INTERVIEW SPOTLIGHT

DR. SHEILA SINGH

Photo Credit: *Unknown*

The Dynamics of Brain Tumors

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WHAT INSPIRED YOU TO PURSUE A CAREER PATH IN PEDIATRIC NEUROSURGERY AND STEM CELL AND CANCER RESEARCH?

So, I think I knew for a long time, since I was a girl, that I wanted to be a doctor and was mostly inspired by family members. My mother was a nurse and my father was a doctor and so the whole sort of caregiving aspect really appealed to me. When I went to medical school, I had an abiding interest in the brain. It started because my father, who is a psychiatrist, had all kinds of books on psychotherapy, and they were the only books that were available in his library. Mostly, they were all Sigmund Freud and stuff like that, so I started reading psychology and became fascinated by how little we know about the brain. When I got to medical school, I knew I wanted to do something related to the brain and did electives in everything that had the word "neuro" in front of it. So, the reason I chose neurosurgery is because, out of all of the fields which were intellectually interesting and cognitively gratifying, I found only neurosurgery had that sense of activism where you threw yourself into a cause where someone was very sick and you were actually able to do something about it. In neurology, I loved the diagnostic process, the whole localizing the lesion and finding out where the central nervous system was injured based on someone's presentation. But, it was depressing because, very often, you'd say, "Oh, you have a neurodegenerative disorder for which there's no known cure and I don't have any medical treatments for you". That was too passive for me. So, I think it was really just the difference between passive and active that made me choose neurosurgery because that just suits my personality. When I was a teenager, I was kind of a social activist and I always wanted to pick up a cause and protest so I think neurosurgery suited me personally because of the activism. Having said that, when I chose neurosurgery in medical school, I didn't pick it lightly; I really tested myself, trying to find out what I enjoyed the most. Once I realized it was neurosurgery, I wanted to make sure that I was able to keep up with the demands of the profession. So, I did enough electives to have experience in it, to know that I enjoyed the pace and the demands of the lifestyle. That's another important thing: just because you like something, the next question is, am I well suited for this? Then, the final thing is that you know at the end of everything in medical school, this was the only thing I loved. It's almost as if when you love something like that, then it chooses you, it's not like you chose it. I couldn't imagine myself doing anything else.

COULD YOU DESCRIBE THE RESEARCH THAT YOU HAVE BEEN CONDUCTING IN YOUR LAB?

I set up a lab at the McMaster Stem Cell and Cancer Research Institute in 2007 when I joined here as a pediatric neurosurgeon. It was really quite an amazing fit for me because they started the institute in 2006, and my PhD was involved in the characterization of the population of cancer stem cells and brain cancer. So, it was a perfectly named institute for me. My lab applies a developmental neurobiology and stem cell biology approach to the study of brain cancer. We don't study cancer in isolation. We study cancer, knowing that it's a dynamic process, and we're trying to imagine what could be the conversion that happens in cancer from a normal state to an abnormal state. So, we always study cancer in comparison to normal tissues, which is a slightly different approach. Another mandate of the institute is that we focus on human model systems, which are much more challenging and difficult to develop. We study all human normal neural stem cells in comparison to human brain cancer stem cells. The reason that I think you need an institute to accomplish something like that is because modeling those systems is not only intense in terms of the experience and training required, but it's also very expensive, so it's a lot better if you have a group of researchers who can focus in this area and then share infrastructure together. That's why an open concept model of the institute was also really appealing with a shared lab space. It sort of promotes team-building as well.

WE WERE WONDERING IF YOU COULD ELABORATE ON THE PATH THAT YOUR RESEARCH TOOK TO BRING YOU TO YOUR GROUNDBREAKING DISCOVERY OF THE BRAIN TUMOUR-INITIATING CELLS.

When I spoke to many other people who made important discoveries or seminal discoveries, what you find is that most of them are serendipitous. So, almost everything that turns into a discovery is something that people have observed before. They've just never made the connection of what the observation could imply. So, for me, I wasn't the first person to visualize these floating spheres of cells in a dish when we placed brain tumor cells into culture without serum. I'm sure I wasn't the first person to observe that there were lovely cells growing in these spheres. However, I think we may have been the first people to realize what those spheres implied because the sphere is just a floating colony of all the cells that are present in a stem cell hierarchy. So, basically a sphere arises from a single stem cell that divides and then gives rise to all this divergent progeny, all of which clump together and float around in this sphere. As a result, I think we realized, when we saw that, that this meant there were stem cells in brain cancer. So, not that it was a novel observation, but simply that we interpreted it in such a way that led us to that discovery.

ARE THERE ANY NEW TECHNOLOGIES ON THE HORIZON THAT MIGHT BE ABLE TO FURTHER AID IN THE ANALYSIS OF BRAIN TUMOR CELLS, ESPECIALLY SINCE YOU HAVE MENTIONED THE DYNAMIC NATURE OF TUMOR GROWTH?

I think one thing is recognizing that cancer is a dynamic system. I think modeling how cancers form, and its heterogeneity, both at a cellular and a genetic level, as well as from a spatial and temporal perspective is important. So building model systems that capture how cancers evolve over time or tumor evolution is a theme that's been really powerful. This relies on capturing tissue from patients at different time points throughout their treatment. So not just basing all your knowledge on the treatment-naive biopsy of the patient's cancer at the beginning, but rather trying to survey the cancer through time and understand how the cells evolve and how genetic mutations evolve over time as well. So the whole field of intra-tumoral heterogeneity and apt cancer evolution has been of great interest. There's been many tools that have been developed for things like lineage tracing where you follow cells through time, or DNA cellular barcoding where you drop a barcode library on cells at the beginning and then observe whatever manipulation you put the cells through. For example, you implant a tumor into a mouse and then you can track all the different barcodes through time and figure out which ones dropped out after therapy. You can try to figure out what cells are actually driving the tumor to recur or relapse. So, those are models and experimental systems that we've been using.

But, last year at the most recent Society for Neuro-Oncology meeting, the first technology that seems to be gripping everyone right now is single cell sequencing. So, everyone likes the idea of deconvoluting something down to its most basic building block and trying to understand what's happening at a single cell level and there's all kinds of new technologies in that regard. And then the second thing that everyone's talking about is organoids. Organoids are like complex cellular systems. Imagine that we right now have cultures filled with spheres that are from a patient's brain tumor, but now imagine if you could build a brain microenvironment using normal brain cells and then sort of graft the tumor into that and try to sort of recapitulate a more realistic model system of how the tumor may grow in the patient. These organoids are cultures where you can mix normal and cancer cells and try to establish a three-dimensional model of what may be happening in the patient. You can do that all in a dish, which is the appeal of it. So, I think those kinds of model systems have everyone excited right now. I don't think they're too close yet to what happens in patients, but they'll get better.

WHAT DO YOU BELIEVE ARE THE NEXT STEPS FOR YOUR LAB OR FOR YOU AS A RESEARCHER-SCIENTIST?

We're very excited in the Singh Lab about the prospect and the hope of immunotherapy because there have been some big breakthroughs with harnessing the immune system to treat cancers like blood cancers and melanoma. We're hoping that some of those approaches can apply to brain cancer. It's a big challenge because the brain is notoriously known for being an immunosuppressive environment. So, things can hide out in the brain and escape detection by the immune system and that's possibly why brain cancers do so well. How do you somehow alert the immune system and notify the brain that there is something that needs to be dealt with? Trying to relieve that immunosuppression using things like new versions of checkpoint inhibitors that kind of wake up the immune system and uncover the tumors' ability to evade immune detection is one option. Another option is developing direct targeted therapies like engineering T-cells to go after a tumor antigen that's expressed on a brain cancer cell and then deploying them to go and attack the antigen. These are therapies that are not like your traditional chemotherapies, but rather, new therapies that are more specific but also may be more organic because they're based on your own immune system.