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Exploring New Research on Melanoma Brain Metastases

Dr. Wilner:
Brain metastases are common in patients with advanced melanoma and are a leading cause of cancer-related death. Little is known as to why melanoma spreads to the brain, but new research from Columbia University that looks at the cells inside melanoma brain metastases may provide some answers.

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Andrew Wilner. Joining me to talk about this exciting research is Dr. Benjamin Izar, Assistant Professor of Medicine at Columbia University Vagelos College of Physicians and Surgeons and the principal investigator of this recent study published in the journal titled, *Cell*. Dr. Izar is also a practicing medical oncologist who specializes in patients with advanced melanoma and other cancers.

Dr. Izar, welcome to the program.

Dr. Izar:
Thank you for having me.

Dr. Wilner:
Let's start with some background, Dr. Izar. Before your current research, what did we know about why melanoma spreads to the brain?

Dr. Izar:
Actually very little. There was some work done prior to the study that we published that used molecular profiling methods, such as transcriptomics and whole exome sequencing. The issue is that some of those studies were limited by the methods used. What I mean by this, is that those were performed using so-called bulk molecular profiling. It means that when we take these tumors out of patients, they are essentially ground up. You sort of know what's in there but not exactly. And it's important to understand precisely the composition of these tumors and not only know what the cancer cells might be doing but also what all surrounding cells might be doing, such as immune cells or other cells. So while the prior work was helpful in getting first insights into why melanoma has such a high tendency to metastasize to the brain, there were still a lot of open questions. One thing that we did learn from prior work was that the cells that go to the brain change their metabolic program, and they differ substantially from metastases to other organs, for example to the lung or lymph nodes, which are also common sites affected in patients with melanoma. So we had some insight, but we really needed to dig much deeper to understand the complexity of this problem.

Dr. Wilner:
Well, that's pretty interesting. So I presume that when the cell arrives in the brain is when it transforms. Do I have that right?

Dr. Izar:
Actually, it's not completely clear. So these cells, by the time they arrive in the brain, are already cancer cells, so the question is why in some patients, about half of patients with metastatic melanoma, do cells decide to colonize in the brain and why sometimes they don't?

All of them are already cancer cells, and there are probably two things going on. One, the cells must acquire some general metastatic tendency. And then they must do something else to be able to get through the very nuanced systems that exist in the brain, like the blood-brain barrier and the very extensive innate immune system that resides in the brain to get there and survive there. The brain is not a very fertile place for anything to grow and that's because it's designed not to be. These cells adopt a phenotype that resembles cells in the brain and neurons because what better way is there to colonize an area than to just look alike? And this is one of the key findings of our study that we were able to glean.

Dr. Wilner:
Okay. So let's move on to the details of the design of your study and the techniques that were innovative that we didn't have 10 years ago.

Dr. Izar:
Yeah. And I'm going to pick up the example of the prior research. If you imagine taking a bunch of foods and putting them in a blender, they all blend together, and we don't know where one signal came from, whether it came from the strawberry or the banana. We kind of know, but we need to know exactly. And so the methods that we used, and this was one of the innovations in the study, was to profile these brain metastases using single-cell genomics. So instead of having a food shake, imagine having a food salad, where we can pick out each of the foods, can inspect them, and ask 'what's going on in the cancer cells?' What's going on in the T-cells? In the macrophages? Or all sorts of other cells in the brain? And how do those all work together or get co-opted to allow the emergence or development of these brain metastases? So we use these really exciting methods that have changed the way we study, do biology, or research these days and that give us a very nuanced view of the thousands of individual cells within the tumor.

Now to take this even a step further, not only do we want to know what's going on in the brain and all of these different cells, but also how they are positioned in space because the position is very important. So understanding how cancer cells interact with the environment in an architecturally preserved context has already provided us with really important insights to understanding biology and also drug response. And this was the first time we could bring these exciting methods together and integrate them to probe these brain metastases. So there's a lot of technical and computational innovation needed to really do this.

The second aspect of this study is we focused exclusively on patients that had not seen any prior therapy such as radiation, targeted cancer therapies, or immunotherapies because we know that those therapies change the makeup of their tumor. And what we're really interested in is what the native biology is. We want to study this first with a clean slate to find out what are we dealing with, without any of those other important confounders that we wanted to exclude up front. And then we took these treatment-naive brain metastases and compared them with treatment-naive extracranial metastases because we need a denominator. We want to understand what the difference is between brain metastases to metastases outside of the body, so we also included patients for all of these methods that had only extracranial metastases of the lung, liver, or the lymph nodes to get a denominator to what we're dealing with in terms of differences, both in the cancer cells as well as in the microenvironment immune cells and immunity, that takes place in these various different sites.

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. Benjamin Izar about new insights into melanoma brain metastases.

Okay, so now coming back to your study, Dr. Izar, can you tell us some of your findings?

Dr. Izar:
Yeah. I would say that one of the key observations we made is that these brain metastases are genomically different from metastases outside of the brain. When I say genomically different, what I really mean is that these tumors were different at a very large scale. So one type of mutation or genomic alteration is aneuploidy, meaning the variable number of old chromosomes, chromosome arms, or large fragments of chromosomes that is driven by a process called chromosomal instability, essentially meaning that with every cell division, a cell that has aberrant numbers of chromosomes, segments, or fragments will perpetuate that chaos. And one of the observations that we made is that the brain metastases were more chaotic. They had more of these large chromosomal aberrations as compared to metastases outside of the brain.

The second difference that we found is that these cells are also phenotypically different, meaning the cancer cells in the brain metastases are different from those outside of the brain, and they are so in a very peculiar manner because what they really do is something akin to molecular mimicry. They adopt many of the transcriptional phenotypic features of cells within the brain, and one of the genes that we identified is one of the key neuronal defining genes. NCAM1 is a fundamental gene or protein important for interactions among neurons, and that happens to be one of the genes that these cancer cells strongly upregulated. We believe that this is one of the reasons to allow these cells to get into the brain and survive there without having this otherwise ensuing response or defenses to such invaders.

Dr. Wilner:
All right. So how is this information going to lead us to novel treatments? Is there any sort of pathway that you anticipate that's going to say, "Hey, now we can do something effective and different that we haven't done before"?

Dr. Izar:
Yeah. I think the first one relates to the genomic changes that I mentioned earlier. We now understand much better what happens in the cell that has such genomic chaos, that it is not a very stable state for any cell, including cancer cells. So it's very possible and there's new novel drugs emerging that directly target such dependency.

There's a couple of other things I mentioned. So for instance, you can imagine trying to target the adaptive process that these cells undergo and upregulation of some of those proteins. Those are essential for survival in the brain. And this is a surface protein so it's very amenable to antibody-mediated therapies or other therapies in terms of trying to prevent brain metastases from developing and to perhaps treating established brain metastases.

And then one last aspect that is based on biology that we haven't talked about yet is evolving around the immune cells in those brain metastases. The immune environment in those tumors is different from those outside of the brain. One particular cell type that looks quite different in the brain are macrophages, or myeloid cells in general, and there is more work on myeloid modulatory therapy, which might help us to program these cells that are being co-opted by the cancer to be protumorigenic and make them good players again in the tumor.

Dr. Wilner:
Well this is very exciting, and hopefully, this and future research efforts will help lead us to some new treatment options for our patients with melanoma brain metastases and maybe other cancer type brain metastases.

I'd like to thank my guest, Dr. Benjamin Izar, for a great discussion. Dr. Izar, it was a pleasure speaking with you today.

Dr. Izar:
Thank you so much for having me.

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.