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Using Mouse Models to Understand Metastatic Cancer

A NEW MOUSE MODEL THAT MANIFESTS ALL OF THE MAJOR HALLMARKS OF HUMAN METASTATIC CANCER

We almost always cure mice of cancer, but the same treatment often fails in humans, is it the mouse model?

Welcome to The Clinician's Roundtable on ReachMD. I am your host, Dr. Bruce Bloom and joining us to discuss a new mouse model that manifests all the major hallmarks of human metastatic cancer is Dr. Thomas Seyfried, Associate Editor of the journal of nutrition and metabolism and professor of biology at Boston College.

DR. BRUCE BLOOM:

Dr. Seyfried, welcome to ReachMD.

DR. THOMAS SEYFRIED:

Thank you Bruce, it's a real pleasure to be here.

DR. BRUCE BLOOM:

So that was a mouthful, the new mouse model that manifests all of the major hallmarks of human metastatic cancer. So how did you decide to try and create a mouse like this?

DR. THOMAS SEYFRIED:

Well, you know, one cannot create a mouse model like this through any kind of genetic engineering, at least not to this point. There is a strain of mouse called the VM strain of mouse that develops spontaneous brain tumors at a higher frequency than any other mouse strain that's available. These tumors have a lot in common with human astrocytomas. We were able to identify, first we had to raise a large number of mice and look carefully for those that developed the spontaneous brain tumors and you can see that by their changed behavior. What we did differently from all other studies is that we selected for the tumors in vivo by taking tumors from the original observed mouse and implanting the tumor tissue itself into the brain of other mice. We were able to select for the kinds of cells that were

responsible for the tumor and in doing this we made a very interesting observation that I've never seen before is we usually implant into the flank of the mouse to grow more tissue for biochemical analysis. It turned out that every mouse that we implanted into the flank developed systemic metastatic cancer back to the brain as well as all organ systems and I immediately recognized that this was something that was absolutely astonishing. So we developed that and exploited and found these cells.

DR. BRUCE BLOOM:

And what happens with other mouse models, so you put cancer cells in the flank and they just stayed there? They never metastasize?

DR. THOMAS SEYFRIED:

Where most of the models are, they are called local tumor growths, and you'll see this for most of your human xenograft models and things like this. They will have local invasion perhaps, but they generally do not show. In fact, there is no model that will show systemic metastatic cancer from flank implantation of the tumor cells or pieces of tissue. There are some that will metastasize to one or two organs, but never show systemic metastasis back also to the brain. So this distinguishes the models from all others and many metastatic models require the injection of the cells directly into the circulation of the mouse in order to get them to see different organs. This model does not require that. So in bodies, it has retained a capacity to intravasate naturally from tissues or from subcutaneous implants or in orthotopic site, the brain site itself.

DR. BRUCE BLOOM:

And does it matter what kind of cells you implant in the flank of these mice; prostate, colon, breast, does it matter?

DR. THOMAS SEYFRIED:

The interesting thing about it when we tried it, our advance was you know identifying what are these kinds of cells that behave similar to what you see in human systemic metastatic cancer. Now they arose in the brain. It's generally known that brain tumors do not generally metastasize outside of the brain to other organs. This is only because the patients who have these tumors usually die, but it has been recognized that some of the aggressive human brain tumors will metastasize. This is seen from organ transplantation and a variety of other reports in the literature. It turns out that the cell is of macrophage origin, it's the local macrophage, the microglial cell that is the origin of this which embodies this very aggressive behavior to invade and metastasize.

DR. BRUCE BLOOM:

Take us through some of the technical research that you did in order to identify this particular cell, how did that come up?

DR. THOMAS SEYFRIED:

Well, I would say the first thing that we noticed in finally culturing the cells and saying you know what kind of cells are these, they wouldn't come off the culture dish and I could hear my students banging, I said what is going on, they said we can't free the cells from the culture dish and that's one of the characteristics of a macrophage, they stick very aggressively, you have to scrape them off the dish in order to isolate them. Then we said, you think it's possible that these things could be macrophages so we then got some standard cell

lines that are macrophages and ran them in a kind of a line-up like you would do for criminals in a line-up and find out how many characteristics do these metastatic cancer cells have in common with macrophages and they were absolutely indistinguishable from macrophages except they rose in the brain and the endogenous macrophage in the brain is a microglial cell, so we identified them as microglial cells, but interestingly enough it turns out that many metastatic cancers have characteristics of macrophages, so we don't think this is unique to the brain. We think this may be a general phenomenon for all metastatic cancers.

DR. BRUCE BLOOM:

And how long did it take you to go from this initial observation to actually making the discovery of these macrophage like cells that are metastatic?

DR. THOMAS SEYFRIED:

Oh, it probably took us 15 years, and that's probably because it's very hard to isolate the tumors. To find them, you need large numbers of animals. We were able to isolate tumors from several different independent mice arising at different times over different periods and then we isolated and characterized, we got the same result only for the metastatic tumors. We identified other tumors that are stem cell like in characteristic, but when you implant these cells, the stem cell like tumors into the flank, they grow only as a large rapidly growing mass, but they never show systemic metastasis. So we actually know that these mice produced different kinds of tumors, some of which are like stem cells and some of which have these macrophage characteristics which behave like human systemic metastatic cancer.

DR. BRUCE BLOOM:

Well, there is a lot in the literature these days talking about different kinds of cancer cells and the different things that they do so in human cancers have we seen a similar evaluation of stem-cell like cancer cells, macrophage-like cancer cells, and other that just, you know, occupy different strata?

DR. THOMAS SEYFRIED:

Yeah, we've seen both. Our hypothesis of cancer is that it's a multicellular kind of disease. You have the rapidly growing stem cells, which represent one form of the cell in the growing tumor mass, but at some point one of the local cells, the endogenous macrophage, either coming as a local resident or one of the cells coming in from the circulation becomes corrupted and that is a fundamentally different kind of a cell than the stem cell population. Those are the cells that we think and eventually intravasated to the circulation and see different organs and they will retain some of the characteristics from the original tumor from which they arose, so we think most metastatic cancer is the disease themselves with macrophage properties. This is a fundamentally different kind of a concept and also explains why it's been so difficult to actually deal with metastatic cancer. If we are correct in our hypothesis, the macrophage is the most powerful cell in the body. It is like the police force and fire department rolled into the same cell. This cell has the capacity to intravasate; extravasate from tissues at will because this is what it was designed to do. If this cell now becomes corrupted and feeds multiple systems, it's clear why it's so difficult to control this.

DR. BRUCE BLOOM:

And can this macrophage then when it gets a distant site can it become a stem cell like cell and begin to grow tumor mass?

DR. THOMAS SEYFRIED:

Well, it grows tumor mass, there is no question about that. It will seed and invade into multiple organ systems. Whether it takes on some characteristics of the stem cells, we are not sure. We have only identified the cells aggressively entering into multiple different organs. We have not isolated those cells directly and examined them, but from their markers on the surface, they seem to be similar to the same cells that were present. Now the other thing you have to realize is we have isolated these cells in tumor form now whereas in humans you have mixtures of all kinds of different cells. So this represents one, and the other thing that is important to mention is that the rate of growth of these highly metastatic cells is much, much slower than the stem cells, so there is tremendous differences in growth rate between the kinds of cells that make up the tumor, which is actually a society in itself of destabilized cellular constituents not only from the tumor cells, but also from the host. So the really aggressive ones are usually more slowly growing than the less metastatic ones.

DR. BRUCE BLOOM:

So what are all the hallmarks of human metastatic cancer?

DR. THOMAS SEYFRIED:

The first thing that you need is the local invasion of the tissue in which the tumor is growing. The second part is the intravasation, which is the entrance of the tumor cells into the circulation. These cells also have to survive the immune system, then they leave the blood stream and extravasate into distant organs and continue to colonize distant organs, which we call secondary tumor formation in other organs. So this cell line, this model that we have, does all of this in an immunocompetent host, the natural host from which the tumor arose. So many models don't have this. They use xenograft, they use immunocompromised systems. They have to inject cells into the circulation, so all of the hallmarks of human systemic metastatic cancer are embodied in these cells and this host to make it very similar to what we see in humans.

DR. BRUCE BLOOM:

And this mouse immune system, is it a good proxy for the human immune system, would we expect the same thing to happen in the humans?

DR. THOMAS SEYFRIED:

Yes, the VM strain of mouse has a normal functional immune system, so this would be similar to what we can see in the human situation.

DR. BRUCE BLOOM:

You mentioned when these cells get into the bloodstream, they have to survive the immune system. Are macrophage-like cells particularly good at that?

DR. THOMAS SEYFRIED:

They are excellent at that. They are part of the immune system, so you are not going to look at them as being foreign. As a matter of fact, there have been reports from scientists in Italy showing that T-cells, which are part of the immune system, are actually eaten by these aggressive macrophages. So this is why these cells are so difficult to control because they have incredible powers that they have evolved to behave in managing disease within the brain and putting out inflammatory conditions and infections, so these are pretty tough cells. They also suppress the immune system as well. They have powerful immune suppressant effects so this then becomes a real dangerous disease.

DR. BRUCE BLOOM:

You mentioned earlier you did a line-up of normal macrophages and these kinds of cells, so you must see some differences though that make these cancerous and the other ones not, what are those?

DR. THOMAS SEYFRIED:

We haven't found that yet, and that's what was most astonishing. It appears from their biochemistry and their genetic profiles at least at this point, they don't appear to be that different from macrophages that are not thought to behave like this. So when one thinks of the number of genes that can create a metastatic, we don't think it's very many at all, may be just a couple of changes in the normal macrophage could make it become tumorigenic, which then you don't have to anticipate hundreds of gene mutations to get one of these kinds of cells, although that may be what's happening in some of the cells, it may not be happening in these cells. These cells already embody what they do naturally, it's just that they are dysregulated now and behaving like, they have the capacity to enter and exit tissues as part of their normal genetic repertoire. It's just now that this is dysregulated.

DR. BRUCE BLOOM:

Are there any macrophage like other diseases that might be a good place for us to start looking at how to control these macrophage-like cancer cells?

DR. THOMAS SEYFRIED:

Well, there are a number of human cancers that have the same properties. This has been described for aggressive malignant melanoma. Melanocytes are endogenous macrophages of the skin and malignant melanoma is a kind of a macrophage disease. Now, of course, people want to <_____> molecular mechanisms. Dr. Pollak at Yale University has been working in this area. He thinks metastatic cancer is a fusion between stem cell or cancer cell like cells and macrophages which you get then the genomic mix of two different kinds of cells, this is his hypothesis. It has been shown in small lung cell carcinoma, breast carcinoma, colon carcinoma that many of the tumor cells have behaviors of macrophages. So we think this is not unique to the mouse, we think this is a general phenomenon that underlies metastatic cancer and that is metastatic cancer appears to be in some cases a disease of macrophages or macrophage like cells.

DR. BRUCE BLOOM:

I'd like to thank our guest Dr. Thomas Seyfried for joining us to discuss a new mouse model that manifests all the major hallmarks of human metastatic cancer.

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