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Diving into the Genetic Pathway: A Look at the STING Pathway & Brain Cancer

Dr. Wilner:
The strategy of immunotherapy continues to grow in the cancer treatment landscape, and stimulation of interferon genes may be a key player in cancer immunotherapy. So, what do we need to know about this genetic pathway?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner. And joining me to talk about the STING pathway, a novel treatment pathway for cancer, is Dr. Sean Lawler. Dr. Lawler is Associate Professor in the Department of Pathology and Laboratory Medicine at Brown University in Providence, Rhode Island.

Dr. Lawler, welcome to the program.

Dr. Lawler:
Thank you for having me. It will be a pleasure to speak to you today.

Dr. Wilner:
To start, Dr. Lawler, please tell us about the STING pathway. What do we know?

Dr. Lawler:
The STING pathway was identified in about 2009 by Glen Barber whose lab is at the University of Miami. And Glen is a biologist who studies pathogens and the responses to pathogens in humans and other mammals, and he was interested in what stimulates interferon genes because interferon genes are one of the key mediators of antiviral immunity. And so, to understand antiviral and antipathogen immunity, Glen searched for a gene or an enzyme in the cell that would respond to viruses and other types of stimulus that would indicate a pathogen infection, and he came across this protein called STING, which is in the cytoplasm of our cells, and it stands for stimulator of interferon genes. And what STING does is it acts as a central hub that coordinates incoming signals that are associated with a pathogen infection and then leads to the activation of a transcriptional program that leads to the production of interferon genes which then lead to a coordinated immune response, which can ultimately lead to the elimination of a pathogen.

And so the pathway really consists of an upstream enzyme, which is called cGAS, and cGAS is a sensor of double-stranded DNA in the cytosol of cells. And double-stranded DNA should not be in your cytosol because double-stranded DNA is normally in the nucleus where all the chromosomes reside. So, when a pathogen infects and double-stranded DNA may accumulate in the cytosol, cGAS sees it, and it turns on this enzyme called cGAS, which produces a cyclic dinucleotide, just a small molecule composed of an adenosine and a guanosine molecule, and the cyclic dinucleotide will go on and bind to STING and cause a confirmational change, which then activates this downstream transcriptional program.

One of the very interesting things about this cyclic dinucleotide, because it's a simple chemical, it can be easily mimicked, and so pharmacologists and chemists have been able to synthesize analogues of this cyclic dinucleotide, various kinds. There are a number of molecules like this that all can be added exogenously to activate the STING pathway, which will stimulate immunity. It can stimulate inflammatory responses, which can be useful in a number of different situations, but what my lab studies is its use in cancer treatment, and the STING pathway has emerged as a very important potential target in cancer immunotherapy in recent years.

Dr. Wilner:
Dr. Lawler, that was a fantastic tour through the nucleus and the cytosol. You mentioned it was just really last decade or so that this STING pathway was discovered. It sounds like this is part of our immune system. Is that right?

Dr. Lawler:
That's correct. It's a very important component of innate immunity, in fact. So innate immunity is the sort of first line of our immune system that recognizes pathogens as they infect and start to get inside cells. And there are a number of components, actually, of this type of pathogen sensing system in our cells, and STING is only one of those, in fact, but it seems to be a very important one. And I think that one of its major strengths is that its target is pharmacologically rather easily, and I think that that's led to the development of the interest in this pathway as a potential target. And then the activation of these innate pathways, of course, then has to link to our adaptive immunity which—and the adaptive immunity consists of T cells and B cells, which make antibodies and, and kill cells that are infected by viruses, so this is really the first step of our immune system, this pathogen sensing.

Dr. Wilner:
Now, what about cancer therapy itself? There is a known tumor. I think you mentioned that there actually is a way to synthesize some of the components of the STING pathway and maybe ramp it up. And is that going to help us treat cancers?

Dr. Lawler:
Potentially. So, I'm going to rewind a little bit and tell you a little bit about the tumor that I work on, just to put it into context. We work on a brain cancer called glioblastoma, and glioblastoma affects about 10,000 to 15,000 people a year in the United States. It's a really aggressive form of cancer, one of the most aggressive you can get. The median survival is about 12 to 15 months, perhaps a little bit more. And the treatment that's given to patients is a chemotherapy, radiation and surgery, and they all inevitably decline.

About 10 years ago, we were very encouraged though by data from other cancers that showed that activating immunity could lead to amazing responses, and this is the subject of immune checkpoint blockade, which is pretty well known now. So, in patients with advanced melanoma, you can reactivate the immune system using antibodies that block negative signals that go to T cells, but basically, the tumor is trying to trick the immune system and hide from it. And so, if you can overcome those mechanisms, you might lead to an antitumor response so you can resolve the tumor completely naturally.

Now, in glioblastoma, the trials with immune checkpoint blockade to try and uncloak the tumor in that way have not really shown great responses, so glioblastoma does not respond to this incredible therapy that works quite well in other tumor types. And so the question really is partly 'Why?' And there can be many reasons why, but another question is—and this is what my group has been trying to address in the lab—is 'Can we add other therapies to glioblastoma that might help this immune checkpoint blockade to work better?' So, is this tumor so immunosuppressive that therapies that work in other cancer types don't really work in glioblastoma because there's other immunosuppressive pathways that are in place, right?

And so I was inspired by some previous work I did with oncolytic viruses. So, these are viruses that you inject into the tumor, and those viruses can replicate. Well, more than that, they cause an immune response that can lead to tumor elimination in some cases. And so, in animal models I did a lot of work that was previously published using combinations of oncolytic viruses with immune checkpoint blockade and showing that we could clear tumors, and that work has gone into clinical trials. But I was really interested in the pathways involved. So, these viruses are stimulating a number of pathways in cells, and so that led us to think about this STING pathway, which can be easily modulated.

We plan to deliver it locally inside the tumor and cause a kind of trick the body into thinking that there's a pathogen infection, thus overcoming the local immunosuppressive mechanisms in the tumor, which are very strong, and then leading to the recruitment of immune cells like NK cells and T cells which will act against the tumor itself. And we showed in our paper, actually, that if we add an immune checkpoint blockade antibody to this mix, that we can actually lead to the clearance of an otherwise resistant tumor in our mouse models. So that's the idea. It's really a setting off the fuse that will then heat up the immune system inside the tumor to allow its recognition by the adaptive immune system, which will then clear it.

Dr. Wilner:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm here with Dr. Sean Lawler discussing the STING pathway for cancer immunotherapy.

Dr. Lawler, thank you for giving us that overview and how the STING pathway may actually help treat tumors that have effectively masked themselves from the immune system. Where are we in the clinical application of this STING pathway?

Dr. Lawler:
So, beyond what my group is trying to do, there are others in my field around and about who have developed STING agonists and who are currently in the process of starting the first phase I trials of STING agonists in glioblastoma. The first, I think, aspect that we have to understand is safety. And I think that's really particularly important in a cancer like glioblastoma where your tumor is basically growing in the brain, and if you overstimulate that tumor and inflammation becomes very high, then you run a serious risk of causing serious

damage to the patient because swelling in the brain, as you know, is a high risk factor, so we have to work out I think initially the kind of dose of a STING agonist to activate the pathway that would be suitable for its application in this particular context.

If we're looking at other cancer types, then this becomes less of a problem, and then we are really focusing on just the right dose to get the right kind of response over the right duration. And I think that's also another challenge in this field in that when you turn on an immune response, one of the things the body does very quickly is to try to turn that immune response off again because you don't want an unchecked immune response in your body which can then lead to autoimmunity and other inflammatory consequences.

So I think one of the key things with this approach is to understand how to apply it at the right dose for the right duration of time to achieve the right response. That's going to be a challenge, but I think that given our progress that's been very rapid over the last few years, we should be able to identify that and overcome it.

Dr. Wilner:
So one potential risk of this kind of therapy is overdoing it is getting an immune response that's so robust that it causes inflammation and edema and a downside particularly in the brain. Are there any other adverse effects that we can anticipate from activating this pathway?

Dr. Lawler:
In terms of adverse effects, we've done some studies on cells in vitro, so one of the things you do when you're working on these things is take the drug, put it on some cells in vitro, see if it's toxic at high concentrations, that type of thing. Certainly, if you just look at a normal cell in vitro, these drugs are not toxic. They require the immune cells companions to induce the toxicity, so there's not going to be a direct toxic effect. So I think that the limitations will really be immune related, overdoing it kind of consequences.

There is some literature out there, and we would agree with that based on some of our experiments in our recent paper, that high doses of STING agonists, you start to lose the effects because a strong STING activation, actually, ends up killing immune cells.

Dr. Wilner:
Well, this is a really exciting avenue of research you have in your lab, and I guess probably internationally now, Dr. Lawler. Before we close, do you have any final thoughts or takeaways you'd like to share with our audience?

Dr. Lawler:
I would say that the final thoughts are, yes, this is one of a number of different, types of approaches that could be potentially used to enhance immunotherapies for cancer. In my field, we're all very excited about it. A lot of us weren't immunologists before but have now become much better versed in the field, and we're all extremely excited, I think, to be part of the development of immunotherapies for cancer at this time in history.

I think that it's going to be complex because cancers are all very unique. Even the same type—within the same type of cancer, there is a lot of heterogeneity, and we have to learn to understand that, so we see that in our experiments when we add immunotherapies to our systems that different tumors even of the same type will respond differently. So there's a long way to go, but I think that we're really heading in the right direction, and our previous successes in the field with immunotherapy for melanoma and some other cancer types have really given us a lot of excitement about taking these types of ideas forward and really helping patients hopefully in the foreseeable future.

Dr. Wilner:
Well, with those thoughts in mind, I want to thank my guest, Dr. Sean Lawler, for shedding light on this important topic.

Dr. Lawler, it was a pleasure speaking with you today.

Dr. Lawler:
Thank you for having me. It was a pleasure to be here.

Dr. Wilner:
For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers where you can be Part of the Knowledge. Thanks for listening.