Exploring hexacorallian models to aid corals affected by climate change

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In this interview, Benyamin Rosental, PhD, from the Shraga Segal Department of Microbiology, Immunology, and Genetics, looks toward hexacorallian models to transplant stem cells to corals affected by global warming

Why are you researching stem cell transplantation on hexacorallian models?

The first step of our research is with our model sea anemones, which are part of the hexacorallia subclass along with stony corals. The purpose of the tool that we are developing is to develop stem cell-based therapies for corals.

We're starting with hexacorallians because they're closely related on the evolutionary scale. Also, this sea anemone is the only hexacorallian organism with transgenic animals. This makes it easy for us to follow transplanted cells and see how they integrate into the tissues. Meanwhile, we're finishing our coral rooms, and hopefully, the tools we're developing with the hexacorallian models can move towards coral systems.

What are hexacorallian models to a layman?

Corals belong to the phylum Cnidaria, which includes soft-bodied organisms containing stinging cells like jellyfish, sea anemones, and corals. Hexacorallia is a smaller subclass within Cnidaria that contains our model sea anemone as well as other organisms, like stony corals.

Using a model is the idea that we can develop the tools or show proof of concept in those organisms, and then translate that into our target organism. We can see examples of this with immunology or cancer. Research is done at the beginning with mice models. There might be better models, like monkeys or even primates, which are much closer to humans, but it's not always easy to do.

In our case, the molecular tools available in the model we're using, Nematostella, are much more robust. Additional laboratories use these animals as models in Europe, the U.S., and Israel. So we can already build on the tools they have developed.

Hopefully, now that we're succeeding with the stem cell transplantation model, we can move on towards the corals, which are much more relevant on the ecological level.

How will this research help these corals to survive temperature changes better?

Our basic research is to develop the tools for stem cell-based therapy. Stem cells are unique in that they are long- lived cells throughout the life of an organism, and they can divide and differentiate into other cell types. The best example of this is bone marrow transplantation, which has been done for almost 50 years in humans. The idea here is that if someone is born with primary immune deficiency, for instance, they cannot create T cells, they will be susceptible to any viral infection. Generally, before the age of one, they would go through bone marrow transplantation taken from a healthy donor. Inside it, it has stem cells of the blood system. Those transplanted stem cells then replenish the whole immune system, including the missing T cells with the healthy genotype. By replacing the immune system of the child, we give this child a chance at survival.

With the whole genetic manipulation capabilities from the last decades, the idea is also to use gene therapies through stem cells. So, for example, we may fix the gene that needs to be fixed in extracted stem cells, and when we transplant it back, those cells are proliferating and differentiating into other cell types. This way, we develop a healthy system based on an individual's stem cells.

One approach is transferring from a healthy donor to a sick patient, and the second is manipulating the stem cells through genes that need to be amended or changed. So, in this case, there can be two different approaches for corals if we specifically talk about the heat stress which has negatively affected the corals.

Some corals are more resilient to heat stress when a heat wave is coming in. Usually, around 10% of the individuals will survive, which suggests that those individuals are more resilient. Research shows there is a genetic variability between those individuals of corals. So, like bone marrow transplantation, we can isolate stem cells from heat- resilient individuals and transplant them to heat-sensitive ones. We create a chimera, an organism with both genotypes, and when a heat wave comes, this coral can withstand the heat wave.

The second approach is important because we have yet to complete the whole life cycle of corals in a lab. With this approach, we could create corals with specific genes by isolating stem cells, manipulating their genes, and then transplanting them back. However, for that to succeed as a therapy, two additional tools need to be developed. Firstly, we need to know which genes are enabling this heat resilience in corals, and secondly, we need to be able to do genetic manipulations in the coral.

Whether just transplanting from a resilient coral to a sensitive one or a self-transplantation after gene therapy for both, what you need is to be able to isolate stem cells and transplant them into these animals, which is what my lab is trying to develop with hexacorallian models.

This is the ability of stem cell isolation and transplantation in corals. I'm not saying it will rescue the corals tomorrow. What I'm saying is that we're developing the tool to do so.

Where are the donor cells coming from? Is this a sustainable source?

If we're talking about the simpler direction, transplantation from a resilient genotype to a sensitive genotype, then the source of the cells will be from resilient genotypes. Many laboratories are looking for more resilient genotypes and are trying to raise them.

Additionally, if we take a certain amount of the stem cells, we can proliferate them outside the organism and then do transplantation. This will help greatly with the ability to use the cells without taking too much from the organism. That way, we can also freeze, store, and ship them.

But the idea is still that those cells are coming from the corals themselves. So if you have your resilience or dominant genotypes, you need to have nurseries of them to raise them and isolate the cells from them.

While I'm not saying it's self-renewing, it can use tools available for raising corals, and hopefully, if we have dominance, then we will succeed in not using a huge amount of the cells. If we're talking about the gene therapy approach, then it's the cells of the organism itself.

Discuss the differentiation of cell types & the populations of cells in your research

Differentiation is how we separate the different cell types. As an immunologist, I work on cell function and isolating different cellular populations.

When I started working on a marine organism, it was a tunicate model.
I needed to isolate the stem and immune cells from the organism to develop all the transplantation assays.

With non-classical model organisms, we didn't have any antibodies that we could use to separate those cells. Generally, different antibodies targeting 'cluster of differentiation' can recognize different cell types in mice and humans. Because we didn't have these antibodies available for our tunicate model, we had to find alternative ways to recognize cell types.

So, together with colleagues and the tools I developed, we screened for many different ways of isolating cells. This became a considerable expertise during my postdoc, where I became an expert in isolating different cellular populations of non-classical model organisms. I worked on lymphatic systems in tuna, sea urchins, sponges, and other fish.

I didn't think I would be working with corals, but luckily, I had a lot of good people and great ideas with whom I worked, and we decided to start establishing this project on hexacorallian models.

In the lab, I still have projects towards classical medical work with rare human diseases and heart inflammation using induced pluripotent stem cells from humans. In addition, we study bone marrow transplantation, taking ideas from marine organisms to improve human bone marrow transportation.

We're essentially taking biomedical tools into ecological questions.

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