kinase and the opposing pathway is PTEN. Another pathway that is in the middle of a lot of things are the mTOR pathway. So curcumin is in the middle of AMP-kinase NF-kappaB, Nrf2, and really has its imprint of efficacy all over some really famous pathways.

David Roberts (03:45):

And so with the anti-apoptotic, can you explain a little bit about that?

Dr. John Gildea (03:51):

So there's a lot of factors that are, I would say, during neoplastic transformation, one of the main ways that that it happens is a cell that normally would die, doesn't. And so a classic pathway is any growth factor receptor that activates PI3-kinase, so it's a lipid metabolism. So PI3-kinase then goes to Akt and Akt is a survival factor, and that's how they void dying in a cancer like states. So PTEN is a tumor suppressor and works in the opposite direction. And then downstream of Akt is a number of signaling pathways that are the classic apoptotic pathways, and then there's also FOXO. So FOXO3a, downstream of Akt, is another big pathway that has to do with longevity, similar to that is AMP-kinase and mTOR. But I think if you talk about too many pathways, it can get confusing, but it seems to push all the pathways in the right direction and it's just astounding that one molecule seems to push and pull correctly on the pathways that are promoting for health just in general.

David Roberts (05:07):

And so the main benefit we hear from testimonials and people is, "Hey, I've had this joint pain for years, if not decades, and took over CurcElite and the joint pain gone." What pathway is that? Or pathways?

Dr. Martin Katz (05:26):

Well, that's the inflammatory pathway. John, I was wondering, you didn't mention [inaudible 00:05:30] or specifically, Interleukins. And I would say...

Dr. John Gildea (05:33):

Yeah. So that's downstream of the NF-kappaB. So those Interleukin-6 are in the TNF-alpha, TNF-alpha receptor down to NF-kappaB and then also signaling from TNF-alpha to the downstream signaling, like IL-6. So [crosstalk 00:05:50].

Dr. Martin Katz (05:50):

And the reason I bring that, I think people may be a little bit more familiar with maybe Interleukin, I don't know that.

Dr. John Gildea (05:57):

Yeah.

Dr. Martin Katz (05:57):

You mentioned a lot of big words that people are not familiar with, but the thing that people are certainly familiar with is inflammation and inflammation certainly drives disease.

David Roberts (06:08):

And the inflammation is the NF-kappaB pathway?

Dr. Martin Katz (06:12):

It is.

Dr. John Gildea (06:13):

Yeah, primarily. So the simple way of understanding that is that if you get an infection, you get your immune system homing to that site. And so most people realize that you have, if you get [inaudible 00:06:28] inflammation, that you're having immune cells infiltrate that tissue, but if you don't really have an infection in a tissue that is inflamed, you're wanting to dampen that signal because there's not an infection in your knee. It's that you just have this state of inflammation going and tamping down that is associated with lack of pain.

Dr. Martin Katz (06:53):

And this is what people don't understand. They don't understand that the disease or ease, let's just start with health. Health, we all look fairly similar, right? When things are working well, we look fairly similar, but in a state of disease, or as we like to say, dis-ease, we may target the heart, we may target the brain, we may target a joint, we may target the gut, we're not exactly sure why some people exacerbate in certain areas as opposed to others, previous injury, where there was trauma, et cetera, et cetera, possibly their genetics, but that's where inflammation starts to show its ugly head in the form of disease. And that's where people are hurting or having morbidity, which is illness or mortality, which unfortunately is death. And so when you're confronted with a molecule like curcumin, which works so effectively, as John is pointing out, in so many pathways or cascades, you're really excited because it can help people in pretty major ways and that's what we're seeing in the clinic.

David Roberts (07:52):

And so John, those studies that you read about, were those looking at pathways and cells or in humans? Because you know this as well as I do, 10 years ago now when we were looking at a treating [inaudible 00:08:07] cancer naturally, there's a whole slew of cell based papers where you put different molecules, plant-based molecules on cancer cells and it was magic, they did all sorts of things. The question was, how do you know that those molecules, that you take in the capsules like curcumin, are getting into your system to do what the papers are talking about. And so can you talk a little bit about that?

Dr. John Gildea (08:37):

Yeah, that's the thing that we talked out about is what's a therapeutic dose. So you want to connect those papers. There's a lot of papers where they put curcumin right on cultured cells and then also papers and animals where the doses sometimes are exceedingly high, you want to be able to match the amount of curcumin that's getting passed into the circulation with the cell culture papers where they're saying, "This is the amount of curcumin that is in contact with the cells, so they're really different." And oftentimes in animal studies, sometimes they're doing it by intravenous infusion of curcumin, sometimes it's done through intraperitoneal, which is a different route, but you can end up getting a lot more curcumin to the target cell that way. And so a lot of papers that are done in clinical studies surprises a lot of people that you see in effect, even though there's very small amounts that is bioavailable. So when you see changes in inflammation sometimes, it's that it didn't really get absorbed at all, it's that the inflammation was based in the intestines or the cells lining the intestines or in the microbiome.

David Roberts (09:52):

And so what is the therapeutic dose of, let's say, our product CurcElite to get these pathways going?

Dr. John Gildea (10:00):

Yeah. So the amounts that are in the circulation from a lot of the studies, where they we're comparing other formulations, are in peak concentrations of micrograms per mill of serum and you can see cellular based effects of that, but you want that concentration sustained for some amount of time. So in the case of our measured concentrations, they're in 10 to 15 micrograms per mill concentrations and so, I think we're right at that threshold where you see the concentrations that can affect the pathways and therefore link to the cell culture papers, where they definitely show effects on cells at that concentration.

David Roberts ([10:46](#)):

And Martin, what are you seeing in your clinic? Because you are very much a proponent of CurcElite to your patients. What are you seeing?

Dr. Martin Katz ([10:55](#)):

Yeah. Again, curcumin has a lot of effects that I'm happy to use with my patients. I have patients coming in using hundreds of milligrams of nonsteroidal anti-inflammatories and unfortunately, people don't really realize the deleterious effects of those. And if you can get them to take something that not only has benefit with regard to inflammation, but many other health benefits, that's a win-win on so many levels. And at this point with the curcumin and the fantastic studies, I feel I'm standing on solid ground saying, "Hey, this is a product you should take because of the effects it has." And then I get these reports back, I'm feeling a lot better. Whether it's acutely or long term, being really excellent to see that in the clinic, again, I'm getting people off what they shouldn't be on and putting them on something that has good benefits of [crosstalk 00:11:47].

David Roberts ([11:46](#)):

What do you suggest for those people with the dosage?

Dr. Martin Katz ([11:50](#)):

Yeah. Again, depends on size of the person, but I tell people to start with two capsules in the morning if they have an acute injury, I'm having them take another two capsules in the evening. If it's more just sort of a chronic osteoarthritic possibility, I would encourage them to take more like two capsules ongoing. John, I've been thinking about this one as well, my athletes who come in, some of them performance athletes, either on the bike or running or in the gym, and this whole adaptation idea where you need to have some damage to have adaptation, I'm fascinated by, in the studies as well, so certainly if somebody's coming in with an acute injury, I'm telling them they need to take something to decrease inflammation, but on an ongoing basis, what do we tell our athletes with regard to, I'm actually a little confused about this, so I'm like, "You should limit inflammation, oxidative stress, but we do need some [inaudible 00:12:54]."

Dr. John Gildea ([12:54](#)):

Yeah. Yeah. So at least from the studies I know, the sensing of the stress from the exercise is the signal for hypertrophy and recovery. So I would generally say that if you take curcumin, it'll still peak through that, you'll still get that stimulation. But if you were worried about it, I would just take it away from when you're doing your peak exercise, and it, for sure, helps with recovery, so afterwards for sure. It doesn't block effects if it's taken after afterwards.

Dr. Martin Katz ([13:43](#)):

Yeah. And that was true, a lot of studies on vitamin C in taken as a fruit, so it seems like that adaptation isn't blocked as far as natural products go. So that's been what I've been telling my patients and again, recovery is key, especially if you're doing more than one workout a day, or if you're doing most days of the week, recovering getting back out there. And I think what John was saying is just so important. Have you ever a product that is bioavailable? So many of my patients don't have the means to afford supplements a or multiple supplements, should I say, and so if they're getting something that is actually working as a great idea, and a lot of them come in with trepidation saying, "It seems like supplements are expensive urine." They've heard it certainly in the news and they've heard it from other practitioners. And so that's what I think, certainly a company like Mara Labs are working hard to put out product there that actually has a significant amount of efficacy. And again, so I'm super proud to be able to present that and have that.

David Roberts ([14:46](#)):

We talk a lot about synergy and I know we all take, not just curcumin, but curcumin with broccoli. Can you, John, explain what happens when you do that and why is that beneficial?

Dr. John Gildea ([14:59](#)):

Yeah, so they have overlapping functions, but I would say they would have differing major functions. So we always describe it as sulforaphane inhibits NF-kappaB, it's very clear and stimulates Nrf2. Well, curcumin does the same thing, but I think curcumin, at similar dose, does the inhibition of inflammation better and sulforaphane does the Nrf2 activation better. And so the combination of the two is getting your maximal stimulation and inhibition. Also sulforaphane doesn't have a problem with bioavailability and travels to every cell in your whole body, can get to your brain for sure, can get to your eyes, can get to the joint space, it's actually measured in the joint space. So it doesn't have any problems with getting cross cell membranes. It lives in hydrophilic and hydrophobic environments really well. And the PEITC, that's in the product, has another layer of penetrability because the [inaudible 00:16:03] that's on that particular [inaudible 00:16:06] has a little bit easier time getting across hydrophobic membrane.

Dr. John Gildea ([16:10](#)):

So it probably has as a better penetrability than sulforaphane to the fatty, more fatty areas, and we know that toxins that are cumulative tend to accumulate in fatty tissues. So it's a benefit to have a combination of those. Curcumin would tend to, even a bioavailable version of it would tend to accumulate it at its first membrane that it comes across and that would be your parasites of your whole digestive tract, and that's also where you're getting the biggest insult with toxins from your food.

Dr. Martin Katz ([16:47](#)):

Well, and also where 80% of your immune system sits, kind of important to see that, and we see that with antibiotics. I have patients come in and say, "My gosh, I felt so much better after I took that antibiotic." And I caution people and certainly, it may have been needed and may have worked where they needed it to work, but oftentimes what I would suspect is they go on to have other problems related to the gut or something else, that the antibiotic's working to decrease microbes, which again, present LPS to the lipopolysaccharide to the immune system, which then increases inflammation. So if you're killing those bacteria through the antimicrobial, you're having an effect on inflammation. So again, the widespread use of inappropriate antibiotics hopefully is decreasing with our improved understanding of the importance of the gut microbiome. But again, going back to curcumin and if you're

having something work so effectively at the gut level, it makes sense that that would have a positive impact throughout the body, especially with inflammation.

Dr. John Gildea ([17:52](#)):

Yeah. That brings up a great point too, is the fact that curcumin is an anti-microbial. So if you're taking huge doses of it to try and get a little bit absorbed, it's accumulating in your intestines and could potentially have of anti-microbial effects. In general, it's having a beneficial effect in that the certain microbes that tend to be associated with inflammation, it tends to slow them down and tends not to slow down the ones that are beneficial. So it has a selective ability to make your palm better but there is probably a limit to that. You don't want to take huge doses, multi-gram doses of curcumin long term. So we really feel like in our case, the dose of curcumin is much smaller in general, and it being absorbed in your small intestines, getting it to the of your body has a big benefit without having as big a hit on your microbiome. We think that's a big benefit.

David Roberts ([18:56](#)):

I want to talk more about that.

Dr. Martin Katz ([18:57](#)):

Yeah.

David Roberts ([18:59](#)):

But let's pause there with the podcast on pathways and synergy and pick it back up and another podcast on microbiome because these are very important topics, but gentlemen, thank you for joining us today. You are listening to the Mara Labs Podcast. We'll be back next week with another podcast. Thank you.

Dr. Martin Katz ([19:21](#)):

Thanks for taking care of your human.

Dr. John Gildea ([19:23](#)):

All right, bye.

David Roberts ([19:24](#)):

Bye.