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Understanding IGF-1R Inhibition: Mechanism & Clinical Implications

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Episode 6

Dr. Kossler:
Hello, I'm Dr. Andrea Kossler, and thank you for joining us today. It is my pleasure to welcome a dear friend and a world-renowned thyroid eye disease expert, Dr. Prem Subramanian.

Prem, we now have so many targeted therapies to the insulin-like growth factor-1 receptor for patients with thyroid eye disease. I always learn so much from you, so can you teach our audience why targeting the IGF-1 receptor is important for active thyroid eye disease?

Dr. Subramanian:
Thanks, Andrea, for this opportunity because it's been an area that we've learned a lot about over the past 20 years or so. And the IGF-1 receptor plays a key role in the activation of orbital fibroblasts, which are the cells that really are at the center of the pathogenesis of TED, both in more acute inflamed states and in the more chronic state.

And in the acute stage, the orbital fibroblast responds to inflammatory cytokines in addition to responding to stimulation from T cells, and then a co-stimulation of the TSH receptor and the IGF-1 receptor on its surface. And this leads to pathogenesis-like transformation into adipocytes and adipocyte proliferation. It can lead to a transformation into an orbital fibrocyte. And it also leads to secretion of hyaluronic acid, glycosaminoglycans, and the accumulation of water edema in the orbit. In the longer-duration or more quiescent disease, it's that latter part of hyaluronic acid maintenance of homeostasis where the IGF-1 receptor and the TSH receptor together are continuing this pathogenic process. It's not as though the whole thing comes to a screeching halt.

And if we look at TED pathogenesis more broadly, we can see that again there are a number of inflammatory cells as well as soluble inflammatory mediators that act on this central cell, the orbital fibroblast, and lead to activation, this differentiation that I talked about, as well as the secretion of other substances into the orbit that, once they are there, they don't go away, and they again are maintained by this dysregulated state. Yes, it's driven primarily at the level of the TSH receptor, but that binding to the IGF-1 receptor, the formation of that complex, really is a central element of what keeps TED going. And so the idea is that if you can interfere with IGF-1 receptor activity, then that is going to not allow that activated TSH receptor to then signal into the cell and lead to that cascade of events that is so detrimental to the function of the orbit and leads to dysfunction of the orbital fat as well as the extraocular muscles.

And so in the previous episode, Andrea, you touched on the fact that we now have a number of different agents that are available for the treatment of our patients that utilize IGF-1 receptor antagonism. Teprotumumab was the first one given by IV. There are other drugs like veligrotug being given by IV, as well as a number of subcutaneous and even oral agents that are in various stages of development right now and really will broaden our ability to tailor treatment to our patients to help to abort this process where that IGF-1 receptor is

leading to further proliferation within the orbit.

And so I think that IGF-1 receptor, because of its key role in the dysregulation of fibroblast metabolism, is going to continue to be a target for our therapies. And again, as these new therapies come into play, our options and our patient outcomes hopefully will only improve.

Dr. Kossler:
What an exciting time in thyroid eye disease. I completely agree. I think that these IGF-1 receptor antagonists have really changed the way we understand thyroid eye disease and especially the way we manage thyroid eye disease. It's really impressive how powerful these drugs can be in the properly selected patient.

I think we still need long-term studies to better understand exactly what's happening in our patients. Is this truly modifying their disease course, or will these patients still need additional treatments? And my guess is that in the years to come, what we're going to find is that patients may require multiple treatment approaches to target this really complex disease, with IGF-1 inhibition being kind of at the core of that treatment algorithm. So I think we have come a long way with these new IGF-1 inhibitors, and I'm so excited to see so many on the market, or at least in the pipeline.

Our time is up for this conversation, and it's been great to learn a little bit about these IGF-1 inhibitors. Stay tuned for our next episode, where we're going to dive into some of the most recent breaking data on these IGF-1 inhibitors. So, thank you all for joining us.

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