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Could T Cells Lead to New MS Treatments?

Dr. Lisk:
Despite the high prevalence of multiple sclerosis, or MS for short, there's still a lot we don't know about this disabling disease. There has been significant strides in MS Research over the years, but we still don't understand how MS causes the immune system to become dysfunctional. This knowledge would help us develop new treatment options and based on a recent study, we might be one step closer to discovering those treatments.

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Jerome Lisk and joining me to talk about this recent study exploring how T cells may lead to new MS treatments is Dr. Shiva Othy. Dr. Othy is a Project Scientist in the Department of Physiology and Biophysics at the University of California Irvine School of Medicine. Dr. Othy, welcome to the program. How are you doing today?

Dr. Othy:
Thank you very much. I'm doing good. How are you doing?

Dr. Lisk:
Doing well. So, to start off, can you tell us how T cells and the protein PIEZO1 are related in the immune system and the importance of both?

Dr. Othy:
So, T lymphocytes are, a subset of our immune system that do go around the body to find infections and then fight anything that is causing damage most likely pathogens and a budding tissue response like cancer and all of that. And as you mentioned about MS and then regarding the role in multiple sclerosis, it is known that MS is an autoimmune disease that effects the central nervous system, where our immune system attacks our brain cells. So it's a misfired setup that leads to all sorts of symptoms in MS.

So, what we study in the lab are the regulatory T cells, which is a specialized subset of T cells that play a very important role in making sure that our immune system does not attack our own tissues. They're like the peacekeepers in our body that keep the other cells in check, for example, effector T cells. There's a fine balance between regulatory T cells and effector T cells that keeps our immune system healthy and then functional, and if there is an imbalance in this homeostatic setup, that will lead to autoinflammatory conditions and MS is one of them.

And PIEZO channels are these mechanically gated ion channels that are commonly expressed in most of the body tissues. And the way they work is if you stretch a cell membrane out and apply some pressure, they will open and they will positively charge ions inside the cells. Sox, these are very recently found ion channels and we are trying to understand how these mechanically activated ion channels play a role in the immune system.

Dr. Lisk:
Now, with that understanding in mind, can you tell us about your study on regulatory T cells and PIEZO1? How was it designed?

Dr. Othy:
Yeah. So, I have been interested in studying the mechanisms of regulatory T cells in vivo for quite some time. And routinely we use this model of autoimmune inflammation that mimics certain features of multiple sclerosis. We use this model because it lets us to study both effector cells and then regulatory T cells in the same animal model. So, our previous study, which was published in 2020 PNAS, identified this unique cellular behavior of regulatory T cells that actually play a very critical role in recovery from the disease. For our current study, we first discovered that T cells in general expressed these PIEZO channels in their membranes. We were super excited about trying to identify what is the role of these PIEZO channels in T cells? So, we designed the experiment to find the role in the immune system using an existing animal model of multiple sclerosis that allows us to comprehensively investigate most of the functions of T cells in vivo.

Dr. Lisk:
And what were the findings, Dr. Othy?

Dr. Othy:
This was a very interesting study because we took these mice that were lacking in PIEZO channels, particularly in T cells, and then we subjected them to this animal model of MS. And we observed that both control and the experimental group developed disease to the same extent and then they have similar severity of the disease. But very interestingly, the experimental animal show a faster recovery from the disease. And then we were like, "OK. Something interesting is going on here." So one particular angle that we explored further is, what's the role of these PIEZO channels in regulatory T cells because regulatory T cells are the cells that are mediating disease recovery from the clinical signs. What we found further is that they did some adoptive transfer experiments where we took the effector cells from our donor mice and then gave them to recipient mice, they developed disease to the same extent. This again kind of hinted that the effector cells functions are probably intact, but the regulatory T cells are the ones that become more active when you remove PIEZO channels in them.

So we tested this hypothesis using a series of assays and then found that genetic deletion of PIEZO1 does not alter our normal T cell activation or the effector functions. However, it unleashes the regulatory T cells. That's why we see a faster recovery in this animal model and we actually observed similar trends, particularly going to delete the PIEZO1 in regulatory T cells. We can do this using some really cool genetic models that exist in animal systems these days.

Dr. Lisk:
Well, thank you for that explanation.

And for those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Jerome Lisk and I'm speaking with Dr. Shiva Othy about how specific T cells may lead to new treatments in multiple sclerosis.

So now, going back to the study, how does this animal model of MS with these genetically altered mice make it easier for you to understand the human immune system when you find proteins like PIEZO1?

Dr. Othy:
This question is very relevant for human MS patients and then also we are fundamental biologists who are trying to understand how proteins work, how particular cell types work and we often rely on genetic models because they offer a very clean system to interpret our research. And from there, what we can do is we can design a blocker, an agonist for these proteins that we have identified that play a critical role in the human immune system and maybe go about designing, a potential drug that we selectively activate T regs and then does not alter the effector T cells.

Right now, we understand that our study is limited in terms of just observations in mice, but it provides a gateway to actually explore the potential of PIEZO1 as a target to treat MS.

Dr. Lisk:
Let's take a few moments to look ahead. Based on everything we discussed today, you mentioned that some of the next steps would be to develop a drug that would inhibit this protein. Can you elaborate on the importance of finding this protein and what are the next steps

in the field including drug development?

Dr. Othy: So currently, there are corticosteroids that are used for acute MS attacks and then there are disease modifying therapies that are used to delay the progression of MS. Some of these therapies actually suppress the immune system in general that actually opens up potential risk of infections in the brain, liver problems, and some malignancies, in some cases. So we really need to actually find an idea of therapy that is more targeted towards the pathophysiology of multiple sclerosis that has as minimum side effects as possible. Not only that, we should be able to reverse the damage that has occurred in the brain because of immune system attacking the neurons. For example, a therapy that is based on regulatory T cells could be a good candidate for future new MS therapeutics because this regulatory T cells are not only inhibiting a budding tissue activation, but an activation of T cells that are also actually reversing the damage that occurs during autoimmune diseases. So, they have a tremendous potential of suppressing the overactive immune system and actually potentiating tissue repairing mechanisms that will help to recover some of the lost functions in the clinics.

My research is focused on trying to understand what are these fundamental mechanisms of regulatory T cells that enable them to aid in recovery from autoimmune diseases and then I use MS model in the lab as a tool. And once we understand this precise mechanism of regulatory T cells and more particularly how PIEZO channels are actually modulating the functions of regulatory T cells, that will be quite useful in designing a T reg cell targeted therapy for MS and other autoimmune diseases as well.

Dr. Lisk:
Dr. Othy, I hope I have the chance to speak with you again when you go further in this research and these next steps are achieved.

It was a pleasure speaking with you today.

Dr. Othy:
Thank you very much for having me on this program.

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