Under the Microscope: AhR Microbes Holding the Keys to Your Gut Health?

There's a lot of evidence that nutrition is now a central cog in the AhR signaling system and that can alter our biology in different ways.

April 7, 2020 By Harriet Sugar Miller

"It's really very predominantly a nutritional story," says Texas A&M's Robert Chapkin, PhD, describing one of his current passions — the aryl hydrocarbon receptor (AhR) signaling system that exists in every cell. It works like a lock and key. When natural keys, or ligands, get inserted into receptors, the doors open to an array of health-promoting activities.

Chapkin, erstwhile chair of the AICR research grant review panel and currently distinguished professor and chair of the university's department of nutrition, oversees a lab investigating dietary/microbial modulators of cancer and chronic inflammatory diseases.

What's the most important factor that drives this healthy cell signaling system?

What seems to primarily regulate the functionality of this critical system is the availability of the ligands—the keys that bind to the lock. And the ligands come from the diet as well as the microbial interaction with the diet.

The bottom line is to eat plants. Their fiber and phytonutrients act synergistically to promote health.

What kinds of health-promoting consequences are you talking about?

There are a wide array of functional outcomes that appear to be regulated, at least in part.

Some researchers are looking at the brain, liver, gut function. There is a lot of focus on chronic inflammation — a whole variety of inflammatory diseases, such as metabolic syndrome and IBD. There's still a lot of speculation, but the data is being solidified slowly but surely.

We're asking the questions relevant to stem cells in the gut and the impact on cancer. Stem cells birth all the lineages of cells in the gut, depending on which kind of stem cells you're talking about. And when we activate the AhR in the gut, the features of stemness are suppressed. Thus, the availability of AhR ligands in the gut can modulate stem cells. In terms of cancer, this is considered to be very important because hyperactive stem cells are definitely considered to be

risk factors for cancer.

What foods contain natural ligands?

There are many phytochemicals — plant-derived ligands like indole-3 carbinol — which come from cruciferous vegetables and quercetin, which is found in many plants like onions, capers and berries.

Some of these plant-derived phytochemicals can be further metabolized by microbes — specific strains of microbes — in the gut.

We're also very interested in coffee now. Certain bioactive compounds in coffee appear to be very strong AhR ligands, and they may favorably impact things like gut leakiness and some of the biology of the gut.

Most of these natural ligands come exclusively from plants, but not all of them. You can even take an amino acid, like tryptophan, and make ligands for the aryl hydrocarbon receptor.

If the system's function depends on the availability of ligands, we need to know what decreases availability. What are you finding?

When you look at obese animals and humans, you see a reduction in those ligands partly because we believe there is a dysbiosis — an abnormal microbiota constituency. When the right microbes are not normally abundant, this impacts the availability of ligands, which would then suppress the responsiveness of the whole signaling network.

What about fiber? Does a low fiber diet also lead to dysbiosis?

Yes. Lack of fiber is bad. One of the consequences is a reduction in ligands. And therefore, the biology of the aryl hydrocarbon receptor is not being optimally regulated.

How does fiber impact the system's function? Tell us about your group's research on fiber and synergy.

We're discovering that there is even more impact of these ligands when you are taking in a high fiber diet. When you eat a lot of poorly digestible carbohydrates, i.e., dietary fiber, what you're doing is giving the microbes in your gut the substrates, or raw materials, to flourish.

The microbes ferment the fiber into short-chain fatty acids such as butyrate and propionate, which have a variety of health-promoting effects. It turns out short-chain fatty acids can amplify the responsiveness of the receptor to the available ligands. So synergism takes place between short-chain fatty acids and the ligands, and we get the greatest AhR responsiveness when the levels of the short-chain fatty acids are elevated in the presence of the ligands. We have certain molecular models that explain why and how this happens.

So, eat fiber. It has natural ligands. You ferment it and you also produce short-chain fatty acids, and those two factors, and probably more, are interacting in a way to reduce our risk of cancer

and chronic inflammatory disease and probably other things. That's why we need to eat a diversified diet and more plant products.

And the epidemiology, to a large degree, supports that.

This concept of synergy seems to be the catalyst for a major paradigm shift. Doesn't it disrupt the way scientists have traditionally done science—investigating one piece at a time?

In our case, we feel that a lot of the functionality may have been missed because of the lack of appreciation for the synergy of adding the AhR ligand in the presence of biologically-relevant concentrations of short-chain fatty acids. All of this exists in the natural environment of the gut, but we tend to be reductionists. And if we leave out important factors, we actually misinterpret the biology.

We'd like to garner additional funding so that we can look at this important interaction.

Classically, the aryl hydrocarbon receptor has been associated with pollutants — harmful compounds like dioxins, which dock to the receptor and then chronically signal inflammation. Is it possible that healthy ligands are attaching to the receptors and taking the place of dioxins and the like?

It is unlikely that dietary and microbial ligands will actually compete and displace dioxins. From a biochemical perspective, dioxins have a very high binding affinity for AhR, and thus, bind irreversibly and chronically activate the receptor. In contrast, "natural" ligands have a much lower affinity for AhR and can act as either agonist (activators) or antagonists (inhibitors) of the receptor. Their effects are much more difficult to predict. Preclinical and clinical data indicate that these type of low-affinity interactions are beneficial to the host and reduce chronic inflammation.

What's next?

There's a lot of evidence that nutrition is now a central cog in the AhR signaling system and that can alter our biology in ways that now appear to be protective or harmful, dependent on the abundance or lack of abundance of these ligands.

What we need are some nice clinical studies to fill in a lot of the gaps and that's where funding becomes a great challenge, unfortunately.

The problem is that there's very little money going into clinical studies involving nutrition and chronic disease prevention. They're expensive, and people are chronic pessimists about this. The only way to move forward is to get the comprehensive data and to do that, we have to do work in human beings, complement it with mechanisms from preclinical studies and use the full array of science to answer these complex questions.

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