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Toxic Short RNAs May Cause Neuronal Cell Death in Alzheimer's Disease

Dr. Wilner:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and joining me today to discuss his research on how Alzheimer's disease may be linked to short strands of toxic RNA is Dr. Marcus Peter. Dr. Peter is a Professor of Medicine in the Division of Hematology and Oncology as well as a Professor of Biochemistry and Molecular Genetics at Northwestern University Feinberg School of Medicine in Chicago.

Dr. Peter, it's great to have you with us today.

Dr. Peter:
Thanks for having me. I'm thrilled.

Dr. Wilner:
Let's start with some background, Dr. Peter. Please tell us about your research and what led you to explore the relationship of these toxic short RNAs and Alzheimer's disease.

Dr. Peter:
Our study is based on the discovery we made a few years back. We found that certain cellular components, so-called short RNAs, could kill all cells we introduced them into in a way that activated many different cellular pathways. We found that in every cell, there is a balance between toxic versus protective short RNAs that determines whether the cells live or die. We believe that in Alzheimer patients, this balance tips towards more toxic short RNAs, causing dysfunctional and eventually dead brain cells.

This project started with the discovery of a short sequence in already short RNAs we call the kill code. This code of just six building blocks, so-called nucleotides, can kill all cells. We realize that this could be a perfect way for nature to kill any cell it wants to eliminate.

All cells contain genes that they cannot exist without. We call them essential survivor genes. This is about 10 percent of all of our genes. It is these genes that are attacked by our toxic sequences. Each of these toxic short RNAs can target dozens of such survivor genes with the results that cells die. That is why we call this process DISE, for death induced by survival gene elimination. Sure enough, we then found that these structures have strong anticancer activities, and we are in the process of developing this into a new form of cancer therapy.

So what has that to do with Alzheimer's disease you ask. Well, we had found evidence that the mechanism we discovered was ancient. In fact, we estimate it to be at least 800 million years old. If there was such a powerful anticancer mechanism that could destroy cells, we wondered what would happen if this mechanism was overactive in certain individuals. Since it's the cell killing mechanism, we postulated that this should result in tissue loss, maybe a form of degeneration. On the flipside, since the anticancer mechanism was overactive, we expected these individuals to have less cancer.

The brain is one tissue where we cannot replace cells that die. We need all our neurons. We were, therefore, searching for a neurodegenerative disease that was characterized by reduced cancer incidence, and that is how we came to Alzheimer's disease. Countless reports showed that patients with advanced Alzheimer's get much less cancer, any type of cancer actually. That is why we started to analyze Alzheimer's and found evidence that the kill code is indeed overactive and may contribute to the disease.

Dr. Wilner:
That's amazing. I was not aware that there was epidemiological evidence that Alzheimer patients—who tend to be elderly and theoretically more susceptible to malignancy (that's, you know, who gets cancer usually is older people, not always but more often)—

would be somehow protected from cancer.

Dr. Peter:
Yeah, we were pretty amazed by that too. We were looking for disease, in fact, and were stunned to see that there at least 20 publications. It's pretty well established. And interesting enough it goes both ways. So late-stage cancer patients get much less dementia, and late-stage Alzheimer patients get less cancer. And this, of course, is age corrected. You're absolutely right. There is a big age component here. But these are pretty solid studies. And, of course, while there may be many reasons why that is, our results are consistent with this observation at least.

Dr. Wilner:
So there's this balance between toxic short RNAs and then the survivor genes, right?

Dr. Peter:
There's a balance between toxic short RNAs and RNAs that have the same size and the same mechanism of action but don't contain this kill code, and they outcompete the protein complex in the cell that mediates this effect and prevent the toxic ones from killing cells. So the balance is between the toxic short RNAs and the nontoxic short RNAs.

Dr. Wilner:
How were you able to manipulate this in your study? What did you do? What did you find?

Dr. Peter:
There are proteins and then another class that's called RNA. Proteins are the workhorses of the cells performing most of the functions, right? They are coded in the genome in the form of genes, which are converted to long RNAs which then serve as templates to produce the proteins. We call these RNAs long-coding RNAs because they code for the proteins. Then they are non-coding RNAs, and one class in particular is relevant here: short non-coding RNAs. They are about 20 building blocks, long only, and a major class of these called microRNAs function by attacking the protein-coding long RNAs. When they do that, this results in the elimination of the proteins they code for, and when these are critical for cell survival, cells die through DISE as we discovered, and our short RNAs act with the same mechanism as these microRNAs.

The process of tacking the protein-coding RNAs is called RNA interference, another term. RNA interference is done with the help of a large protein complex where the short non-coding and the long-coding RNAs meet in the cell. We used a method to isolate this big protein complex from brain cells and sequence its content. This way we could determine the amount of short RNAs that carry the kill code and the ones that don't, and these are actually protecting cells from the effects of the toxic ones. In fact, we found, as I said, it is the ratio of the two short RNA species bound to the protein complex that determines whether the cells live or die.

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. Marcus Peter about his study that links short strands of toxic RNA to brain cell death in Alzheimer's disease.

So, Dr. Peter, if we continue focusing on your study's results, tell us where the super-agers come in.

Dr. Peter:
Well, we found that in a number of models, both animal models as well as human data, that the toxic RNAs actually can kill the brain cells. And we also realized by studying young and old mice that the amount of protective RNAs actually get reduced with age, particularly in the brain. It's a pretty dramatic finding. Then the theory was born that maybe with age, we're losing the amount of protective RNAs and making more susceptible to the killing activities of the toxic RNAs with age.

In reverse, we were wondering whether so-called super-agers—this is a population, a group of people that are studied here at Northwestern University. These are individuals that are 80 years or older that have the memory capacity of 50 year olds. We were wondering whether their brains contained a higher amount of these protective RNAs compared to the regular folks. So we got a small number of their donated brains to analyze, and indeed, their brains contained a slightly higher amount of protective short RNAs, consistent with the idea that aging in their brains may be delayed and that makes them less susceptible to dementia.

Dr. Wilner:
How could this evolve to a medication for Alzheimer's disease, for example?

Dr. Peter:
First, of course, the next step will be to confirm our data with more patient samples and more models and see how solid it is, and then we are in the process of designing assays with the goal to screen for drugs that may slow down the loss of these protective microRNAs we're losing in our aging brains. We hope that this will eventually have a beneficial effect for the increasing number of Alzheimer

patients we are dealing with over the next decades as our population ages, as we all know. These efforts at the moment, since it's the first description of this phenomenon, are very early, and results will likely take years to make it into the clinic. But as I always say, if we don't start, we'll never get there.

Dr. Wilner:
Now is there any way to assay these protective RNAs or short killer RNAs in vivo, you know, in a patient? They come to the clinic. Do you need cerebrospinal fluid or a brain biopsy or a blood test? Is there any way to get this information?

Dr. Peter:
There has been a lot of efforts in recent decades to find biomarkers that would predict outcomes or allow us to interfere. The problem with this method is that this mechanism really acts on this protein complex inside the cell. We literally need to isolate the protein complex and peek inside, and so far, we don't have an assay one could use in vivo that is noninvasive to test that. Unfortunately, when it comes to brain diseases, people are very picky giving up their brain cells, so we don't have access to that. It's all postmortem, after they died, and that limits, of course, the studies.

I got some interesting questions about, you know, red wine and working out and eating well. And yes, of course, I would love to be able to study this and how that affects the brain, but all these studies will have to be done in animal models. There we can do it, and then we can test it in humans later.

Dr. Wilner:
Well, before we close, Dr. Peter, do you have any takeaway messages for our audience?

Dr. Peter:
There's a lot of progress lately. There are the first FDA-approved drugs and more to come. So we're making slow progress, and we'll only move forward from there. And, of course, to the young scientists, so people who want to study this, I would say there are still a lot of unknowns that are to be discovered, and don't be shy or discouraged to walk on an unusual path. Don't doubt everything you hear, but be critical about what you are hearing, study and form your own opinion, and follow your path. And that's what I've been doing for the last three decades, and that is how a cancer researcher got to study Alzheimer's disease.

Dr. Wilner:
Now with those final comments in mind, I want to thank my guest, Dr. Marcus Peter, for joining me to discuss his research that links short strands of toxic RNA to brain cell death in Alzheimer's disease.

Dr. Peter, it was a real pleasure having you on the program.

Dr. Peter:
Pleasure was all mine. Thank you.

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