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The Cell Death Pathway: Leveraging Glioblastoma Treatments

Dr. Wilner:
Glioblastoma is the most common type of brain tumor and one of the most aggressive cancers in adults. There is no cure, and progress toward effective treatment has been agonizingly slow. However, a team of researchers and neurosurgeons appear to be making some progress. So what could this mean for patients diagnosed with glioblastoma?

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Andrew Wilner. And joining me today is Dr. Dominique Higgins. Dr. Higgins is an Assistant Professor of Neurosurgery at the University of North Carolina School of Medicine.

Dr. Higgins, thanks for joining me today.

Dr. Higgins:
Hi. Thanks for having me. It's a pleasure to be here.

Dr. Wilner:
Well, let's dive right in, Dr. Higgins. Can you explain why the tumor glioblastoma has such a poor prognosis?

Dr. Higgins:
Yeah. It's "Multifactorial," I would say is the best way to cover why this is such a difficult tumor to treat. One, in terms of brain tumors, we don't have screening paradigms as you do for other organ systems, like prostate or breast, so typically, we don't find anything in the brain unless it's by accident—someone has a trauma, and we get a scan and happen to see it, or they start to develop symptoms, and sometimes, in that case, the tumor has progressed along pretty far, and so you could imagine that that limits what you can do going forward. The other issues are that the brain barrier protects the tumor in a sense from treatments that would normally be able to effectively kill the tumor cells, so by the brain protecting itself, the tumor hides in that space and can avoid or evade a lot of the chemotherapies that are available. And secondly, we know that it's a very invasive—or I guess the third point is we know it's a very invasive tumor. Even surgically, when I can take out all of the tumor that you could see on an MRI or a scan, we know there's microscopic cells that exist beyond that tumor that we can see on the MRI, and those cells have the potential to grow back or recur. There were studies done long ago when they did hemispherectomies, taking out the entire hemisphere of patients with glioblastoma, and it just recurred on the other side, so that just speaks to how aggressive these tumors have the potential to be.

Dr. Wilner:
Right. So I think from the patient's point of view, but also the neurosurgeon's point of view, it's an incredibly frustrating tumor to treat. So what are you doing differently? Tell us about your research.

Dr. Higgins:
Indeed. I'd love to see gains made in this, and that's part of why I've committed my career to research, as well as the clinical practice. And from a strategic perspective, what we need are therapies that can, not just target what we can see but target the cells that we can't see. And so in designing the project, we wanted to look at this new cell death pathway that's called ferroptosis, which involves iron-dependent lipid peroxidation to see if it can provide some new avenues of treatment for this terrible disease, glioblastoma. On top of that, we wanted to combine it with something that can sensitize the entire environment to treatments by ferroptosis, and that's why we approached it from a nutritional combination standpoint.

What we showed in the study that we recently published was that ferroptosis can occur in brain tumors, so we treated cells in mice with drugs that specifically target the pathway. This is something that's intrinsic to every cell. There is programmed cell death that occurs, and the most popular one, or most commonly known one, that you learn in medical school was apoptosis, but since then we've

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discovered there's different branches of what we call regulated cell death. And within the past decade, we discovered that ferroptosis is one of those independent regulated cell death pathways, which was discovered by Brent Stockwell, who was a mentor of mine and one of the senior authors on the paper at Columbia.

And so basically, what happens is that in the setting of oxidative stress or reactive oxygen species, the cell has a built-in mechanism to clear these free radicals from essentially wreaking havoc in the cell. What they can do is interact with lipids in the membrane, and those form lipid peroxides, and those can go on to trigger a programmed cell death, and that's essentially what ferroptosis is. But there's an enzyme in the family of glutathione peroxidases called glutathione peroxidase 4, or GPX4, which has the ability to clear these free radicals and lipid peroxides, and it uses glutathione as a substrate to do that in the presence of iron as well.

And so there are drugs that we have that can block glutathione peroxidase, or GPX4, and essentially, that lets that free radical process go unchecked. And what we found is that the tumor cells are more sensitive to death by that process, and so it's an effective way to selectively kill the tumor cells and protect the surrounding brain. And what we also showed is that the key components that GPX4 needs, which are cysteine and methionine, if you take those away, then the cell is even more sensitive or the tumor cell is even more sensitive to death by this pathway. And so we treated mice that had glioblastomas with a diet that was low in cystine and methionine, and we assessed their survival, and the mice that were on the diet lived longer than the mice that were on control diets. And then when we treated the mice with drugs that activated ferroptosis, the mice also lived longer than the control mice.

So what our plan is to do—this is encouraging preclinical data, but again, nothing that you can't replicate it in patients actually suffering from this—is to do early phase I clinical trial where we have patients that have glioblastoma and place them on these diets and see if we can elicit the same response in the tumor cells.

Dr. Wilner:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. Dominique Higgins about his research and findings on glioblastoma.

Okay, Dr. Higgins, that was a great explanation. So to follow up, what might a patient's diet look like who's being treated for glioblastoma?

Dr. Higgins:
I guess that's the million-dollar question and the short answer is we don't know, but we're going to try to figure it out. If we want to promote ferroptosis, what it boils down to is a low protein diet, if you have to put it in a catch-all bucket. But the truth is it's a little bit more complicated than that because there's different amino acids that goes into it, there's compensation that happens from the body, and then there's a timing effect. So what we're aiming to figure out is—what's the right combination of dietary components that's needed to maximize this effect? And what's the timing that's the most beneficial? Because nobody wants to be on a restricted diet for several months, and so what we're trying to do is maximize a short window of time that someone can be on this and still obtain the benefit.

Dr. Wilner:
And just to clarify, the diet would only be of value in conjunction with the chemotherapy? Or might the diet be of value in and of itself?

Dr. Higgins:
Great question. We believe that the diet would be of benefit in and of itself. The benefit is greatest though in combination with a specific drug that would target ferroptosis.

Dr. Wilner:
Now we use the ketogenic diet for epilepsy, and through mechanisms after a hundred years of use, it's still mysterious, but it does work in many patients, but it's a tough diet to adhere to. But would something like the ketogenic diet fulfill your criteria of a low protein?

Dr. Higgins:
Yeah. So the ketogenic diet, it's a little different. In the traditional sense, the protein consent isn't always altered. The fat is what you target and the carbohydrates, whereas we're more focused on the protein. The fat content does matter, but it gets a little bit more granular in terms of the types of fats that you alter, and that's also something that we're looking into. I think there's a lot of value in the ketogenic diet, and there's a lot of groups that are studying that, and I think there's a lot of promise. And what it will boil down to is there's no right answer. I think it will depend on what a patient is willing to eat or do or how long they want to be on it, and then it may also depend on the tumor itself. We know that these tumors have different types of metabolism based on their histology, and so there may not be a one-hat-fit-all type of approach, and that's what we're trying to figure out.

One thing that we looked at—is this something that's just for glioblastoma? So as you know, glioblastoma is the highest grade of astrocytomas, a grade 4, but grade 2s also have an indolent process that can also ultimately, either convert to a grade 4 or lead to

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seizures or decrease quality of life or even be fatal in and of themselves. What we found is that these lower-grade tumors are also sensitive to ferroptosis, and so we have some ongoing studies in my lab that's trying to address—what's the mechanism of the lower-grade glioma's response to ferroptosis? And we hope to be able to bring that into translational study as well in the future.

Dr. Wilner:
Right. So it's very encouraging that these treated mice are doing better. Where are we with the human trials?

Dr. Higgins:
So we're working with the protocols office here at UNC to get it through the IRB, so we're still in the early stages, but everything is moving along according to schedule I'll say, and we're hoping to have it open to enrollment by the end of the year so.

Dr. Wilner:
Oh, coming right up. Okay. And it sounds like it's always risk/benefit with treatment, but it sounds like the risk is pretty small as long as the patient's nutritional needs are addressed, and that ought to be fairly straightforward to make sure they're getting the minimal amount of protein and calories and all of that. I'm sure you're working with nutritionists on this project. And the downside is they just can't eat exactly what they want to eat, but hypothetically, they might just be on the diet for a week, and then get the treatment, and then off and on, something like that, or are they just going to have to be on it indefinitely, or what do you think?

Dr. Higgins:
Yeah. For the study, what we're shooting for is a week or less for when patients will be under the specific conditions for the diet, and yes, we are working very closely with our nutritionists and dietitians. I am by no means a nutrition expert, but it's something that I'm learning as this process goes on. And we have a great nutrition institute here at UNC that's completely dedicated to these test diets and studies around this and an entire campus over in Kannapolis for this, so I'm fortunate to be surrounded by experts in the field, and also partnering with the Columbia bio nutrition program to get this off the ground. So, a lot of work going into it, and we're very excited about the potential.

Dr. Wilner:
Yeah. Well, this is exciting because ever since I've been a medical student—which was, as you could see from the gray hair, a while ago—glioblastoma has been a real challenge, so this sounds like a novel approach. Now before we close, are there any final thoughts you'd like to share with our audience today?

Dr. Higgins:
Yeah. I'd like to say, I think, like you said, there's been very little progress in terms of moving the needle for glioblastoma patients, and we're hopeful that this will lead to something. I just want to say it's in the early stages, and so we have cautious optimism, but we'll follow the data and see where it goes, but it looks very promising, and we hope to be able to bring this to patients so they could potentially benefit in the near future.

Dr. Wilner:
Well, I agree. This certainly sounds like a positive step towards better treatments for patients with glioblastoma. I'd like to thank my guest, Dr. Dominique Higgins, for sharing his research and insights.

Dr. Higgins, thanks for joining me today.

Dr. Higgins:
Thanks for having me. It's been a pleasure.

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.

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