Sulforaphane's Nrf-2 Independent Benefits

With Dr. Martin Katz and Dr. John Gildea

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David Roberts (00:00):

Hey everybody. It's David Roberts and you're listening to the Mara labs podcast. And today I have Dr. John Gildea and Dr. Martin Katz, and we are going to be discussing the impact. sulforaphane has outside of Nrf2 mechanisms. I think it's called independent of Nrf2. John, since you introduced the topic, why don't you start?

Dr. John Gildea (00:23):

Sure. It actually came from a question at a conference that we just spoke at recently. It was one of the questions from a physician from the audience. And she actually noticed in one of our slides that there was a difference in a Nrf2 knockout mouse. And it was actually very instructive for us that we went out and looked for Nrf2 independent functions and there's three papers that we found. There's probably more, but they had the words Nrf2 independent in it. So they're really easy to find

Dr. Martin Katz (00:59):

Low hanging fruit.

Dr. John Gildea (01:00):

Right? And so the three different processes that they're talking about are, two of them related to inflammation and one related to mitochondrial function. And so we can talk about what is the function, but in mitochondria, it's a known function of sulforaphane but I think the paper shed light on the fact that it was Nrf2 independent. And so that was a very interesting finding. That mitochondrial fusion that happens, it's also induced by exercise and it had a very specific mechanism in which it works through a number of intermediate factors. So they could really isolate where it was working, but, long story short, it was an Nrf2 knockout, they saw a similar function. And so that was the conclusion of the paper was that you have this mitochondrial benefit that is independent of Nrf2 activation, which seems to be directing most of the activity of sulforaphane.

Dr. Martin Katz (02:18):

Yeah. I love that study.

David Roberts (02:20):

Let me just, I'm going to dive in real quick, because I have a clarifying question before you go deep.

Dr. Martin Katz (02:25):

Okay.

David Roberts (02:26):

So just to clarify, so basically, they tested this Nrf2 independent function using mice that did not have an Nrf2 gene and they saw the benefit and then mitochondrial fusion specifically, what is that?

Dr. Martin Katz (02:49):

Yeah, I was going to talk about that. So...

David Roberts (02:51):

Good, thank you.

Dr. Martin Katz (02:52):

Yeah. Again, because of why I love this study and why I love exercise so much. Everybody needs to understand what mitochondria are, probably first of all. And there's a lot to mitochondria. They are understood to certainly be our energy producers, how we are able to function day to day, develop our ATP, our hearts, everything is functioning on this energy, but they also have another very important function and that's to produce something called oxidative stress. And there's oxidative stress. Everybody says, well, why is that important? It seems like that's damaging. That's bad, but it's actually a very important way that our cells communicate. Now if our cells are healthy, we are very able to balance that Nrf2, excuse me, that oxidative stress and we're able to function well and our cells go on. If that oxidative stress is a messenger, we then pull in cells that help heal the process hopefully.

Dr. Martin Katz (03:55):

If the cell's unable to do that, there's a possibility it goes through something called apoptosis, which is beneficial. So the cell dies, but it can also go through senescence and the cell's just sitting there producing this oxidative stress. While now, if you're giving the cell a stress such as exercise or fasting, or as we're demonstrating sulforaphane, those mitochondria that are damaged can actually fuse. They actually come together and the beneficial parts of those mitochondria are matched and the bad parts are replaced, so to speak. And so here we have now, better functioning mitochondria, which again is extraordinarily important to our health, our ongoing health. And if you have this molecule that's functioning independently of Nrf2, we now understand why sulforaphane looks so darn tootin' good because Nrf2 is so powerful. Again, remember when you increase Nrf2, you increase that whole Antioxidant response element. 2, 3, 400 genes that are supporting our health. Well, now we have other mechanisms which are incredibly important to our health and that's supporting these mitochondria, which we're not going to live without.

David Roberts (05:11):

No, we will not live without.

Dr. Martin Katz (05:14):

Or even live healthily with damaged mitochondria. And that's why this study for me was so wonderful and why exercise is so important.

David Roberts (05:22):

So the mitochondria actually fused, they could come together. All right. That's great. So a side note, I have to throw it in about mitochondria. They do not have human DNA, is that right?

Dr. Martin Katz (05:40):

They have their own DNA.

David Roberts (05:42):

They have their own DNA, which is not human DNA.

Dr. Martin Katz (05:44):

Right. They're thought to be part of the human cell that has allowed us to use oxygen as a form of being able to live.

David Roberts (05:54):

Yeah. So they seem to be outside of us.

Dr. John Gildea (05:57):

The oxygen independent metabolism. And that's why it's so important is as you're aging, your mitochondria function goes down, in general. And that's probably what exercise is doing is it's gleaning the bad mitochondria and constantly selecting for the highest functioning ones. And part of that process is fusion. So it is like it. Similar to the oxidative metabolism of Nrf2, it's mimicking a stress without producing the damaging part of the stress. So they kind of match in that regard.

David Roberts (06:39):

And so are there other, besides mitochondrial fusion, are there other independent mechanisms, independent of Nrf2 that sulforaphane impacts?

Dr. John Gildea (06:51):

Yeah. So the other two papers are more inflammation related. A newer form of inflammation is mediated through what's called an inflammasome. And so this pathway is sort of defined by a molecule that is altered in that inflammatory state and to sort of make it a long story short it has to do with when you react to an inflammatory event.

Dr. John Gildea (07:24):

So say there's a really out of control inflammatory event. And in one of the papers they actually used anthrax. It was just an obviously out of control inflammatory process. And during that out of control process, you actually kill your mitochondria. So think about how smart that is for that bacteria, spore forming bacteria, to kill the actual thing that normally mops it up. So it's a defense kind of like the war scenarios of cancer and immune system. They're sending out decoys to derail the cancer. That's the kind of Pd1 association that's in cancer. And then similar here, you have bacteria that is derailing the inflammatory process that's going in there. And sulforaphane is basically in that case is preventing the inflammasome dependent death of mitochondria. And they used it in a scenario where again, it was Nrf2 knock out animal and then you still have this protective effect of not killing the mitochondria. So you would have a better inflammatory response in that case.

Dr. Martin Katz (08:41):

And I think this was in the brain, wasn't it? Which is even...

Dr. John Gildea (08:45):

Yeah, you're right.

Dr. Martin Katz (08:46):

I think it was in the brain, which again, sort of points us to a lot of our findings that sulforaphane can be very helpful in some of these neurodegenerative processes as a good support mechanism.

Dr. John Gildea (08:59):

Yeah. Brain inflammation is a big component of it. So many diseases are associated with that, brain inflammation and the Nrf2 dependency of that, we just always assumed it was Nrf2 being induced in the brain and be able to defend against toxins and also reactive oxygen species. But it turns out there's an inflammatory component to it as well. And then the third paper is a little bit simpler to understand is they also had a similar inflammatory model. And in that case, they saw a direct NF-kB effect. So that would be more like curcumin. So there is a curcumin like effect within sulforaphane that's independent of Nrf2. And that was the paper that I remembered and how I answered it in the question and answer period from our presentation was that there is an NF-kB direct effect. That's Nrf2 independent and in that case, it's a little bit different than the other ones in that you need a little bit more sulforaphane in order to see it.

Dr. Martin Katz (10:05):

Yeah, that was interesting. They used the lower dose and there was some response that I can't remember exactly what the response was to the lower, but to see the full response you needed to use a higher dose. And again, that's why having a biologically active or molecule such as ours that gets in is so important to these processes. The other interesting thing about that paper, John was Interlukin related rich again, NF-kB, but I think they mediated through LPS, which is something that we're so...

Dr. John Gildea (10:36):

Lippa polysaccharides.

Dr. Martin Katz (10:38):

The LPS, Lippa polysaccharides, which again, is likely coming from your gut, which is again, a massive problem in this country. And likely we're all dealing with just because our guts are likely not, they're not whole. They have holes in them. They're not whole, they have holes in them.

David Roberts (10:56):

They're holy.

Dr. Martin Katz (10:58):

And so these bacteria getting through at least part of the capsid of this viral or bacterial capsid is getting through and near these proteins on them called LPS that the system reacts to very strongly again, because it's foreign. And so this is how this was mediated. And again, lots of benefits through sulforaphane there, as well as the effect sulforaphane has on the gut and the negative bacteria in the gut.

David Roberts (11:29):

What dose was that?

Dr. Martin Katz (11:31):

Five and 50 microgram I think.

Dr. John Gildea (11:33):

Yeah, in the animal studies, they metabolize sulforaphane quite a bit faster. So it's hard to do a direct comparison because mice and rats have somewhere along a hundred times faster metabolism than humans. So if you hear micromolar concentrations or micrograms per mill, it's hard to go between mice and humans, but the larger dose was 50 micro mole, which is quite a bit higher than we've measured in human cells from our products.

David Roberts (12:11):

Our product, so we have one capsule has five milligrams of Sulforaphane. And what does that translate into approximately?

Dr. John Gildea (12:20):

Yeah. With synergy it's equivalent to five micro mole at the cell

David Roberts (12:24):

At the cell, yeah. The synergy being the PITC from watercress and the other isethionates that we extract from the seed along with sulforaphane. Sulforaphane, it's hard enough to get people to understand what that is. And so we don't often highlight the other Isethionates, but we have about how many?

Dr. Martin Katz (12:45):

10.

Dr. John Gildea (12:46):

Yeah. Somewhere around 10 or 11.

David Roberts (12:51):

10 or 11 isethionates. And so, but I'm going to press a little bit more, what's your instinct say as far as a dose? So if we took two capsules, that would be 10 micro mole, how many... Nobody's going to hold you to it, but what's your thought on just what you know about the broader science of what a dose would be to...

Dr. John Gildea (13:17):

To get at this mechanism?

David Roberts (13:18):

Yeah.

Dr. John Gildea (13:19):

I think the first two were normal doses. So you can expect to get at that. I think, if I remember correctly, the LPS dependent signal was the higher dosage. And you kind of expect that because that model is like one of those botulism toxin or a model that actually kills the mouse. If you get that model tuned in, they normally measure death rates of the animal. So these are infections that are related to endotoxemia. And so a larger dose to avoid that would be more like a dose that is not attainable usually. So I would say there's probably not people out there trying to block death by anthrax or salmonella overload. So I think in that scenario a normal dose would do the mitochondrial fission. And if I remember correctly,

there's quite a number of elite athletes that are taking our product, that's where that their recovery times are better and that would make sense in the mitochondrial world.

David Roberts (14:42):

Absolutely and since we did bring up anthrax in this conversation, which we, I don't think ever have before, John, would you share some of your story about anthrax and the assay you created?

Dr. John Gildea (14:56):

Yeah. So during the Gulf war, I had a reputation for developing assays that are sensitive and fast and got recruited by the army to develop the test that goes on the back of Humvees to protect the soldiers. And so we had to be able to detect anthrax in the air of 500 spores, which is what kills you in 90 seconds. So we were able to develop that device and it was deployed and in the production of that assay, because I was dipping into a very high dose source of anthrax over and over and over and over and over for a couple of years, I actually sensitized myself to anthrax and tested as having the highest tighter of anti anthrax antibodies ever. And so the director of that particular program said if I ever wake up in the middle of the night and I have some blood missing from my arm, you'll know it's for the president and just ignore the...

Dr. Martin Katz (16:05):

Go back to sleep.

David Roberts (16:07):

Nothing to see here.

Dr. Martin Katz (16:09):

Aren't you glad you take sulforaphane?

Dr. John Gildea (16:11):

Yeah.

David Roberts (16:13):

Yeah. And before you developed the 92nd test for anthrax, how long did it take to measure anthrax?

Dr. John Gildea (16:22):

24 hours, usually.

Dr. Martin Katz (16:23):

That's a little late.

David Roberts (16:25):

Yeah. Yes. Yeah. So that's really good.

Dr. John Gildea (16:29):

Yeah, their criteria is crazy. Army, that's a long story, but anyways,, you have to be able to measure it in three cubic meters of air. So impinging that amount of air down into a liquid slug that you can then test in an automated assay was a big breakthrough in that area. So, the army oftentimes has deep pockets, but for a reason where they have a goal and an unlimited resource to save their soldiers when they're deployed. And I was happy to be part of that one.

Dr. Martin Katz (17:10):

Yeah. That's a great story. Love that. And are they still using it today, John? Do you know? I

Dr. John Gildea (17:15):

I think some version of that is still deployed on Humvees along with the biochemical detector does the airborne nerve gases as well.

David Roberts (17:26):

All right. Well, we're going to wrap it up and thank you all for listening. And you've been listening to the Marlabs podcast and we'll be back next week with another episode.

Dr. Martin Katz (17:38):

Thanks, please take care of your human.

Dr. John Gildea (17:40):

All right bye.

David Roberts (17:40):

Bye.